# GRAS NOTIFICATION FOR SOY LEGHEMOGLOBIN PROTEIN PREPARATION DERIVED FROM *PICHIA PASTORIS*

**Submitted by:**
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## PART 1: SIGNED STATEMENTS AND CERTIFICATIONS

1. This GRAS notice is submitted in accordance with 21 C.F.R. Part 170, Subpart E.

2. Name and Address of Submitting Company:
   Impossible Foods Inc.
   525 Chesapeake Drive
   Redwood City, CA 94063
   Phone: (650) 461-4385

3. Name of Notified Substance: Soy leghemoglobin protein preparation

4. Intended Conditions of Use:
   a. List of foods and/or drinking water to be added to: Ground beef analogue products.

   b. Proposed levels of use: Soy leghemoglobin protein preparation will be added to the ground beef analogue product to deliver not more than 0.8% soy leghemoglobin protein.

   c. Purpose of substance in the food product: The primary purpose of the characterizing component of soy leghemoglobin protein preparation, soy leghemoglobin protein, is to create a flavor impact in ground beef analogue products. In addition, soy leghemoglobin protein has a nutritive value as a source of iron, analogous to the role of myoglobin as an iron source in meat.

   d. Subpopulation expected to consume product: (if appropriate): No subpopulations are anticipated.

5. Statutory Basis for GRAS Conclusion:
   The statutory basis for the GRAS conclusion for soy leghemoglobin protein preparation is scientific procedures. Impossible Foods has assembled the scientific data to conclude that soy leghemoglobin protein preparation is generally recognized as safe for use as a component of ground beef analogue products.

6. It is the view of Impossible Foods that the substance is not subject to premarket approval requirements of the Federal Food, Drug, and Cosmetic Act based on Impossible Foods' conclusion that soy leghemoglobin preparation is GRAS for the intended use as a component of ground beef analogue products.

7. Availability of Information for FDA Review: The data and information that are the basis for Impossible Foods GRAS determination are available for FDA's review, and copies will be sent to FDA upon request, in either electronic format or by paper copy. Requests for copies and arrangements for review of materials cited herein may be directed to:

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Morgan, Lewis and Bockius, LLP
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8. Exemptions from FOIA Disclosure:
   The information provided in this application does not contain confidential or proprietary information, and therefore no FOIA exemptions are claimed.

9. Authorization to Share Trade Secrets with FSIS:
   Should FDA find the need to share the information in this application with FSIS, Impossible Foods has no objections.

10. Certification
    On behalf of Impossible Foods, I certify that, to the best of my knowledge, the GRAS notice is a complete, representative, and balanced submission that includes unfavorable information, as well as favorable information, known to me and Impossible Foods, and pertinent to the evaluation of the safety and GRAS status of soy leghemoglobin protein preparation for use as a component of ground beef analogue products.

    Signed:

    (b) (6)

    10/02/2017

    Gary L. Yingling — Date
    Senior Counsel
    Morgan, Lewis, and Bockius LLP

# PART 2: IDENTITY OF THE NOTIFIED SUBSTANCE

## 2.1. Chemical Name

The preparation containing soy leghemoglobin protein (along with other components) that is used as a food ingredient in Impossible Foods Inc. ("Impossible Foods") ground beef analogue products is referred to as "LegH Prep".

Soy leghemoglobin protein (UniProtKB/Swiss-Prot #: P02236, GeneInfo Identifier (GI) 126241) is the chemical name of the characterizing component of LegH Prep. The source of soy leghemoglobin protein is the soy plant *Glycine max* gene *LGB2*. Soy leghemoglobin protein is found in the root nodules of the soy plant.

In this report, the terms "soy leghemoglobin" and "soy leghemoglobin protein" are used interchangeably to refer to the characterizing component of LegH Prep.

## 2.2. Common or Usual Name

As discussed in greater detail in other sections of this GRAS notification, Impossible Foods has determined that the use of LegH Prep as a component of ground beef analogue products is generally recognized as safe.

According to the section 403(I)(2) of the Federal Food, Drug, and Cosmetic Act and 21 C.F.R. § 101.4, a food product must list the common or usual name of each ingredient in the food. Impossible Foods recognizes, in this GRAS notification, that an appropriate common or usual name for the LegH Prep used in its products is "leghemoglobin (soy)". Impossible Foods will include "soy" on the label. In addition, Impossible Foods will notify consumers that the product "Contains Soy" as required by the statute.

## 2.3. Applicable Conditions of Use

LegH Prep, a mixture containing soy leghemoglobin protein, *Pichia* (yeast) proteins, sodium chloride, and sodium ascorbate, is to be used as a plant-based protein component in nonanimal-derived food products with the texture, nutrition, flavor and aroma of traditional animal-derived foods.

LegH Prep, along with several other Food and Drug Administration ("FDA" or "Agency") recognized plant proteins, will be components of the ground beef analogue products. Other proteins may include, but are not limited to, commercially available proteins from soy, pea, mung bean, lentil, corn, potato and wheat. LegH Prep will function to catalyse flavor chemistry and contribute to the nutritional quality of ground beef analogue products. A typical ground beef analogue product will contain:

| Component | Ground Beef Analogue |
|---|---|
| Protein | 10%-25% |
| Oils | 0%-25% |
| Miscellaneous[1] | 2% |
| Water | 50%-75% |

[1]Miscellaneous ingredients include salt, flavors, vitamins, essential amino acids, etc.

### 2.3.1 Levels of Use

LegH Prep will be added to the ground beef analogue product to deliver not more than 0.8% soy leghemoglobin protein. The use of LegH Prep in ground beef analogue products is self-limiting based on unacceptable organoleptic properties at higher levels.

### 2.3.2 Purposes

The primary purpose of the characterizing component, soy leghemoglobin protein, in LegH Prep is to create a flavor impact in ground beef analogue products. In addition, soy leghemoglobin has a nutritive value as a source of iron, analogous to the role of myoglobin as an iron source in meat. Once cooked and digested, both soy leghemoglobin and animal-based myoglobin release identical heme B molecules into the digestive system (Annex 1). Studies using cell models of iron bioavailability have shown that the bioavailability of iron in soy leghemoglobin is equivalent to that of bovine myoglobin when in a food-like substrate (Proulx & Reddy, 2006). Thus, the use of LegH Prep in ground beef analogue products will enhance both the flavor and the dietary profile of those products (Carpenter & Mahoney, 1992).

## 2.4. Composition

Hemoglobin proteins are found in most organisms, including bacteria, protozoa, fungi, plants and animals (Hardison, 1998). Hemeproteins are classified as globin/non-globin and symbiotic/non-symbiotic. Hemoglobin, myoglobin, and leghemoglobin are examples of globin proteins. Cytochrome oxidases, hemocyanins, and methemalbumin are examples of non-globin hemeproteins (Everse, 2004; Jokipii-Lukkari, 2009). Plant hemoglobins are classified according to function as symbiotic or non-symbiotic (Gupta, 2011). Symbiotic hemoglobins are found predominantly in legumenous plant species. The most studied symbiotic hemoglobins are the leghemoglobins of nitrogen-fixing legumes where they facilitate oxygen diffusion within root tissues. Nonsymbiotic hemoglobins have been identified in a wide range of legume and nonlegume plants. The highest expression levels for nonsymbiotic plant hemoglobin are observed in metabolically active or stressed tissue (Anderson C. R., 1996).

Impossible Foods has analyzed globin sequences from various sources, including the soy leghemoglobin protein presented in this notification, as well as widely consumed globin proteins from corn, rice, barley, lupine, horse, tuna, and pig. As detailed in Annex 1, these hemeproteins - animal myoglobins, plant hemoglobins and plant leghemoglobins - are structurally very similar, and all contain the identical heme B cofactor. The abundant consumption of the heme B cofactor is widespread in humans and other animals, as heme proteins, like myoglobins and hemoglobins, are abundant in animal tissues consumed as meat, and also are present in the leaves and other

routinely consumed parts of plants. Thus, even though soy leghemoglobin itself is not widely consumed in the human diet, there is overwhelming evidence that heme B-containing globin proteins have been safely consumed throughout human history.

### 2.5. Specifications for food grade material

LegH Prep, the ingredient used in Impossible Foods's ground beef analogue, is standardized to contain at least six percent (6%) soy leghemoglobin protein. LegH Prep is stabilized with food-grade sodium chloride and sodium ascorbate. The product specification of LegH Prep is presented in Table 1.

Proximate composition and heavy metal composition of LegH Prep were determined by Silliker Inc. (Salida, CA). Impossible Foods measured soy leghemoglobin protein concentration using ultra performance liquid chromatography (UPLC). Soy leghemoglobin protein purity was measured by Impossible Foods using SDS-PAGE, coomassie staining, and gel densitometry. Impossible Foods tested LegH Prep for total aerobic plate counts (AOAC OMA 990.12). AEMTEX Laboratories (Fremont, CA) tested LegH Prep for *Salmonella* (AOAC OMA 2011.03), *Listeria monocytogenes* (AOAC OMA 2010.02), and *E. coli* O157:H7 (AOAC RI 020801).

Five LegH Prep production runs and their respective batch analyses are shown in Table 1. All five batches fall within the specifications outlined in Table 1. Genotoxicology assessments were performed on batch PP-PGM2-16-015-101. To generate a sufficient quantity of material for testing, PP-PGM2-16-015-101 was generated by blending lots PP-PGM2-15-321-101, PP-PGM2-15-341-101, and PP-PGM2-16-004-101. Each of the individual lots that went into the blend conformed to the LegH Prep specifications. Rat systemic toxicology assessments were performed on a freeze-dried sub-lot of PP-PGM2-16-088-101, as freeze-drying was necessary for incorporation of LegH Prep into the animal feed. The relative percent composition of the solid ingredients was consistent between batch PP-PGM2-16-088-101 and PP-PGM2-16-088-301 (the freeze-dried sub-lot).

Table 1. LegH Prep specifications and batch analyses from five independent production runs.

| | Specifications | PP-PGM2-16-015-101 | PP-PGM2-16-088-101 | PP-PGM2-16-102-101 | PP-PGM2-16-144-101 | PP-PGM2-16-200-101 |
|---|---|---|---|---|---|---|
| **Soy Leghemoglobin Protein (w/w)[1]** | 6 – 9% | 6.74% | 6.39% | 6.28% | 6.74% | 6.95% |
| **Soy Leghemolglobin Protein Purity (w/w)[2]** | ≥65% | 82% | 71% | 85% | 77% | 86% |
| **Fat (w/w)** | ≤2% | 0.05% | <0.01% | <0.01% | 0.03% | 0.08% |
| **Carbohydrates (w/w)** | ≤4% | 1.72% | 0.99% | 1.67% | 2.01% | 2.73% |
| **Ash (w/w)** | ≤4% | 1.87% | 0.67% | 2.63% | 2.62% | 2.74% |
| **Solids (w/w)[3]** | ≤24% | 14.85% | 12.55% | 14.92% | 17.31% | 18.44% |
| **Moisture (w/w)** | ≥76% | 85.15% | 87.45% | 85.08% | 82.69% | 81.56% |
| **pH** | 6.5 – 8.5 | 7.19 | 7.19 | 7.38 | 7.01 | 6.77 |
| **Lead (ppm)** | <0.4 | <0.01 | <0.01 | <0.01 | <0.01 | <0.01 |
| **Arsenic (ppm)** | <0.05 | 0.01 | <0.01 | <0.01 | 0.01 | <0.01 |
| **Mercury (ppm)** | <0.05 | <0.005 | <0.005 | <0.005 | <0.005 | <0.005 |
| **Cadmium (ppm)** | <0.2 | <0.001 | <0.001 | 0.001 | 0.003 | 0.001 |
| **Aerobic plate count (CFU/g)[4]** | <10^4 | <10 | <10 | <10 | <10 | <10 |
| ***E. coli 0157:H7*[5]** | Absent by test | Absent by test | Absent by test | Absent by test | Absent by test | Absent by test |
| ***Salmonella spp.*[6]** | Absent by test | Absent by test | Absent by test | Absent by test | Absent by test | Absent by test |
| ***Listeria monocytogenes*[7]** | Absent by test | Absent by test | Absent by test | Absent by test | Absent by test | Absent by test |

[1]Soy leghemoglobin protein may exceed 9% if additional water (moisture) is removed during the concentration step of the manufacturing process. Additional concentration (i.e. less water) does not change the composition of the dry solids.
[2] The balance of the proteins in the preparation is residual *Pichia* proteins.
[3] Percent solids specification is based on the sum of the maximum concentrations of total protein, fat, carbohydrates and ash. Maximum total protein was calculated as the maximum soy leghemoglobin protein concentration divided by the minimum soy leghemoglobin protein purity.
[4] AOAC OMA 990.12
[5] AOAC RI 020801
[6] AOAC OMA 2011.03
[7] AOAC OMA 2010.02
n/a = not applicable

The *Pichia* production organism, MXY0291, does not contain antibiotic resistance genes. Therefore, LegH Prep does not contain antibiotic resistance genes. LegH preparations also do not contain viable MXY0291, the *Pichia pastoris* production organism. The soy leghemoglobin gene (*LGB2*) was generated by DNA synthesis and is the only recombinant DNA within MXY291 that is not native to *Pichia*. Impossible Foods has been able to isolate detectable amounts of *Pichia* DNA from the final heme solution, and it has determined that about 0.2 mg/L of *Pichia* DNA will be present in LegH Prep.

LegH Prep may be stored at -20 °C as a frozen liquid for at least 12 months with no observable change in soy leghemoglobin protein stability or performance in ground beef analogue products.[1]

## 2.6. Method of Manufacture

LegH Prep is prepared in four stages: construction of the production strain of *Pichia pastoris*, expression of soy leghemoglobin protein in submerged fermentation, enrichment and stabilization of the expressed soy leghemoglobin protein. All materials used in the production of LegH Prep are standard food grade or pharmaceutical grade ingredients or of a purity and quality suitable for their intended use (Aunstrup, Andersen, Falch, & Nielsen, 1979) (Taylor & Baumert, 2013) (Enzyme Technical Association (ETA), 2005) and processing conditions are appropriate for food production under GMP. The product is standardized to a concentration of at least six percent (6%) soy leghemoglobin protein.

### 2.6.1 Raw Materials

Raw materials used in the fermentation and recovery process for soy leghemoglobin are standard ingredients used in the food/enzyme industry, and follow internal specifications (in line with Foods Chemical Codex, Ninth Edition requirements). These specifications include limits on lead and other pertinent heavy metals. The raw materials are of a purity and quality suitable for their intended use (Aunstrup, Andersen, Falch, & Nielsen, 1979); they are food grade and GRAS, or high-quality chemical or pharmaceutical grades (USP, NF, or ACS grades) from approved suppliers.

### 2.6.2. Fermentation

Soy leghemoglobin protein is expressed during submerged fed-batch fermentation using the *P. pastoris* MXY0291 production strain described above. Frozen cell banks for the production organism MXY0291 are maintained at -80 °C in 20% v/v glycerol as the source inoculum for soy leghemoglobin production. The master cell bank is stored at multiple locations. Working cell banks are prepared from the master cell bank and are tested for microbial purity, specific growth rate, and soy leghemoglobin yield prior to production fermentation. Fermentation broth is periodically analyzed microscopically to ensure culture purity. Process parameters including pH, temperature, agitation, dissolved oxygen, methanol concentration and glycerol concentration are routinely monitored throughout fermentation. Fermentations that incur microbial contamination and/or other process deviations that affect safety and/or quality are sterilized by steam in place and discarded.

### 2.6.3 Recovery Process

The *P. pastoris* cells in the fermentation broth are lysed by bead mill mechanical shearing. Insoluble material within the lysate is removed by centrifugation and microfiltration.

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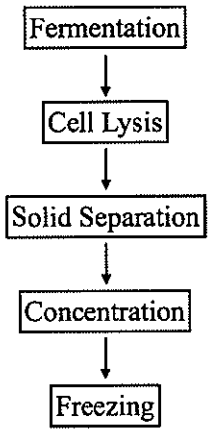
[1] Soy leghemoglobin is stable within Impossible Foods vacuum packed ground beef analogue product for at least 30 days at 4 °C and at least 95 days at -20 °C.

Ultrafiltration is used to concentrate soy leghemoglobin protein. The resulting concentrated sample is formulated with sodium chloride and sodium ascorbate and stored as a frozen liquid. A schematic overview of the manufacturing process is presented in Figure 1.

Figure 1. Schematic overview of the manufacturing process for LegH Prep: fermentation, cell lysis, solid separation, concentration and freezing.




Impossible Foods tests each independent fermentation broth to ensure the absence of *Salmonella* AOAC OMA 2011.03, *Listeria monocytogenes* AOAC OMA 2010.02, and *E. coli* O157:H7 AOAC RI 020801. The final product from every LegH Prep production run is tested for total aerobic plate count AOAC OMA 990.12 and *Salmonella*, *Listeria monocytogenes*, and *E. coli* O157:H7 as described above. The presence of a pathogen, $>10^4$ CFU/g aerobic count, or failure to comply with the specifications outlined in section 3.2 Table 3, would result in the batch being discarded, the execution of additional sanitization standard operating procedures (SSOPs) in compliance with Impossible Foods' internal food-safety standards, and a root cause analysis.

## 2.7. Strain Construction

### 2.7.1 Production Strain

Production strain *Pichia pastoris* MXY0291 was constructed from recipient strain Bgl1 (MXY0051) using a series of transformations with different expression constructs, in order to express soy leghemoglobin protein. In addition to the protein coding sequence for soy leghemoglobin, MXY0291 contains extra copies of native *Pichia pastoris* heme biosynthetic enzymes and modified *Pichia pastoris* transcription factor Mxr1, all expressed under the strong native *Pichia pastoris* alcohol oxidase promoter (*pAOX1*). This promoter has been demonstrated to produce high levels of recombinant proteins after producing biomass on glycerol, and inducing *pAOX1* with methanol (Cereghino & Cregg, 2000). The genome of MXY0291 is fully sequenced and well-characterized.

The *Pichia pastoris* production strain background complies with the Organization for Economic Development (OECD) criteria for Good Industrial Large Scale Practice (GILSP) microorganisms (OECD, 1992; OECD, 1993). It also meets the criteria for a safe production microorganism as described by Pariza and Foster, Pariza and Johnson, and several expert groups

(EU Scientific Committee for Food, 1992) (FAO/WHO, 1996) (International Food Biotechnology Council, 1990) (Jonas, et al., 1996) (OEDC, 1993) (Pariza, M.W. et al., 1983) (Pariza, M.W. et al., 2001).

### 2.7.2 Recipient Strain

The recipient strain is *Pichia pastoris* Bg11 (MXY0051), which in turn is a derivative of Bg10. Both strains are commercially available and were purchased from BioGrammatics, Inc. (Carlsbad, CA). BioGrammatics, Inc. describes the lineage of their commercially available Bg10 and Bg11 *Pichia pastoris* strains as follows:[2]

The general taxonomy of *P. pastoris* is:

Name: *Pichia pastoris*
Kingdom: Fungi
Phylum: Ascomycota
Class: Hemiascomycetes
Order: Saccharomycetales
Family: Endomycetaceae
Genus: Pichia
Species: pastoris

The recipient *Pichia pastoris* strain Bg11 was derived from the well-characterized strain Y-11430, which is deposited in the collection at the Northern Regional Research Laboratories (NRRL). The lineage *of P. pastoris* strain NRRL Y-11430 is detailed below, and was previously included in GRN 204, reviewed by the Agency in 2006.

According to the definitive source of yeast taxonomy (Rij, 1984), as well as a thorough literature search, there are no indications that *P. pastoris* has been associated with animal or human illness. The following lineage for the *P. pastoris* Bg10 strain is based on genomic sequencing, literature sources, and from discussions with experts in this area.

The first *P. pastoris* strains were isolated from an oak tree and a chestnut tree and were deposited in the collection at the Northern Regional Research Laboratories (NRRL)[3] (see Figure 2, and www.biogrammatics.com). Yeast strains screened by Phillips Petroleum for growth on methanol included two *P. pastoris* strains, designated NRRL Y-1603 (ATCC accession 28485) (ATCC, 2006b) and NRRL YB-4290 (NCAUR, 2006). Phillips Petroleum identified a *P. pastoris* strain with improved growth characteristics. The strain was designated 21-1 and deposited at NRRL, as NRRL Y-11430 (Wegner, E.H., 1986). This strain is now available from ATCC as 76273 (ATCC, 2005). No records are available confirming that NRRL Y-1603 or NRRL YB-4290 is the progenitor of NRRL Y-11430, but it seems likely that one of them is the progenitor strain (Madden, K.R., 2014). NRRL Y-11430 was the progenitor strain for GS115, a

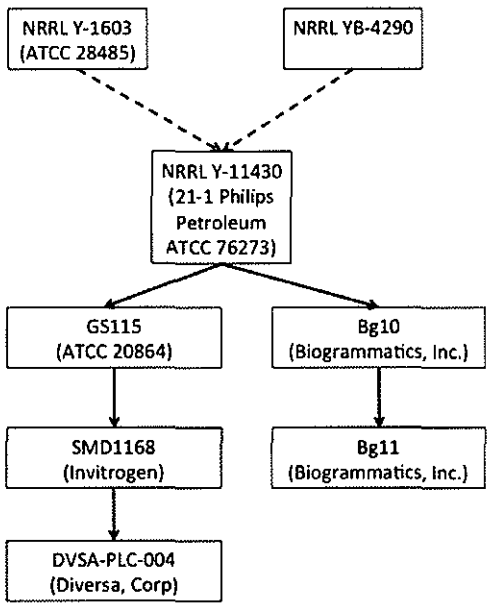
[2] Biogrammatics, Inc. supplied this information and the four paragraphs that follow to describe the recipient strain lineage.
[3] The NRRL collection is now known as the Agriculture Research Service Culture Collection and is at the Microbial Genomics and Bioprocessing Research Unit (MGB) of the National Center for Agricultural Utilization Research (NCAUR) in Peoria, IL.

histidine auxotrophic mutant (his4-) (ATCC, 2006a; (Cregg, 1985)), a common *Pichia pastoris* strain provided in commercial kits by Invitrogen Corporation, and widely used as the parental strain of many biotechnology products. Additionally, the GS115-derived strain SMD1168 is used for the GRAS approved production of BD16449 Phospholipase C (GRN 204). Like GS115, the BioGrammatics, Inc. strain, Bg10 is also a derivative of NRRL Y-11430, and genomic sequencing data performed by BioGrammatics, Inc. confirm the similarity of NRRL Y-11430, Bg10 and GS115 (Figure 2). Additional taxonomic history of these strains is available in a 2009 manuscript by C. Kurtzman (Kurtzman, 2009) and on the Biogrammatics webpage (biogrammatics.com).

BioGrammatics, Inc. further developed the NRRL-Y-11430 strain to remove the native *P. pastoris* plasmids. PCR primers unique to the plasmids were used to screen multiple single-colony isolates for the presence of the plasmids. One isolate without plasmids was selected to become the wild-type (wt) BioGrammatics strain, Bg10. Genomic sequence from Bg10 indicates the plasmids are no longer present, and, benchmarks the similarity of Bg10 with NRRL-Y11430, as well as with GS115. Like NRRL Y-11430 and GS115, Bg10 does not contain antibiotic-resistance genes.

*P. pastoris* is a methyltrophic yeast that is capable of using methanol as sole carbon source. Alcohol oxidase 1 (Aox1) is the primary enzyme responsible for methanol metabolism, and strains lacking this enzyme have a reduced rate of methanol utilization and are therefore preferred in industrial fermentations due to decreased heat generation and rate of oxygen consumption. Biogrammatics, Inc. deleted the gene encoding for Aox1 from Bg10 using homologous recombination to generate a strain that grows more slowly on methanol-containing induction media. The antibiotic resistance gene and background vector sequences used during homologous recombination were subsequently removed to generate a clean, antibiotic resistance gene-free Bg11 strain, which was purchased by Impossible Foods (Figure 2).

Figure 2. Strain lineage of recipient strain Bg11 (MXY0051)

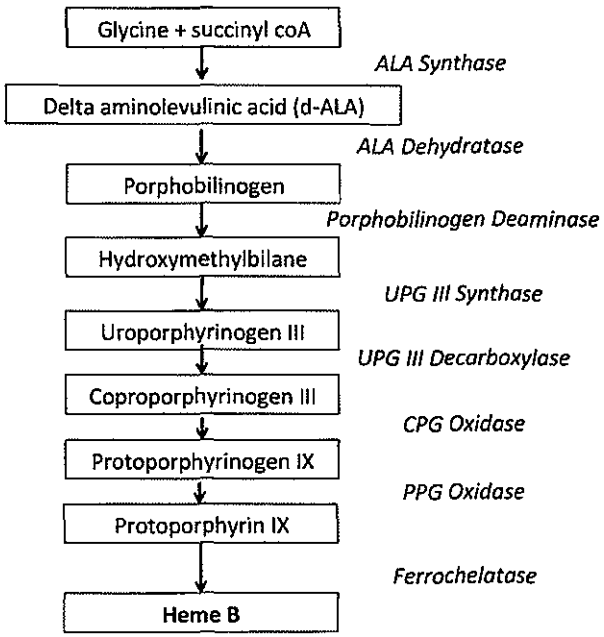


### 2.7.3 Construction of the Production Strain

#### 2.7.3.1 Construction of MXY0213: Strain Overexpressing the Heme Biosynthesis Pathway

In order to increase the intracellular concentration of heme to generate sufficient heme-bound soy leghemoglobin protein, the heme biosynthetic pathway of Bgl1 was up regulated. Heme biosynthesis is the result of an 8-step pathway, each catalyzed by a distinct, highly conserved enzyme (Figure 3).

Figure 3: The highly conserved heme biosynthesis pathway. The enzymes catalyzing each step are shown on the right in italics.




Genes encoding all 8 enzymes of the *Pichia* heme biosynthesis pathway were amplified from the *Pichia* genome and cloned into two plasmids, *pMX349* and *pMX346*. The two plasmids were linearized using restriction enzyme (Pme1) digestion and sequentially transformed into the recipient strain Bgl1 leading to integration of the entire cassette expressing the sets of heme enzymes in the genome. Following each round of transformation, the antibiotic resistance gene was removed from the strain. This resulted in MXY0213, a stable strain that contained extra copies of the native *Pichia* heme biosynthesis enzymes under extra copies of the native *pAOX1* promoter.

#### 2.7.3.2 Construction of MXY0260: Strain Overexpressing Mxr1 and the Heme Biosynthesis Pathway

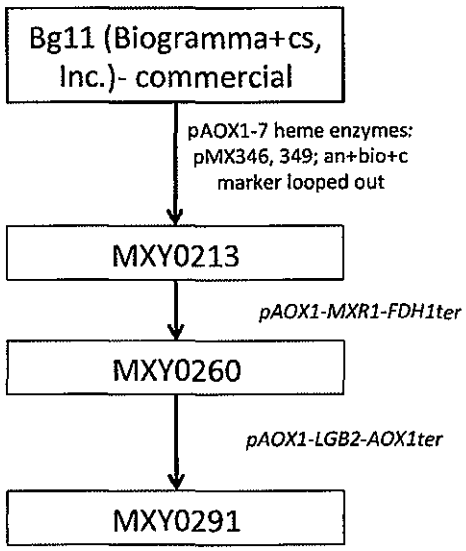
Mxr1 is a transcriptional activator of the *pAOX1* promoter. The presence of Mxr1 leads to improved production of the recombinant protein leghemoglobin. A linear cassette of DNA

containing modified *Pichia pastoris MXR1* gene under the control of *pAOX1* promoter and *FDH1* terminator (*FDH1ter*) was introduced into MXY0213 by co-transformation. Due to the cloning strategy, the overexpressed Mxr1 protein contains 6 extra amino acids on its N-terminus compared to the native *Pichia pastoris* Mxr1. Mass spectrometry analysis demonstrates that neither the modified Mxr1 protein nor the native Mxr1 protein is detectable in LegH Prep final product. The *pAOX1-MXR1-FDH1ter* DNA cassette and an empty vector containing an antibiotic resistance gene were co-transformed into MXY0213. This enabled selection of transformants containing the empty vector, which were then screened by colony PCR for integration of the cassette at the *pAOX1* locus. Transformants containing the desired *MXR1* integration were subsequently cured of the empty vector by screening for antibiotic sensitivity. Loss of the empty vector was confirmed by PCR. The resulting strain was MXY0260, the parent to the production strain MXY0291.

#### 2.7.3.4 Construction of MXY0291: Production Strain Overexpressing Soy Leghemoglobin

The protein coding sequence from *Glycine max* leghemoglobin *LGB2* was synthesized and codon-optimized for expression in *Pichia pastoris*. A linear cassette of *pAOX1-LGB2-AOX1ter* was PCR amplified and introduced into MXY0260 by co-transformation as described above. qPCR and protein expression assays identified the production strain, MXY0291, which contains 16 copies of the recombinant *LGB2* gene (Figure 4). As described above, antibiotic selection and PCR were used to demonstrate absence of plasmid following co-transformation.

Figure 4. Construction of production strain using recipient strain Bg11 (MXY0051)




### 2.7.4 Genome Sequence of the Production Strain

The genome of production strain MXY0291 has been completely sequenced and confirmed to contain the following sequences in addition to the background *Pichia pastoris* DNA.

- 16 copies of *pAOX1-LGB2-AOX1ter*
- 1 copy of *pAOX1-MXR1-FDHter*
- 1 copy of a portion of *pMX349* (no antibiotic resistance genes, no origin of replication)
- 2-3 copies of a portion of *pMX346* (no antibiotic resistance genes, no origin of replication)

### 2.7.5 Stability of the Production Strain

All changes introduced into production strain MXY0291 are stably integrated in the genome and confirmed to be present after > 150-200 generations of growth on non-selective growth media. No plasmid sequences are present in the production strain. Hence, the plasmid sequences will not be transferred from the production strain to a non-related organism.

### 2.7.6 Absence of Antibiotic Resistance Genes

The production strain MXY0291 does not contain antibiotic resistance genes.

### 2.7.7 Absence of the MXY0291 Production Organism in the Final Product

The MXY0291 production organism is not detected in LegH Prep in accordance with the recommendations for safety evaluation by the International Food Biotechnology Committee (Coulston and Kolbye, 1990).

## 2.8. Potential Toxicants

The LegH Prep production strain and manufacturing process do not produce any known toxicants.

# PART 3: DIETARY EXPOSURE

## 3.1 Estimated Dietary Intake

LegH Prep will be marketed for use in ground beef analogue products that provide consumers a flavorful and nutritious alternative to ground beef containing products. Therefore, Impossible Foods has estimated daily intakes of soy leghemoglobin protein by assuming consumers will substitute the ground beef analogue product for the traditional meat product on a 1-for-1 basis. The ground beef analogue will constitute not more than 0.8% soy leghemoglobin protein of the total composition. The use of soy leghemoglobin protein in ground beef analogue products is largely self-limiting based on unacceptable organoleptic properties at levels well above the recommended use level of not more than 0.8% soy leghemoglobin protein of the total composition.

As the highest use case, Impossible Foods has assumed it will capture 100% of the total ground beef market with soy leghemoglobin protein-containing meat analogue products. One hundred percent (100%) of the total meat market represents approximately 500 times the volume of the current meat analogue market size, based on sales estimates.[4]

The Estimated Daily Intake (EDI) of soy leghemoglobin in the target ground beef analogue applications was established using beef consumption data from the National Health and Nutrition Examination Survey (NHANES), conducted in 2007-08 (as published by Bowman, Martin, Clemens, Lin, & Moshfegh, 2013). Because the intended use of LegH Prep is limited to ground beef analogue products, the per capita beef consumption data was multiplied by the percentage of beef that is sold as ground beef, which is 42%, to estimate consumption for this intended use.[5]

### 3.1.1 EDI for Soy Leghemoglobin Protein

The mean daily consumption of all types of beef is 59 grams for males and females ages 2 and older (Bowman, Martin, Clemens, Lin, & Moshfegh, 2013). For ground beef, the mean consumption is 25 grams (59 grams x 42%). Using a conservative approach, Impossible Foods assumes capturing 100% of the ground beef market.

The ground beef analogue product will not contain more than 0.8% soy leghemoglobin protein by mass. This equates to a maximum EDI of 200 mg/person/day of soy leghemoglobin (25 ground beef grams/person/day x 100% market x 0.8% soy leghemoglobin). However, Impossible Foods anticipates the soy leghemoglobin protein to constitute, on average, 0.6% of the ground beef analogue product by mass. This results in an estimated typical daily intake of 150 mg/person/day. These results are presented below in Table 2.

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[4] Datamonitor estimates the US meat analogue volume was 53M kg in 2009. USDA-FAS Livestock and Poultry Report, April 2014 estimates 2014 US consumption of 11B kg beef, 8.5B kg pork, and 14B kg broilers. Therefore, the current meat analogue market is less than 0.2% of the overall meat market and capturing 100% of the meat market represents 500 times the current meat analogue market in the US.

[5] http://usda.mannlib.cornell.edu/usda/ers/LDP-M/2000s/2005/LDP-M-10-07-2005_Special_Report.pdf

Table 2. Estimated daily intake of soy leghemoglobin protein

| Food Category to be Replaced | Consumer Age (years) | Mean Consumption Ground Beef (g/day) | Anticipated Market Share Replacement (%) | Typical Use Rate (%)* | Soy Leghemoglobin Estimated Typical Daily Intake (mg/person/day) | Max Use Rate (%)* | Soy Leghemoglobin Estimated Maximum Daily Intake (mg/person/day) | Soy Leghemoglobin 90th Percentile EDI (mg/kg/day) |
|---|---|---|---|---|---|---|---|---|
| Ground Beef | 2 and over | 25 | 100 | 0.6 | 150 | 0.8 | 200 | 6.67 |

* Use rate is percent soy leghemoglobin protein in the ground beef analogue product by mass.

### 3.1.2 EDI for LegH Prep (dry solids)

While soy leghemoglobin protein is the characterizing component of the LegH Prep, it is the LegH Prep (containing soy leghemoglobin, *Pichia* proteins and other components) that is added to the ground beef analogue product. Therefore, an EDI was also calculated for the LegH Prep. Due to the high water content (≥76%) of the LegH Prep, the EDI was calculated based on LegH Prep dry solids (*see* Table 1).

The EDI for LegH Prep dry solids was calculated as follows: The typical and maximum EDIs for the soy leghemoglobin protein were divided by 9% (which represents the maximum amount of soy leghemoglobin protein within LegH Prep, *see* Table 1). This represents the typical and maximum EDI for LegH Prep (liquid formulation). To obtain the EDI for the LegH Prep dry solids, the liquid formulation EDI was multiplied by 24% (which the maximum percent solids within LegH Prep, *see* Table 1). For example, the typical use EDI for LegH Prep dry solids was calculated as:

> (150 mg/person/day soy leghemoglobin protein) ÷ (9% maximum soy leghemoglobin protein within LegH Prep) x (24% maximum solids within LegH Prep) = 400 mg/person/day LegH Prep dry solids.

The estimated maximum daily intake for LegH Prep dry solids was calculated using the same equation with 200 mg/person/day soy leghemoglobin protein (assuming a 0.8% use rate). The results are presented in Table 3.

Table 3. Estimated daily intake of LegH Prep (dry solids)

| Food Category to be Replaced | Consumer Age (years) | Mean Consumption Ground Beef (g/day) | Anticipated Market Share Replacement (%) | Typical Use Rate (%)* | LegH Prep Dry Solids Estimated Typical Daily Intake (mg/person/day) | Max Use Rate (%)* | LegH Prep Dry Solids Estimated Maximum Daily Intake (mg/person/day) |
|---|---|---|---|---|---|---|---|
| Ground Beef | 2 and over | 25 | 100 | 0.6 | 400 | 0.8 | 533 |

* Use rate is percent soy leghemoglobin protein in the ground beef analogue product by mass.

### 3.2. Estimation of the 90th Percentile Intake for Soy Leghemoglobin Protein

Following the FDA's "Guidance for Industry: Estimating Dietary Intake of Substances in Food"[6] to estimate daily intake values, the pseudo 90th percentile for soy leghemoglobin protein consumption would be 2 times the mean EDI. The maximum mean EDI is 200 mg soy leghemoglobin/person/day at the maximum anticipated use rate (0.8%). Therefore, the exposure to high users (90th percentile) will be approximately 400 mg soy leghemoglobin /person/day if soy leghemoglobin protein is used at the maximum anticipated rate (0.8%).

For the basis of safety testing, the 90th percentile consumption of soy leghemoglobin was calculated using 25 grams ground beef/person/day x 0.8% soy leghemoglobin/ground beef / 60 kg/person x 2. Therefore, the 90th percentile consumption equates to 6.67 mg/kg/day, which was used as the basis for safety testing.

Impossible's products, formulated with soy leghemoglobin, deliver approximately the same amount of heme protein as is found in beef. Therefore, if consumers substitute Impossible's ground beef analogue for conventional beef, overall consumption of heme proteins is approximately the same.

It is important to note that the vast majority of heme proteins consumed in the diet are myoglobins contained in meat and poultry products. For the US population, per capita mean consumption of meat and poultry products is 154 g/person/day (Bowman, Martin, Clemens, Lin, & Moshfegh, 2013). Assuming an average myoglobin concentration for meat and poultry products of 0.5% (Yip & Dallman, 1996), the average per capita myoglobin consumption would be 0.77 g/person/day myoglobin and the 90th percentile intake would be 1.54 g/person/day. In contrast, the 90th percentile EDI for soy leghemoglobin is lower, at 0.4 g soy leghemoglobin protein/person/day.

[6] http://www.fda.gov/food/guidanceregulation/guidancedocumentsregulatoryinformation/ingredientsadditivesgraspackaging/ucm074725.htm

## PART 4: SELF-LIMITING LEVELS OF USE

Use of soy leghemoglobin in ground beef analogue products is self-limiting because use rates that exceed the maximum recommended level of 0.8% soy leghemoglobin protein result in an increasingly unacceptable organoleptic profile.

## PART 5: EXPERIENCE BASED ON COMMON EXPERIENCE IN FOOD BEFORE 1958

This section is not applicable to this application.

# PART 6: NARRATIVE

## 6.1 History of Safe Use

### 6.1.1 Soy

Soy leghemoglobin is derived from the root nodule of the soy plant. While the root nodules are not typically consumed, soy has been part of the human diet for more than 5000 years (Lee, Crawford, Liu, Sasaki, & Chen, 2011). The safety of soy proteins found in the soybean is well established (Riaz, 2006). In the 2010 marketing year, 249 million metric tons of soybeans were produced worldwide (Food and Agricultural Organization of the United Nations, 2010). Although the majority of the crop is used for animal feed, approximately 14% is used for human food in the form of traditional soy foods, such as tofu, soymilk, natto, miso, and bean sprouts. Soy protein ingredients are also used to formulate a wide range of food products, including infant formula, dairy and meat alternatives, nutritional supplements and energy bars (Golbitz & Jordan, 2006). The use of soy proteins is widely accepted in the United States. The FDA has affirmed the safety of soy protein isolates for inclusion in many products (GRN 134, GRN 186, and GRN 283), and has approved a health claim for consumption of soy protein reducing the risk of coronary heart disease (21 CFR 101.82). In 2000, the U.S. Department of Agriculture (USDA) issued a ruling allowing soy protein to completely replace animal protein in the National School Lunch Program (Messina, 2006). Thus, the safety of soybeans in human food has been clearly demonstrated and its use reviewed extensively by United States regulatory agencies.

### 6.1.2 Soy Leghemoglobin

Heme proteins are found in most organisms, including bacteria, protozoa, fungi, plants and animals (Everse, 2004) (Hardison, 1998) (Wajcman & Kiger, 2002). Soy has been shown to express three hemoglobin proteins: symbiotic, nonsymbiotic and truncated (Lee, Kim, & An, 2004). The proteins share a common evolutionary origin (Vinogradov et al. 2007) and, based on structural studies and homology modeling, share a common three-dimensional structure involving an alpha helical globin-fold wrapped around a heme B molecule (Ellis et al. 1997) (Annex 1). The members of this protein family are all involved in selective transport, storage or buffering of oxygen levels in cells and tissues (Vinogradov and Moens 2008). The shared and well-characterized physiology of these proteins strongly supports the inference that the shared three-dimensional structure of these globin proteins evolved to bind oxygen.

Symbiotic hemoglobins, found predominately in legume species, function in the nitrogen fixation process in concert with the bacterium Rhizobium where they facilitate oxygen diffusion within host tissues. Symbiotic plant hemoglobins, which evolved from non-symbiotic hemoglobins (Gupta, 2011) (Wajcman & Kiger, 2002), are commonly referred to as leghemoglobins. Leghemoglobins' structure and their oxygen binding mechanism are similar to those of animal muscle myoglobin proteins (Hargrove, 1997). The primary sequence of soy leghemoglobin is not homologous to the primary sequences of mammalian myoglobins. However, the primary sequence of soy leghemoglobin does not contain significant homology to any known allergens or toxins, and therefore does not present a known safety concern (see section 6.4.4).

Non-symbiotic plant hemoglobins from soy, barley, rice, corn, and mung beans are widely consumed in the diet. Anderson *et al.* demonstrated that the nonsymbiotic hemoglobin in soy was expressed in various plant tissues including stems, shoots, cotyledon, leaves, and root hair (Anderson C. R., 1996). These soy tissues are commonly consumed in the diet in the form of soybean sprouts. Sprouted barley, which is widely used in the beverage industry (malted barley) and in the baking industry (malted barley flour), has been shown to express hemoglobin one day after imbibition (Duff, Guy, Xianzhou, Durnin, & Hill, 1998). Non-symbiotic hemoglobins are expressed in the rice embryo as well as in the coleoptiles and seminal root of sprouted rice, which is consumed as part of the diet as well (Lira-Ruan, Ruiz-Kubli, & Arredondo-Peter, 2011). Non-symbiotic hemoglobin is expressed in corn seedlings and may provide a good source of bioavailable heme in mature corn seeds (Bodnar, 2011). Impossible Foods has detected non-symbiotic hemoglobin in mung bean sprouts by mass spectrometry. The three dimensional structure of soy leghemoglobin is highly similar to the non-symbiotic hemoglobins of corn, rice, and barley (Annex 1), and although there are no crystal structures for non-symbiotic hemoglobins from soy or mung beans, based on the highly similar structures of non-symbiotic hemoglobins from corn, rice and barley to each other and to soy leghemoglobin, Impossible Foods expects that they (soy and mung) are likewise structurally similar to soy leghemoglobin.

Thus, hemoglobin proteins of plant and animal sources are widely consumed in the human diet, and represent a highly bioavailable source of dietary iron for human nutrition. Proulx and Reddy demonstrated that soy leghemoglobin and bovine hemoglobin showed similar iron bioavailability within a food matrix, both of which were higher than free iron (Proulx & Reddy, 2006). Furthermore, plant-derived hemoglobins are already prevalent in our food system through malted grain products and sprouted seeds, grains, rice and beans (pulses) (Anderson, Jensen, Leewellyn, Dennis, & and Peacock, 1996) (Duff, Guy, Xianzhou, Durnin, & Hill, 1998) (Lira-Ruan, Ruiz-Kubli, & Arredondo-Peter, 2011).

The heme B moiety plays a central role in oxygen binding, and the structure of the globin protein serves to isolate the heme from other molecules by creating a small binding pocket inaccessible to most other molecules (Ellis et al. 1997). Thus, heme B-containing globin proteins remain largely inert so long as the three dimensional structure is maintained. When globin proteins are heated, as in cooking, or exposed to a low pH environment, as in the human stomach, the protein unfolds and the heme B molecule is released (Annex 1). Impossible Foods has shown that heme B, released when myoglobin is heated to cooking temperature, plays a major role in catalyzing the production of the flavors and aromas characteristic of cooked meat. Crucially, however, this catalysis is a function of the heme B molecule, and is independent of the specific protein in which it was bound prior to cooking.

The abundant consumption of heme B is widespread in humans and other animals, as heme proteins are abundant in animal tissues consumed as meat, and are also present in the leaves and other routinely consumed parts of plants. Thus, there is overwhelming evidence that heme B-containing proteins, which are functionally equivalent to soy leghemoglobin presented in this notification, have been safely consumed throughout human history.

There is no evidence that any of the globin subfamily that contains the plant hemoglobins have any biochemical activities other than the binding of oxygen ($O_2$) or the structurally similar carbon dioxide ($CO_2$), nitrous oxide (NO), and carbon monoxide (CO). The three-dimensional structure of leghemoglobin contains no additional active sites to distinguish it from widely consumed heme proteins, nor is there any biochemical or physiological evidence that this protein has any enzymatic activity or other function outside of controlled binding to oxygen.

Thus, there is no evidence to suggest that soy leghemoglobin in food will behave any differently from the myriad other functionally equivalent and widely consumed globin proteins in the human diet. However, due to a lack of widespread human consumption, Impossible Foods has used rigorous scientific procedures to evaluate soy leghemoglobin for potential toxicity or allergenicity, with results confirming that LegH Prep is non-toxic and poses negligible risk of allergenicity.

### *6.1.3 Pichia pastoris*

As discussed in greater detail in other sections of this GRAS notification, soy leghemoglobin protein is produced in the well-characterized expression host *Pichia pastoris* (Cereghino & Cregg, 2000). *Pichia* belongs to the same family of yeast (Saccharomycetaceae) as several yeast genera widely used in food: Saccharomyces, Torula, Yarrowia, Dekkera and Brettanomyces. Brettanomyces, a yeast traditionally used in brewing Belgian beers, belongs to the same sub-family of yeast as *Pichia* - the Pichiaceae. Yeast extract (from *S. cerevisiae* and Torula) is frequently directly consumed in substantial quantities in human diets. Impossible Foods' genetically modified *Pichia* production strain complies with the OECD (Organization for Economic Development) criteria for GILSP (Good Industrial Large Scale Practice) microorganisms (OECD, 1992). It also meets the criteria for a safe production microorganism as described by Pariza and Foster, Pariza and Johnson, and several expert groups (Berkowitz & Maryanski, 1989) (EU Scientific Committee for Food, 1992) (FAO/WHO, 1996) (International Food Biotechnology Council, 1990) (Jonas, et al., 1996) (OEDC, 1993) (Pariza, M.W. et al., 1983) (Pariza, M.W. et al., 2001).

The American Association of Feed Control Officials (AAFCO) has approved the *E. coli* enzyme phytase derived from the fermentation of recombinant *Pichia pastoris* for use in animal feed (AAFCO, 2013). *Pichia pastoris* is also the host used for production of nitrate reductase (The Nitrate Elimination Co. Lake Linden, MI), an enzyme used for treatment of potable water. *P. pastoris* is also approved by FDA as an animal feed protein source allowed in broiler feed up to10% of the total feed (FDA 21 CFR Part 573, 1993).

*Pichia pastoris* does not produce active toxins (Pariza & Johnson, 2001). *Pichia pastoris* has been placed in the Biosafety Level 1 (BSL-1) class by the ATCC organization, indicating *Pichia* is a well-characterized agent not known to cause disease in healthy human adults, and to be of minimal hazard to laboratory personnel and the environment (Center for Disease Control, 1999). Toxicity studies done in support of the above-referenced *P. pastoris*-approved animal feed also demonstrated that *P. pastoris* is neither pathogenic nor toxigenic (FDA 21 CFR Part 573, 1993). Moreover, Impossible Foods commissioned

systemic toxicity and genotoxicity testing on LegH Prep to ensure that the residual *Pichia* proteins and cellular components present in LegH Prep are non-toxic.

Impossible Foods' *Pichia pastoris* production strain MXY0291 is derived from a strain lineage with a long history of safe use, as outlined in GRN 204. All genetic modifications made to generate MXY0291 are well-characterized by full genome sequencing and conform to the guidelines for generating safe production strains for the recombinant production of food ingredients (Olempska-Beer, Merker, Ditto, & DiNovi, 2006). LegH Prep does not contain the production organism or antibiotic resistance genes. Impossible Foods has been able to isolate detectable amounts of *Pichia* DNA from the final LegH Prep solution, and it has determined that about 0.2 mg of *Pichia* DNA will be present in about one liter of LegH Prep. Impossible Foods has used mass spectrometry to identify the *Pichia pastoris* proteins that are present in LegH Prep at ≥1% of the total protein fraction. As described below, the sequence of each protein was analyzed to ensure that the *Pichia* proteins present in LegH Prep do not contain significant homology to known allergens. All of the identified co-purifying proteins have highly conserved orthologues in yeast species used in food, such as *S. cerevisiae.*

### 6.1.4 Method of Manufacturing

All materials used in the production of LegH Prep are standard food grade or pharmaceutical grade ingredients used in the food industry. The raw materials are of a purity and quality suitable for their intended use (Aunstrup, Andersen, Falch, & Nielsen, 1979). The process to isolate soy leghemoglobin protein from a well-characterized fermentation medium that complies with the Enzyme Technical Association's guidelines for microbially derived recombinant proteins follows current Good Manufacturing Practices (GMP) (Enzyme Technical Association, 2005) (Taylor & Baumert, 2013). The product is standardized to a concentration of at least six percent (6%) soy leghemoglobin protein. The soy leghemoglobin protein has highly advantageous properties in meat and poultry analogue products, which will provide consumers a nutritious and flavorful alternative to foods derived from animals, with a much-reduced environmental impact.

## 6.2 Summary of Adverse Findings in the Literature

Impossible Foods is not aware of any studies in the literature indicating that either soy leghemoglobin or *Pichia pastoris* is not safe for the intended use proposed in this GRAS notification.

## 6.3 Toxicology Studies

### 6.3.1 Subacute Toxicity

**<u>14-Day non-GLP Dietary Toxicity and Palatability Study in Rats (Study 43167)</u>**

Impossible Foods commissioned a non-GLP 14-day dietary toxicity/palatability study in rats to assess the feasibility of oral administration of LegH Prep (which contains soy

leghemoglobin, *Pichia* proteins and other components; *see* Table 1) and to establish the dose range for a subsequent GLP 28-day dietary toxicology study. The study was conducted by Product Safety Labs (Dayton, NJ, USA). The LegH Prep test article was freeze dried; freeze drying allowed for increased test article concentration in the feed and facilitated homogeneous dietary mixing. Doses of 0, 125, 250, and 500 mg soy leghemoglobin/kg bw/day were administered in the diet to CRL Sprague-Dawley CD® IGS rats (6 male, 6 female per group) for 14 days. Experimental observations included clinical observations, food consumption, body weight, hematology, and liver, spleen and bone marrow weight and histopathology. There were no reported treatment-related adverse findings that were statistically different from the controls. Therefore, it was concluded that 500 mg soy leghemoglobin/kg/day would be well-tolerated by rats in a feeding study of longer duration.

### 6.3.2 Repeated Dose Toxicity

#### 6.3.2.1 28-Day GLP Dietary Toxicity Study in Rats (Study 43166)

Impossible Foods commissioned a GLP 28-day dietary toxicology study in rats to determine the no observed adverse effect level (NOAEL) for LegH Prep (containing soy leghemoglobin, *Pichia* proteins and other components; *see* Table 1) (Annex 2). The study was conducted by Product Safety Labs (Dayton, NJ, USA). The study was designed to meet the guidelines in the US FDA Toxicological Principles for the Safety Assessment of Food Ingredients, Redbook 2000, IV.C. 4. a. Subchronic Toxicity Studies with Rodents (2007) and the OECD Guidelines for Testing of Chemicals and Food Ingredients, Section 4 (Part 407): Health Effects, Repeated Dose 28-Day Oral Toxicity Study in Rodents (2008). The study was conducted in compliance with U.S. FDA GLP: 21 CFR Part 58, 1987, which is compatible with OECD Principles of Good Laboratory Practice (as revised in 1997) published in ENV/MC/CHEM (98)17, OECD, Paris, 1998.

##### 6.3.2.1.1 Study Details

The LegH Prep test article (containing soy leghemoglobin, *Pichia* proteins and other components; *see* Table 1) was freeze-dried lot PP-PGM2-16-088-101, which was given a new sub-lot of PP-PGM2-16-088-301. As in the 14-day dietary study, freeze drying allowed for increased test article concentration in the feed and facilitated homogeneous dietary mixing. Dietary doses of 0, 512, 1024, and 1536 mg/kg/day of freeze dried LegH Prep (LegH Prep solids) were selected to correspond to 250, 500, and 750 mg/kg/day of soy leghemoglobin (Table 4). The maximum dose of 750 mg/kg/day soy leghemoglobin was selected to achieve a concentration greater than 100-fold above the anticipated 90$^{th}$ percentile EDI (section 3.1). A control group received unformulated feed. To maintain target dietary doses throughout the study, concentrations in the test diets were calculated based on the most recent group body weight and food consumption data. The rats were CRL Sprague-Dawley CD® IGS. There were 10 rats per sex per group.

Table 4. Dosing information for groups in 28-day rat feeding study.

| Group | Number of Animals per Group (Male/Female) | Target Exposure of Test Substance LegH Prep Dry Solids (mg/kg/day) | Target Exposure of Soy Leghemoglobin (mg/kg/day) |
|---|---|---|---|
| 1 | 10/10 | 0 | 0 |
| 2 | 10/10 | 512 | 250 |
| 3 | 10/10 | 1024 | 500 |
| 4 | 10/10 | 1536 | 750 |

Experimental observations included ophthalmologic evaluations, clinical observations, body weights, food consumption, clinical pathology including blood chemistry, hematology, coagulation, and urinalysis, gross necropsy, organ weights, and histopathology.

#### 6.3.2.1.2 Study Results

There were no mortalities, clinical observations, ophthalmology, body weight, body weight gain, food consumption, or food efficiency changes attributable to LegH Prep administration for either sex. Additionally, there were no test substance related changes in hematology, serum chemistry or urinalysis parameters for males or female rats. Changes in coagulation parameters were limited to a non-dose-dependent increase in activated partial thromboplastin time observed in Group 3 and 4 males which, due to its very slight magnitude and lack of correlating pathological or clinical finding, is considered non adverse.

There were no test substance-related effects reported during necropsy, organ weights, macroscopic observations, or histopathology in the male and female animals, with a single exception of an increased incidence in the metestrus stage of the estrous cycle in groups 2 and 4 (Annex 2). As discussed in detail below, the control animals used in this study, as well as the treated animals, all had distributions of estrus cycle stages that deviated significantly from published reports, suggesting the possibility of a sampling artifact unrelated to the treatment. A follow-up study (section 6.3.2.2) demonstrated that the observed distributions were very likely due to sampling and assessing estrous cycle distribution on a single day, rather using a longitudinal study that would assess the totality of the estrous cycle, and is not indicative of an adverse health effect.

Because of the estrous cycle distributions reported in the control group as well as the test animals in the 43166 study, Impossible Foods elected to carry out a more extensive and rigorous longitudinal study focusing on the effects of the LegH Prep on the estrous cycle of a larger group of female rats. The results of that study, described below, provide strong evidence that the estrous cycle distribution of a group of rats on a given day commonly deviates greatly from their distribution over time, and provides a highly unreliable picture of estrous cycle function.

#### 6.3.2.2 28-Day Investigative Study in Rats with 14-Day Estrous Cycle Pre-Screen (Study 44856)

To directly address the estrous cycle distributions observed in study 43166, Impossible Foods commissioned a non-GLP investigative 28-day dietary study (44856) in rats with a focus on estrous cyclicity (Product Safety Labs, Dayton, NJ, USA) (Annex 3). The study design included a 14-day estrous cycle pre-screen to ensure that only animals with regular cyclicity advanced to the test article-dosing phase. The estrous cycle was monitored daily for the last 14 days of the 28-day dosing period, which is consistent with the OECD 421 guidelines for estrous cycle evaluation. At study termination, the reproductive organs were evaluated macroscopically and microscopically.

##### 6.3.2.2.1 Study Details

The freeze-dried LegH Prep (containing soy leghemoglobin, *Pichia* proteins and other components; *see* Table 1) test article from study 43166 was also used in study 44856 (PP-PGM2-16-088-301). Dietary doses of 0, 512, 1024, and 1536 mg/kg/day of freeze dried LegH Prep were selected to correspond to 0, 250, 500, and 750 mg/kg/day of soy leghemoglobin. A control group received unformulated feed. To maintain target dietary dose levels throughout the study, concentrations in the test diets were calculated based on the most recent group body weight and food consumption data. There were 15 female CRL Sprague-Dawley CD® IGS per group.

Prior to the 28-day dosing phase, estrous was determined daily for 14 days, by vaginal lavage, to ensure that each animal had an average estrus cycle length that was consistent with published literature. Estrous was also determined daily for the last 14 days of the 28-day dosing period to detect any changes in average estrous cycle length as a result of LegH Prep consumption. By monitoring the estrous cycle over time in each rat, the study avoided the sampling artifact of the previous study. The estrus cycle was not monitored for the first 14-days of the dosing period to avoid over-manipulating the animals.

Additional experimental observations included clinical observations, body weights, food consumption, gross necropsy, reproductive organ weights (uterus and ovaries with oviducts), and histopathology on reproductive organs (vagina, cervix, uterus, ovaries, and oviducts).

##### 6.3.2.2.2 Study Results

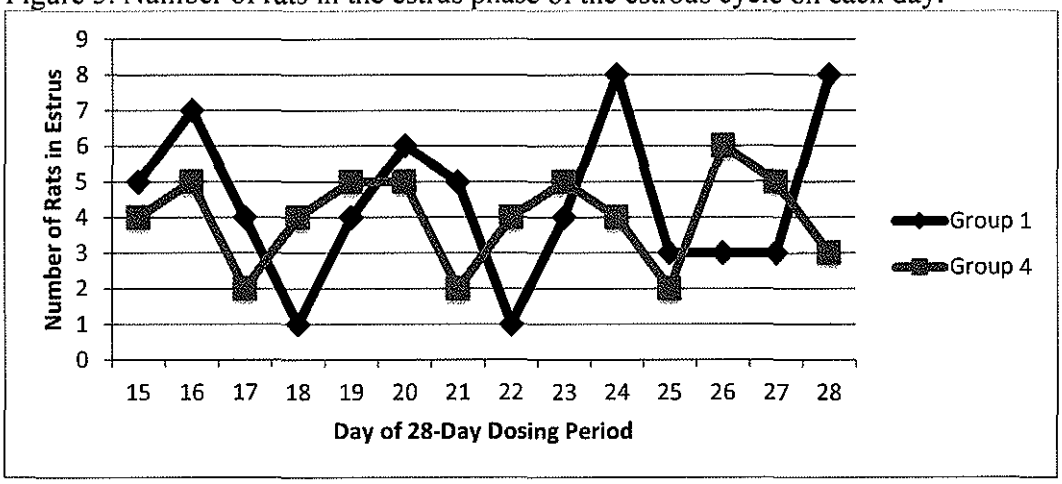
During the 14-day pre-dosing period, there was no significant change in average estrous cycle length between groups 1 through 4, and all animals showed regular estrous cyclicity. Therefore, all animals were advanced to the 28-day dosing phase. During the dosing phase, there were no clinical observations attributable to the administration of LegH Prep. There were no changes in body weight, rate of body weight gain, food consumption, and food efficiency attributable to LegH Prep administration. Mean number of estrus cycles for female rats in groups 2-4 were comparable to control group 1 throughout the study. There were no macroscopic and microscopic observations or organ weight changes attributed to the LegH Prep administration. Therefore, under the conditions of this study and based on the toxicological endpoints evaluated, administration of LegH prep at doses up to 1536 mg/kg/day total dry solids

or 750 mg/kg/day of active ingredient (soy leghemoglobin) did not cause any effect in estrus cyclicity or reproductive organ pathology of female Sprague Dawley rats.

The results from study 44856 fully address the potential concerns raised by study 43166, and demonstrate that LegH Prep does not affect the female rat estrous cycle. Each point is discussed below in greater detail.

Despite intrinsically normal estrous cycles, the distribution of estrous cycle stages on any given day can often be extremely deviant from the within-rat distribution over time (Figure 5). Indeed, had the animals been analyzed by necropsy on day 18 of the dosing period, one would have drawn a completely different conclusion regarding the test article effect on estrous cycle than had the necropsy been performed on day 21. Thus, to avoid sampling artifacts, proper evaluation of the effect of a test substance on the estrous cycle requires an extended longitudinal observation as performed in study 44856, in which no test article-dependent effect on the female estrous cycle length or progression was reported.

Figure 5. Number of rats in the estrus phase of the estrous cycle on each day.




There was no difference in mean number of estrous cycles between groups in either the pre-dosing or dosing phase of the study. All animals showed estrous cyclicity that was consistent with published literature (Westwood, 2008). The daily estrous cycle monitoring that was performed in study 44856 follows OECD 421 guidelines, and demonstrates that all groups were cycling normally as expected based on published literature (Westwood, 2008).

Study 43166 showed a decrease in uterine weights that corresponded to a decreased incidence of fluid filled uteri in group 2 and 4 females. In study 44856, there was no significant difference in organ weights for the uterus or ovaries with oviducts between groups 1 through 4. Moreover, the presence of fluid filled uteri did not differ across groups (Table 5). Published literature demonstrates that the presence of fluid filled uteri and uterine weight correlates with estrous cycle stage (Westwood, 2008). Our results from study 44856 reveal a similarly consistent correlation. Thus, the simplest explanation for the decrease in uterine weights observed for groups 2 and 4 in study 43166 is that the animals within those groups had a

different distribution of estrous cycle stages that typically correspond to lower uterine weight in healthy rats, compared with groups 1 and 3.

Table 5. Study 44856 summary of necropsy observations in the uterus.

| | **Group 1 0 mg/kg/day Soy Leghemoglobin N=15** | **Group 2 250 mg/kg/day Soy Leghemoglobin N=15** | **Group 3 500 mg/kg/day Soy Leghemoglobin N=15** | **Group 4 750 mg/kg/day Soy Leghemoglobin N=15** |
|---|---|---|---|---|
| Number of uteri submitted for examination | 13 | 14 | 15 | 15 |
| Fluid filled | 2 | 1 | 1 | 2 |

In study 44856, Impossible Foods commissioned Karen Regan, DVM, DACVP, DABT (Regan Path/Tox Services, Inc., Ashland, OH, USA) for histological evaluation of the female reproductive organs. Dr. Regan has extensive experience in the evaluation of rat reproductive systems, and currently serves as FDA advisory committee member for reproductive toxicology. Prior to finalizing the pathology report, Impossible Foods shared the draft report for study 43166 with Dr. Regan to ensure that she would look for the potential effects noted in that study.

In study 44856, Dr. Regan performed a blind estrous cycle determination as well as a histological assessment on the vagina, uterus, ovaries, oviducts, and cervix of the control (group 1) and high dose (group 4) animals. Dr. Regan concluded that there were no test article-related microscopic observations in the reproductive tissues examined. All animals were considered to be cycling normally, with the exception of a single control animal that appeared to have a prolonged estrus based on the morphology of the ovaries and uterus. This control animal finding was considered to be spontaneous and incidental because of the lack of similar findings in animals at the higher dose levels. Within groups 1 and 4, all animals had evidence of old and recent corpora lutea and follicles at various stages of development in the ovaries, and had reproductive tissue morphology consistent with the stage of the cycle they were in. One Group 2 animal had prolonged estrus based on morphology of the ovaries, including large atretic follicles, multiple corpus lutea at a similar state of atresia, and presence of squamous metaplasia of the uterus. These findings were considered spontaneous and incidental due to the lack of similar findings at higher dose levels. One control animal had large atretic follicles observed in both ovaries, and one group 4 animal had lutenized follicles (follicles with evidence of lutenization in the wall but have not ovulated) in both ovaries. Both of these observations are reported as background findings in rats of the strain and age used in this study (Dixon et al. 2014) and were considered incidental because of their singular occurrences.

In summary, in study 44856, Dr. Regan and Product Safety Labs concluded that there was no test substance-related effect on reproductive macroscopic or microscopic observations, reproductive organ weights, or estrous cyclicity.

#### 6.3.2.3. Pathology Peer Review on 28-Day GLP Dietary Toxicity Study in Rats (Study 43166)

Because no test article-related effects on the female estrous cycle were seen in study 44856, Impossible Foods commissioned a pathology peer review on the reproductive organs from study 43166. Dr. Regan served as the review pathologist. The review pathologist received and evaluated histological slides for the cervix, ovaries, oviducts, uterus and vagina, along with the corresponding macroscopic and microscopic finding noted by the study pathologist. Both the study pathologist and review pathologist met and performed an in-person slide review in June 2017, and reached a consensus evaluation that is reflected in the pathology report for study 43166. Both pathologists were in agreement on the estrous cycle staging; however, the presence of old and recent corpora lutea suggests that the animals were cycling normally. Moreover, study 44856 clearly illustrates that that there is no test article-dependent effect on estrous cyclicity. In summary, although the study pathologist for study 43166 initially reported a possible change in the estrous cycle, following peer review, a consensus was reached that there were no test article-dependent effects on the female estrous cycle and reproductive organs.

#### 6.3.2.4. NOAEL

In the 28-Day GLP Dietary Toxicity Study in Rats (Study 43166), there were no test article-related adverse effects observed in the male or female animals at the maximum dose tested. Therefore, the no observed adverse effect level (NOAEL) for administration of LegH Prep solids in the diet of male and female Sprague Dawley rats was the maximum dose tested, 1536 mg/kg/day, which corresponds to 750 mg/kg/day of the active ingredient soy leghemoglobin. The Acceptable Daily Intake (ADI) is determined by dividing the NOAEL by an acceptable Uncertainty Factor; 100-fold is generally accepted.[7] The ADI for soy leghemoglobin is 750/100 or 7.5 mg/kg/day. The 90$^{th}$ percentile EDI for soy leghemoglobin is 6.67 mg/kg/day. Since the EDI is lower than the ADI, these results suggest there are no safety concerns.[8]

### 6.3.3 Mutagenicity/Genotoxicity Studies

To evaluate the potential genotoxic activity of LegH Prep (containing soy leghemoglobin, *Pichia* proteins and other components; *see* Table 1), Impossible Foods commissioned a bacterial reverse mutation assay performed by Product Safety Labs (Dayton, NJ, USA) and an *in vitro* mammalian chromosome aberration test in human lymphocytes performed by Eurofins (Munich, Germany). Both studies were conducted consistent with OECD Principles of Good Laboratory Practice (as revised in 1997) and OECD Testing Guidelines for test 471 (reverse mutation) and test 473 (chromosomal aberration). The test article for both studies was batch PP-PGM2-16-

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[7] The food additive regulations recommend a safety factor of 100, in the absence of extenuating circumstances. 21 C.F.R. 170.22.

[8] FDA. Chapter II: Agency Review of Toxicology Information in Petitions for Direct Food Additives and Color Additives Used in Food. Available at: https://www.fda.gov/downloads/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/IngredientsAdditivesGRASPackaging/UCM078724.pdf

015-101. These studies used the standard liquid formulation of LegH Prep since, unlike the animal feeding studies, freeze drying was not required for test article administration. Reports for each study are located in Annexes 4 and 5.

#### 6.3.3.1 Bacterial Reverse Mutation Assay

The bacterial reverse mutation (Ames) test evaluated the potential for LegH Prep to induce gene mutations in bacteria (Annex 4). Point mutations which involve substitution, addition or deletion of one or a few DNA base pairs were measured in amino acid-requiring strains of *Salmonella typhimurium* (*S. typhimurium*, ST) and *Escherichia coli* (*E. coli*, EC) by their ability to functionally reverse mutations. These reverse mutations resulted in revertant colonies of bacteria with restored capability to synthesize the essential amino acid. The bacterial strains evaluated were *S. typhimurium* TA1535, TA1537, TA98, TA100, and *E. coli* WP2 uvrA. LegH Prep was tested up to a maximum concentration of 74,000 µg/plate, which corresponded to a maximum soy leghemoglobin concentration of 5,000 µg/plate. Eight dose levels without precipitation, toxicity or plate contamination were evaluated for all strains; therefore bacterial mutagenicity was adequately assessed. The main test was conducted using the plate incorporation method in both the absence and presence of metabolic activation (chemically-induced rat liver S9 mix). The results of the test were confirmed using a similar study design, but employing the pre-incubation modification of the Ames test. No signs of precipitation or contamination were reported in any of the strains. No signs of toxicity were reported in any strains in either plate incorporation or pre-incubation method in presence or absence of S9. In conclusion, based on these findings and on the evaluation system used, LegH Prep possesses no mutagenic activity in the Ames assay.

#### 6.3.3.2 *In Vitro* Mammalian Chromosome Aberration Test in Human Lymphocytes

A chromosome aberration assay was carried out in order to investigate a possible potential of soy leghemoglobin and the LegH Prep to induce structural chromosome aberrations in human lymphocytes (Annex 5). The metaphases were prepared 24 hours after start of treatment with the test item. The treatment interval was 4 hours without and with metabolic activation (Experiment I) and 24 hours without metabolic activation (Experiment II). Duplicate cultures were set up. Per culture, 150 metaphases were scored for structural chromosomal aberrations.

The following soy leghemoglobin concentrations were evaluated. Experiment I: 500, 1000, 2500 and 5000 µg/mL soy leghemoglobin; Experiment II: 100, 200, 500 and 1000 µg/mL soy leghemoglobin. In Experiment II, precipitation occurred at concentrations 500 µg/mL and higher during the fixation of the cells. In contrast to Experiment I, in the experiment with long-term treatment, the test item was not removed by repeated washing steps, as the treatment period is stopped by the fixation step directly. When the cells were spread on the object slides, the precipitation appeared as a greenish lacquer coat, visible by eye and with the aid of an inverted microscope. The evaluation of aberration rates was not affected.

In each experiment, percent relative mitotic index was measured for each soy leghemoglobin concentration. A relative mitotic index greater than 45% is required to accurately measure chromosome aberrations. In Experiment I without metabolic activation, the decrease below 70% relative mitotic index was seen at concentrations of 1000 µg/mL (69%), 2500 µg/mL (56%) and 5000 µg/mL (54%) (Annex 5, *see* Table 5). In Experiment I with metabolic activation no decrease below 70% relative mitotic index was observed. As noted by the OECD guidelines, mitotic index is an indirect measurement of toxicity that can be influenced by a number of factors such as time and cell cycle disruption, and additional data such as cell cycle delay is often helpful in assessing toxicity.[9] In the current experiments, cell cycle delay was assessed in the cell proliferation using the BrdU technique. No biologically significant decrease in proliferation was noted in Experiment I, and the levels of the mitotic index remained above the 45% required to accurately assess chromosomal aberrations. Further, as the report in Annex 5 notes, the cytotoxicity is likely even lower than shown in Experiment I without metabolic activation, as there appeared to be a detoxification in the Experiment I with metabolic activation.

In Experiment II without metabolic activation, cytotoxic effects regarding the mitotic index were reported at concentrations of 500 µg/mL (69%), 1000 µg/mL (53%), 2000 µg/mL (26%), 3000 µg/mL (13%), 4000 µg/mL (38%) and 5000 µg/mL (42%) (Annex 5, *see* Table 7).

In Experiments I and II, no biologically relevant increase in the frequencies of polyploid cells was reported at concentrations up to 5000 µg/mL. In experiment I, no biologically relevant decreases of the proliferation index were reported at concentrations up to 5000 µg/mL. In experiment II, the values of the proliferation index of the negative controls were 1.56. The proliferation index of the 500 and 1000 µg/mL groups were 1.23 and 1.12. Decrease of 79% at 500 µg/mL and 72% at 1000 µg/mL of the proliferation index were observed. These decreases were not a consequence of chromosome aberrations.

In Experiments I and II, no biologically or statistically significant increase of the aberration rates was reported after treatment with LegH Prep containing soy leghemoglobin compared to the solvent control cultures (Annex 5, *see* Tables 6 and 8). The $\chi^2$ Test for trend was performed to test whether there was a concentration-related increase in chromosomal aberrations. No statistically significant increase was reported in all experimental conditions. EMS (400 and 900 µg/mL) and CPA (7.5 µg/mL) were used as positive controls and induced distinct and biologically relevant increases in cells with structural chromosomal aberrations, thus proving the efficiency of the test system to indicate potential clastogenic effects.

In conclusion, under the conditions of these studies, LegH Prep did not induce structural chromosomal aberrations in human lymphocyte cells. Therefore, LegH Prep is considered to be non-clastogenic in this chromosome aberration test.

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[9] OECD Guideline for the Testing of Chemicals: *In vitro* mammalian chromosomal aberration test, TG 473. Available at: https://ntp.niehs.nih.gov/iccvam/suppdocs/feddocs/oecd/oecd-tg473-2014-508.pdf

## 6.4. Assessment of Allergenicity

### 6.4.1 Assessment of potential soy and legume cross-reactivity

#### 6.4.1.1 Soy Cross-Reactivity

Soybeans are acknowledged as a commonly allergenic food. Soybeans are known to contain several allergenic proteins (Taylor, Panda, Goodman, & Baumert, 2014). However, soy leghemoglobin is not identified among the known soybean allergens, nor is it detectably present in soybeans. It is the expert opinion of Dr. Taylor, co-founder and co-director of the Food Allergy Resource and Research Program (FARRP) at the University of Nebraska, that Impossible Foods does not need to perform experiments to demonstrate that LegH Prep does not cross-react with soy-allergic individuals (Annex 6). Nevertheless, Impossible Foods will notify consumers by labeling that the product "Contains Soy" as required by the statute.[10] Because Impossible Foods will identify the potential allergen on its label, there is no necessity to prove that soy-allergic individuals will not react to soy leghemoglobin.

Furthermore, the size of adult population of soy-allergic individuals is insufficient to acquire enough subjects to perform a statistically significant clinical study. While 0.4% of children are allergic to soy, the large majority of them outgrow it by the age of 10 (Savage, et al., 2010). Finally, leghemoglobin is natively expressed in the root of the soy plant, whereas the allergens – Gly m 4, Gly m 5, and Gly m 6 are located in the seeds. These allergens are completely absent from LegH Prep, which is produced by *Pichia pastoris* genetically engineered to express only soy leghemoglobin. This physical separation, as well as the lack of sequence homology to known soy allergens, indicates that soy leghemoglobin is highly unlikely to elicit a reaction in a soy-allergic consumer.

Additionally, soy leghemoglobin was evaluated to determine if this protein had the potential to become a novel food allergen. In accordance with the consensus recommendations of the Codex Alimentarius Commission, it is the opinion of Dr. Taylor that sequence homology and pepsin digest analyses are the most predictive methods known to date to assess allergenicity of novel proteins. Therefore, besides these two tests, there are no additional tests that Impossible Foods could perform that would strengthen the evidence against potential allergenicity of soy leghemoglobin.

#### 6.4.1.2 Legume Cross-Reactivity

Clinical cross-reactivity among various foods from the legume family is rare (Bernhisel-Broadbent and Sampson, 1989). In the largest study reported to date, in 793 persistent peanut-allergic subjects, 9.5% were considered allergic to other legumes by oral challenge including 48 to soy, 19 to pea, 7 to lentil, 4 to chickpea and 3 to green bean (Neuman-Sunshine et al., 2012). Based upon the prevalence and severity of peanut allergy, potential cross-reactions between soy

[10] While not required by the labeling statutes, in addition to the allergen statement on the business to business labeling, Impossible Foods will provide training materials and information about the product to restaurants who purchase the product, including language and instruction indicating it is a soy-protein based product.

leghemoglobin and peanut allergens is the key area of potential concern. The various peanut allergens are very well identified and characterized. No significant sequence homology exists between soy leghemoglobin and any of the peanut allergens (section 5.3.2.2). Moreover, soy leghemoglobin is found in the root of the soy plant and bears no structural resemblance or sequence homology to these seed storage proteins which are found in the peanut kernel. It is the expert opinion of Dr. Taylor that Impossible Foods does not need to perform experiments to demonstrate that LegH Prep does not cross-react with legume-allergic individuals (Annex 6).

### 6.4.2 Assessment of soy leghemoglobin and *Pichia* proteins within LegH Prep

The potential allergenicity of soy leghemoglobin as well as the *Pichia* proteins present in LegH Prep were assessed in the same manner as used for the novel proteins expressed in genetically engineered foods. The Codex Alimentarius Commission developed an assessment scheme for the analysis of the potential allergenicity of proteins derived from biotechnology (2003). This assessment is a multi-factorial approach which includes assessing the source of the protein for allergenicity, the sequence homology of the protein to known allergens, resistance to pepsin degradation and, if there is a high suspicion of allergenicity, specific serum screening. This analysis provides a likelihood of allergenic response by considering the totality of the evidence. Several prominent organizations support this approach: the 1996 ISLI-IFBC decision tree, the 1996 FAO/WHO consultation on biotechnology and food safety, the 2000 FAO/WHO consultation on food derived from biotechnology, the 2001 FAO/ WHO consultation on allergenicity assessment of GM foods, the 2002 Codex ad hoc task force on safety assessment of biotechnology, and the 2003 Codex Alimentarius Commission guidelines to assess the allergenicity of genetically modified crops (Metcalfe, Astwood, Townsend, Sampson, Taylor, & Fuchs, 1996) (FAO/WHO, 1996) (FAO/WHO, 2000) (FAO/WHO, 2002) (FAO/WHO., 2001) (Codex Alimentarius, 2003).

Impossible Foods enlisted Dr. Richard E. Goodman, research professor at FARRP of the University of Nebraska, to assess the potential allergenicity and toxicity of soy leghemoglobin and the *Pichia pastoris* proteins present in LegH Prep at ≥1% of the total protein fraction, consistent with the Codex recommendations. Approximately 17 *Pichia pastoris* proteins were found to be present in LegH Prep at ≥1% of the total protein fraction. These proteins are consistent from batch to batch and were identified by Impossible Foods using mass spectrometry. This multifactorial approach, which included a comprehensive literature search, sequence homology, and pepsin digestion assessments to assess the allergenic potential of new proteins, is widely used in the food industry (Fuchs, Ream, Hammond, Naylor, Leimgruber, & Berberich, 1993) (Reed, et al., 1996) (Harrison, et al., 1996) (Hileman, 2006) (Noteborn, et al., 1995) (Hashimoto, et al., 1999) (Momma, et al., 1999) (Goodman, 2007) (Moran, 2014). A summary of Dr. Goodman's evaluation is provided in Annex 7. Final reports on sequence homology and pepsin digestion are provided in Annexes 8-10.

### 6.4.3 Literature search

Dr. Goodman's assessment included a full literature search to identify any published literature regarding possible allergenicity or toxicity associated with leghemoglobin proteins or the *Pichia pastoris* proteins present within LegH Prep. The conclusion of this assessment was

that no published literature could be found that suggested allergic, toxic or adverse health effects related to consumption of leghemoglobin or *Pichia pastoris* proteins (Annexes 8-9).

### 6.4.4 Sequence homology

Dr. Goodman's assessment also determined if the amino acid sequence of soy leghemoglobin or the *Pichia pastoris* proteins in LegH Prep contained sufficient similarity with any known allergen or toxin to suggest possible cross-reactivity. Soy leghemoglobin and *Pichia pastoris* protein sequences were compared to the 2016 Allergen Online Database (www.allergenonline.org) and the NCBI-Entrez database, first without any keyword selection, and again with keywords "allergen", "toxin" or "toxic". Soy leghemoglobin protein did not produce significant (>35%) homology to known allergens or toxins (Annex 8).

All of the 17 *Pichia pastoris* proteins have homologs that are ubiquitous in nature. Therefore, a search of the NCBI database for sequences related to each of the 17 proteins, using BLASTP without keyword limits, identified good alignments with related proteins from many molds and yeasts. For all 17 proteins, these alignments included *Saccharomyces cerevisiae* and *Saccharomyces bayanus*, which are commonly used in making wine, bread, and beer, and *Saccharomyces boulardii*, which is widely used as a probiotic (Moyad, 2008) (Munoz-Bernal, 2016) (Liu, 2016). The long history of consumption of these close homologs of all 17 *Pichia pastoris* proteins with no reports of allergenicity or toxicity offers strong general evidence for their safety in food (Annex 9).

Bioinformatics searches with the 17 most abundant residual *Pichia pastoris* proteins found in LegH Prep identified a few related protein sequences with sufficient similarity to exceed the Codex suggestion for potential cross reactivity (>35%) (Table 6). However, the sequence-related putative allergens identified in this search were not potent, common allergens, nor were any of them known to be allergenic when ingested. Moreover, comparison of the same *Pichia pastoris* proteins with all proteins in the NCBI Protein database identified far more significant matches to proteins found in commonly consumed fungi, including baker's yeast (*Saccharomyces* species).

Table 6. Summary of sequence alignments for Soy Leghemoglobin and the 17 most abundant residual *Pichia pastoris* proteins found in LegH Prep.

| Protein Name | GeneInfo Identifier | Accession | No. of AA[1] | AOL[2] Matched Allergen[3] | AOL Best ID[4] | *Saccharomyces sp.* Best ID |
|---|---|---|---|---|---|---|
| Soy leghemoglobin | 126241 | P02236.2 | 145 | n/a[5] | n/a | n/a |
| Alpha aminoadipate reductase | 238030060 | CAY67983.1 | 1400 | n/a | n/a | 60% |
| Cobalamin-independent methionine synthase | 238030843 | CAY68766.1 | 768 | Sal k 3 | 77.50% | 77% |
| Aconitase | 254564667 | XP_002489444.1 | 780 | n/a | n/a | 81% |

| | | | | | | |
|---|---|---|---|---|---|---|
| Transketolase | 238030057 | CAY67980.1 | 679 | n/a | n/a | 70% |
| Glycerol kinase | 238034027 | CAY72049.1 | 621 | n/a | n/a | 53% |
| Catalase A | 254569930 | XP_002492075.1 | 510 | Pen c 30 | 60% | 66% |
| G6PD | -238031000 | CAY68923.1 | 504 | Bla g 3 | 37% | 64% |
| Hypothetical protein PAS | 238031215 | CAY69138.1 | 525 | Cla h 10 | 72.50% | 69% |
| | | | | Alt a 10 | 72.50% | |
| | | | | Lep d 13 | 35.40% | |
| Mitochondrial aldehyde dehydrogenase | 238033249 | CAY71271.1 | 501 | Cla h 10 | 76.20% | 62% |
| | | | | Alt a 10 | 76.20% | |
| Delta-aminolevulinate dehydratase | 238033645 | CAY71667.1 | 341 | n/a | n/a | 76% |
| Mitochondrial alcohol dehydrogenase isozyme III | 238031179 | CAY69102.1 | 350 | Cand a 1 | 85% | 74% |
| Malate dehydrogenase | 238034064 | CAY72086.1 | 342 | Mala f 4 | 70% | 57% |
| | | | | Pis s 2 | 36.20% | |
| Putative protein, unknown function | 238033788 | CAY71810.1 | 328 | n/a | n/a | 86% |
| Triose phosphate isomerase | 238032989 | CAY71012.1 | 248 | Tri a 31 | 62.50% | 71% |
| | | | | Der f 25.0101 (isoform) | 60.00% | |
| | | | | Der f 25.0201 (isoform) | 60.00% | |
| | | | | Cra c 8 | 57.50% | |
| Hypothetical protein (cyclophilin) PP7435 | 328350030 | CCA36430.1 | 161 | Mala s 6 | 87.50% | 74% |
| | | | | Asp f 27 | 85% | |
| | | | | Cat r 1 | 81.30% | |
| | | | | Der f 29 | 80% | |
| | | | | Asp f 11 | 80% | |
| | | | | Bet v 7 | 80% | |
| | | | | (Unassigned by IUIS) PPIase[6] from *Dauces carota* | 78% | |
| Cytosolic superoxide dismutase | 238034030 | CAY72052.1 | 154 | Ole e 5 | 60% - 55% | 79% |
| | | | | 23 isoforms | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Mitochondria ATPase Inhibitor | 238029769 | CAY67692.1 | 84 | n/a | n/a | 62% |

[1]AA: amino acids;
[2]AOL: AllergenOnline
[3]Allergen name in IUIS allergen list unless denoted as unassigned by IUIS;
[4]ID: identity (%);
[5]n/a: not available or no answer.
[6]PPIase: peptidylprolyl isomerase.

While a number of organisms with known toxicity (e.g., *Bacillus sp., Enterococcus faecalis, Streptomyces sp., Clostridium sp.*) contained proteins with sequences similar to those of the *Pichia pastoris* proteins of interest, these proteins were ubiquitous and highly conserved across diverse species, and are not themselves known or suspected to be toxic. As a further evaluation step, a comparison of the sequence-related proteins from toxin-producing species with proteins from diverse non-toxic species revealed far more closely-related proteins from sources that are known to be safe and non-toxic (Annex 9).

AllergenOnline (AOL) has been updated every year since 2004. A panel of allergen experts evaluates each entry using published acceptance criteria (Goodman et al. 2016). AOL is based on published studies characterizing the proteins and evidence for their allergenicity using allergic human subjects as challenge subjects, serum donors, or basophil donors in well-accepted methods. In addition to using the AOL database, the NCBI protein database, which is updated weekly, was queried to identify any sequences that may have been identified after the most recent AOL update.

While the information discussed above is more than adequate to demonstrate that both soy leghemoglobin and the *Pichia* proteins within LegH Prep have little or no allergenic potential, Impossible Foods was encouraged to conduct a support-vector machine (SVM) analysis.[11] While Impossible Foods is aware that there is some controversy as to the reliability of this method, Impossible Foods agreed to perform an SVM analysis for soy leghemoglobin.

In addition to the AOL method, Impossible Foods identified eleven alternative support vector machine-based (SVM-based) methods to assess potential allergenicity, five of which had active, useable web interfaces (Tables 7 and 8).

Four of the five SVM-based methods indicated that soy leghemoglobin is not an allergen (Table 7), in concurrence with the AOL method. Although, a fifth SVM-based test, AlgPred, indicated that soy leghemoglobin may be a potential allergen, further investigations into the methodology underlying AlgPred suggest that it may have a high false positive rate. For example, AlgPred identifies 46% of all proteins in SwissProt as potential allergens, even after all known allergens and related proteins have been removed from the SwissProt database (Saha and Raghava, 2006). However, a conservative assumption is that only small percentage of proteins are potential allergens. Based on the weight of evidence (concurrence between AOL and 4

[11] This analysis was not conducted or endorsed by FARRP or Dr. Goodman.

alternative SVM-based methods) and the potential methodological pitfalls of AlgPred, soy leghemoglobin has a low potential risk of allergenicity.

Table 7. Summary of SVM-based methods and results.

| Name | Website | Brief Description | Result | Comments |
|---|---|---|---|---|
| PREALw | http://lilab.life.sjtu.edu.cn:8080/prealw/predict.html | Weighted average assessment based on SVM and sequence searches suggested by FAO* | Non allergen | |
| AlgPred | http://webs.iiitd.edu.in/raghava/algpred/submission.html | AlgPred uses five different methods to assess allergenicity. | Mixed** | Published version of website is non-functional but author was contacted to obtain functioning link |
| SVMProt | http://bidd2.nus.edu.sg/cgi-bin/svmprot/svmprot.cgi | Is a broad SVM classifier of protein function. One of the categories they train their predictor against is whether or not the protein is a known allergen. | The SVMProt classifier does not predict that soy leghemoglobin is an allergen. | |
| SortAller | http://sortaller.gzhmu.edu.cn/ | SORTALLER is an online SVM based allergen classifier based on the allergen family featured peptide (AFFP) dataset. | SORTALLER predicted the query sequence soy leghemoglobin as a non-allergen with score of 0.265 | |

* A protein is identified as a putative allergen if it contains at least six contiguous exact amino acids matches (rule 1) or at least 35% sequence similarity within an 80 amino acid window (rule 2) when compared with known allergens (Wang, 2013)
** The AlgPred algorithm uses five different classifiers. Three (mapping of IgE motifs, a search for allergen related motifs and a BLAST search of the database) are negative for potential allergenicity. The two (closely related) SVM classifiers suggest that soy leghemoglobin is a potential allergen based on its amino acid composition.

Table 8. Non-functional SVM-based sites.

| Name | Website | Status (as of August 21, 2017) |
|---|---|---|
| ProInFlam | http://metagenomics.iiserb.ac.in/proinflam/prot.php | Website exists but searches using all available tools on the site return errors and no results. |
| Allerdictor | http://allerdictor.vbi.vt.edu/ | Website online but search returns error. |
| AllergenFP | http://ddg-pharmfac.net/AllergenFP/ | Website online but search returns error. |
| AllerHunter | http://tiger.dbs.nus.edu.sg/AllerHunter | Website offline. |
| WebAllergen | http://nabic.rda.go.kr/allergen/allergenIntroduction.do | Search not available. |
| FuzzyAPP | http://fuzzyapp.bicpu.edu.in/ | Webserver not available. |

### 6.4.5 Pepsin digestion

Dr. Goodman assessed the stability of the soy leghemoglobin and the *Pichia pastoris* proteins within LegH Prep to pepsin degradation in a simulated gastric fluid. Several peer-reviewed studies have shown that low *in vitro* pepsin digestibility is an important risk factor for food allergy (Astwood, 1996) (del Val, 1999). Bannon *et al.* (2003) reviewed a broad range of published pepsin digestion studies and found a strong positive predictive value of the digestion protocol when comparing the stability of allergenic and non-allergenic dietary proteins (Bannon, 2003). A published multi-laboratory study demonstrated the rigor and reproducibility of using pepsin digestion to evaluate the stability of a number of food allergens and non-allergenic proteins across nine laboratories (Thomas, 2004). The pepsin digest protocol conducted in the Goodman Lab is identical to the robust procedure used in Thomas *et al.*, 2004. In addition to the recommended ratio of 10 U pepsin enzyme to 1 μg target protein, the Goodman lab also evaluated a more stringent ratio of 1 U enzyme to 1 μg target protein. Dr. Goodman's laboratory-based assessment demonstrated that soy leghemoglobin protein as well as the *Pichia pastoris* proteins are readily digested by pepsin at ratios of 10 U pepsin enzyme to 1 μg target protein and 1 U enzyme to 1 μg target protein, confirmed with SDS-PAGE analysis (Annex 10). It is the expert opinion of Dr. Goodman that using a lower than standard activity of pepsin in this assay is not scientifically justified due to insufficient published data on the sensitivity of known allergens and non-allergenic proteins under these conditions, and thus the inability to interpret the results.

In summary, based on a weight of evidence approach including literature search, sequence homology analysis and pepsin digestion, Dr. Goodman concluded that consumption of the soy leghemoglobin protein as well as the *Pichia pastoris* proteins present in Impossible Foods' LegH Prep raise no health or safety concern as they do not pose any significant risk of allergy (Annex 7).

### 6.4.6 Assessment of potential cross-reactivity with meat allergic individuals

Tick-bite induced allergy to mammalian meat (e.g., beef, pork) and organs (e.g., liver, kidney) has been reported in the United States, Europe, Australia and parts of Asia (Stinke JW, 2015). However, the allergic reaction is due to an IgE antibody response to the oligosaccharide galactose-alpha-1,3-galactose (alpha-gal), which is located on glycoproteins and glycolipids in non-primate mammalian meat and organs (Commins SP, 2016). The allergic reaction is not caused by myoglobin, and therefore consumers with alpha-gal specific IgE antibodies will not cross-react with soy leghemoglobin.

Impossible Foods is aware of only a single case of meat allergy linked to bovine myoglobin (Fuentes et al., 2004), although implication of bovine myoglobin in this case has been disputed (Fiocchi et al., 2005). The reactions reported in this patient were specific to bovine myoglobin, and not porcine myoglobin, suggesting that this is not a general allergy to oxygen-binding globin proteins, but rather a specific response to a bovine-derived protein. Given the widespread consumption of meats containing oxygen-binding globins at concentrations comparable to those proposed for use of soy leghemoglobin in this notification, the low incidence of meat allergies in general (and the cause of those few reactions is predominantly due to bovine serum albumin sensitivities), and only a single reported case of myoglobin allergy, this argues that these proteins as a class have low allergenicity.

## 6.5 Summary of Safety Testing

LegH Prep is a solution of proteins, containing not less than 65% soy leghemoglobin, plus proteins from the yeast *Pichia pastoris*. These components were evaluated for history of safe use as well as potential risks of allergenicity, general toxicity in rats, and genotoxicity.

The Impossible Foods' *Pichia pastoris* production strain is derived from a strain lineage with a long history of safe use. *Pichia* is non-pathogenic and non-toxigenic (21 CFR Part 573). *Pichia* has been used to express proteins for use in human food (GRN 204), potable water treatment (The Nitrate Elimination Co. Lake Linden, MI), animal feed (AAFCO, 2013), and FDA approved therapeutics. Although the soy leghemoglobin protein does not have a history of wide consumption in the human diet, heme B-containing proteins, which contain the chemically identical heme B co-factor (Annex 1), have been safely consumed in meat and plants throughout human history. Moreover, the soy leghemoglobin polypeptide does not pose any significant risk of allergy or toxicity.

LegH Prep was evaluated for potential risk of allergenicity using a weight of evidence approach in accordance with the 2003 Codex Alimentarius Commission guidelines for assessment of potential allergenicity of proteins derived from biotechnology. No published literature could be found that suggested allergic, toxic, or adverse health effects related to consumption of soy leghemoglobin or *Pichia pastoris*. The soy leghemoglobin protein does not contain significant (greater than 35%) sequence homology to known allergens or toxins. The most abundant *Pichia* proteins within LegH Prep are ubiquitous in nature and contain high sequence identity to homologues in yeast and molds that are commonly used in making cheese,

wine, bread, and beer. LegH Prep is rapidly digested by pepsin in a simulated gastric fluid. Although there is no scientific evidence to suggest that soy-allergic individuals will cross-react with soy leghemoglobin, Impossible Foods will include "soy" on the label. In addition, Impossible Foods will notify consumers that the product "Contains Soy."

LegH Prep showed no evidence of toxicity in rats at the maximum dose tested, which was 750 mg/kg/day soy leghemoglobin. In a 28-day GLP feeding study in rats (43166), there were no clinically significant differences between groups in clinical observations, body weights, hematological parameters, clotting potential, or clinical chemistry for both sexes. In the male rats, there were no test article-related macroscopic or microscopic findings or differences in absolute organ weights and organ weight to body ratios. In the female rats, it was suggested that there might be a test article-related effect on the estrous cycle. However, a follow up 28-day feeding study (44856) with estrous cycle monitoring confirmed that there were no test article-related effects on the female rat estrous cycle or reproductive organs at the maximum dose of 750 mg/kg/day soy leghemoglobin, the highest dose tested. The NOAEL is used to determine. the Acceptable Daily Intake (ADI). The NOAEL is divided by an acceptable Uncertainty Factor, 100 fold is generally accepted.[12] The ADI for soy leghemoglobin is 750/100 or 7.5 mg/kg/day. The 90$^{th}$ percentile EDI for soy leghemoglobin is 6.67 mg/kg/day. Since the EDI is lower than the ADI, there are no suggested safety concerns.[13]

Genotoxicity of LegH Prep was assessed using the bacterial reverse mutation assay and the chromosomal aberration assay in human lymphocytes. LegH Prep was found to be non-mutagenic and non-clastogenic in each assay.

In conclusion, LegH Prep does not appear to present any significant issues of safety that would preclude its use in meat analogue products.

## 6.6 Expert Panel Report

The Expert Panel Report is included in the following pages.

[12] The food additive regulations recommend a safety factor of 100, in the absence of extenuating circumstances. 21 C.F.R. 170.22.

[13] FDA. Chapter II: Agency Review of Toxicology Information in Petitions for Direct Food Additives and Color Additives Used in Food. Available at: https://www.fda.gov/downloads/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/IngredientsAdditivesGRASPackaging/UCM078724.pdf

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# The Report of the Expert Panel on the Generally Recognized as Safe Determination of the Proposed Uses of Soy Leghemoglobin Protein Derived from *Pichia pastoris* as a Food Ingredient

**04 August 2017**

## Introduction

Impossible Foods Inc. (Impossible Foods) convened a panel of independent scientists (Expert Panel), qualified by their scientific training and relevant national and international experience in the evaluation of the safety of food ingredients, to conduct an independent, critical and comprehensive evaluation of the available safety information on soy leghemoglobin protein preparation (LegH Prep), and to determine if the proposed uses as a protein component in ground beef replacement (analogue) products would be Generally Recognized as Safe (GRAS) based on scientific procedures. The Expert Panel consisted of Professor Joseph F. Borzelleca, Ph.D. (Virginia Commonwealth University School of Medicine), Professor Michael W. Pariza, Ph.D. (University of Wisconsin-Madison), and Professor Stephen L. Taylor Ph.D. (University of Nebraska-Lincoln).

An initial review was conducted and a summary of the results was made available to the Expert Panel as part of the "GRAS NOTIFICATION FOR SOYBEAN LEGHEMOGLOBIN PROTEIN DERIVED FROM *PICHIA PASTORIS*" (not dated) and a "TECHNICAL SUMMARY OF SOYBEAN LEGHEMOGLOBIN PROTEIN DERIVED FROM *PICHIA PASTORIS* " (dated May 30, 2014). Impossible Foods conducted further studies to confirm the safety and GRAS status of the proposed uses of LegH Prep and made this information and data available to the Expert Panel. A comprehensive search of the scientific literature on plant and animal hemoglobins and related products was conducted by Impossible Foods as part of the preparation of the new GRAS notice that is the subject of this report, as well as during the preparation of the supportive Technical Summary. Impossible Foods reported to the Expert Panel that their search failed to identify anything further on the safety of LegH Prep. The Expert Panel, independently and collectively, critically evaluated the new information and data

and re-evaluated the original information and data, and other information deemed appropriate or necessary and information pertaining to the method of manufacture, product specifications, batch analyses, intended levels of use, exposure estimates, and the safety of LegH Prep.

Following its independent, critical evaluation of the available information, the Expert Panel convened by teleconference and email correspondence, and unanimously concluded that the intended use in ground beef analogue products of soy leghemoglobin protein derived from *Pichia pastoris*, manufactured consistent with current Good Manufacturing Practice (cGMP) and meeting appropriate food-grade specifications, is GRAS based on scientific procedures. A summary of the basis for this conclusion appears below.

Impossible Foods proposes to market the soy leghemoglobin protein produced in the yeast *Pichia pastoris* in the United States for use as a protein component to create a flavor impact in ground beef analogue products.

Hemoglobin proteins are found in most organisms, including bacteria, protozoa, fungi, plants and animals (Hardison, 1998). Hemeproteins are classified as globin/non-globin and symbiotic/non-symbiotic. Hemoglobin, myoglobin, and leghemoglobin are examples of globin proteins. Cytochrome oxidases, hemocyanins, and methemalbumin are examples of non-globin hemeproteins (Everse, 2004) (Jokipii-Lukkari, Frey, Kallio, & Haggman, 2009). Plant hemoglobins are classified according to function as symbiotic or non-symbiotic (Gupta, Hebelstrup, Mur, & Igamberdiev, 2011). Symbiotic hemoglobins are found predominantly in leguminous plant species. The most studied symbiotic hemoglobins are the leghemoglobins of nitrogen fixing legumes where they facilitate oxygen diffusion within root tissues. Non-symbiotic hemoglobins have been identified in a wide range of legume and non-legume plants. The highest expression levels for non-symbiotic plant hemoglobin are observed in metabolically active or stressed tissue (Anderson, Jensen, Leewellyn, Dennis, & and Peacock, 1996).

Impossible Foods analyzed structures of plant non-symbiotic hemoglobins and symbiotic leghemoglobins and animal myoglobins including rice, soy, corn, barley, lupine, horse, tuna, and pig. Animal myoglobins, plant leghemoglobins and plant hemoglobins adopt the same globin fold and are structurally very similar. All globin proteins described above bind the chemically identical heme B prosthetic group involved in binding and/or transport of oxygen. The globin protein family is large, present in a wide range of organisms, and is well studied.

## Identity and Characterization of Soy Leghemoglobin Protein

The chemical name of the characterizing component of LegH Prep is soy leghemoglobin protein. The source of the protein is the soybean plant *Glycine max* gene *LGB2*. Soy leghemoglobin protein is derived from the root nodules of the soy plant.

There is no Chemical Abstracts Number for soy leghemoglobin.

The proposed common or usual name of LegH Prep is "leghemoglobin (soy)."

## Production of LegH Prep

The method of production involves four stages: construction of the production strain of *Pichia pastoris*, expression of soy leghemoglobin protein in submerged fermentation, enrichment, and stabilization of the expressed soy leghemoglobin protein.

All materials used in the production of LegH Prep are food grade and GRAS or high-quality chemical or pharmaceutical grades (USP, NF, or ACS grades) from approved suppliers and processing conditions are appropriate for food production and consistent with cGMP.

## Preparation of the Production Strain for Fermentation

Production strain *Pichia pastoris* MXY0291 was constructed from recipient strain Bg11 (MXY0051) using a series of transformations with different expression constructs, in order to express soy leghemoglobin protein. In addition to the protein coding sequence for soy leghemoglobin, MXY0291 contains extra copies of native *Pichia pastoris* heme biosynthetic enzymes and modified *Pichia pastoris* transcription factor Mxr1, all expressed under the strong native *Pichia pastoris* alcohol oxidase promoter (*pAOX1*). This promoter has been demonstrated to produce high levels of recombinant proteins after producing biomass on glycerol and inducing *pAOX1* with methanol (Cereghino & Cregg, 2000). The genome of MXY0291 is fully sequenced and well characterized.

The production strain parent, *Pichia pastoris* Bg11, was derived from the well-characterized strain Y-11430, which is deposited in the collection at the Northern Regional Research Laboratories (NRRL). The lineage of *P. pastoris* strain NRRL Y-11430 was previously included in GRN 204, reviewed by the Agency in 2006.

There are no indications that *P. pastoris* has been associated with animal or human illness. The first *P. pastoris* strains were isolated from an oak tree and a chestnut tree and were deposited in the collection at the Northern Regional Research Laboratories (NRRL) (www.biogrammatics.com). Yeast strains screened by Phillips Petroleum for growth on methanol included two *P. pastoris* strains, designated NRRL Y-1603 (ATCC accession 28485) (ATCC, 2006b) and NRRL YB-4290 (NCAUR, 2006). Phillips Petroleum identified a *P. pastoris* strain with improved growth characteristics. The strain was designated 21-1 and deposited at NRRL, as NRRL Y-11430 . This strain is now available from ATCC as 76273. No records are available confirming that NRRL Y-1603 or NRRL YB-4290 is the progenitor of NRRL Y-11430, but it seems likely that one of them is the progenitor strain. NRRL Y-11430 was the progenitor strain for GS115, a histidine auxotrophic mutant *(his4-)*, a common *Pichia* strain provided in commercial kits by Invitrogen Corporation, and widely used as the parental strain of many biotechnology products, including FDA approved proteins such as Kalibitor® (ecallantide, for the treatment of acute attacks of hereditary angioedema, 2009). Additionally, the GS115 derived strain SMD1168 is used for the GRAS approved production of BD16449 Phospholipase C (Food and Drug Administration, 2006). Like GS115, the BioGrammatics, Inc. strain, Bg11 is also a derivative of NRRL Y-11430, and genomic sequencing data performed by BioGrammatics Inc. confirm the similarity of NRRL Y-11430, Bg11 and GS115. Additional taxonomic history of these strains is available in a 2009 manuscript by C. Kurtzman and on the Biogrammatics webpage (biogrammatics.com).

BioGrammatics, Inc. further developed the NRRL-Y-11430 strain to remove the native *P. pastoris* plasmids using PCR primers unique to the plasmids to screen multiple single-colony isolates for the presence of the plasmids. One isolate without plasmids was selected to become the wild-type (wt) BioGrammatics strain, Bg10. Genomic sequence from Bg10 indicates the plasmids are no longer present, and, benchmarks the similarity of Bg10 with NRRL-Y11430, as well as with GS115. Biogrammatics, Inc. deleted the gene encoding for Aox1 from Bg10 using homologous recombination to generate Bg11, a strain that grows more slowly on methanol-containing induction media. Like NRRL Y-11430 and GS115, Bg11 does not contain antibiotic resistance genes.

## Expression of Soy Leghemoglobin Protein in Submerged Fermentation, Enrichment and Stabilization

Soy leghemoglobin protein is obtained by fed-batch fermentation using the *P. pastoris* production strain MXY0291 described above. All media components are FCC approved or food-grade ingredients. The *P. pastoris* cells in the fermentation broth are lysed by bead mill mechanical shearing. Insoluble material within the lysate is removed by

centrifugation and microfiltration. Ultrafiltration is used to concentrate soy leghemoglobin protein to at least 60 g/l. The resulting concentrated sample is stabilized with sodium chloride and sodium ascorbate and stored as a frozen liquid.

## Specifications for Soybean Leghemoglobin Protein Product

LegH Prep is standardized to contain at least 60 grams per liter (g/l) soy leghemoglobin protein. Sodium chloride and sodium ascorbate are used to stabilize the product. All stabilizing agents are food grade. The product specifications, and batch analysis results, are presented below.

Table 1. LegH Prep specifications and batch analyses from five independent production runs.

| | Specifications | PP-PGM2-16-015-101 | PP-PGM2-16-088-101 | PP-PGM2-16-102-101 | PP-PGM2-16-144-101 | PP-PGM2-16-200-101 |
|---|---|---|---|---|---|---|
| Soy Leghemoglobin Protein (w/w)[1] | 6 – 9% | 6.74% | 6.39% | 6.28% | 6.74% | 6.95% |
| Soy Leghemolglobin Protein Purity (w/w) | ≥65% | 82% | 71% | 85% | 77% | 86% |
| Fat (w/w) | ≤2% | 0.05% | <0.01% | <0.01% | 0.03% | 0.08% |
| Carbohydrates (w/w) | ≤4% | 1.72% | 0.99% | 1.67% | 2.01% | 2.73% |
| Ash (w/w) | ≤4% | 1.87% | 0.67% | 2.63% | 2.62% | 2.74% |
| pH | 6.5 – 8.5 | 7.19 | 7.19 | 7.38 | 7.01 | 6.77 |
| Lead (ppm) | <0.4 | <0.01 | <0.01 | <0.01 | <0.01 | <0.01 |
| Arsenic (ppm) | <0.05 | 0.01 | <0.01 | <0.01 | 0.01 | <0.01 |
| Mercury (ppm) | <0.05 | <0.005 | <0.005 | <0.005 | <0.005 | <0.005 |
| Cadmium (ppm) | <0.2 | <0.001 | <0.001 | 0.001 | 0.003 | 0.001 |
| Aerobic plate count (CFU/g)[2] | <10^4 | <10 | <10 | <10 | <10 | <10 |
| *E. coli 0157:H7*[3] | Absent by test | Absent by test | Absent by test | Absent by test | Absent by test | Absent by test |
| *Salmonella spp.*[4] | Absent by test | Absent by test | Absent by test | Absent by test | Absent by test | Absent by test |
| *Listeria monocytogenes*[5] | Absent by test | Absent by test | Absent by test | Absent by test | Absent by test | Absent by test |

## Stability of Soy Leghemoglobin

LegH Prep has been stored at -20 °C as a frozen liquid for at least 12 months with no observable change in soy leghemoglobin protein stability or performance in ground beef analogue products.

## Intended Uses in Food

LegH Prep is proposed to be used as a plant-based protein component in non-animal derived food products with the texture, nutrition, flavor and appearance of traditional animal derived foods. LegH Prep will impart a unique flavor impact to meat analogue products.

The high bioavailability of the heme iron component of soy leghemoglobin makes it suitable to enhance the dietary profile of many processed foods (Carpenter & Mahoney, 1992).

LegH Prep may be one of several Food and Drug Administration ("FDA" or "Agency") recognized plant proteins that will comprise ground beef analogue products. Other proteins may include, but are not limited to, commercially available proteins from soy, pea, mung bean, lentil, corn, potato, and wheat. Soy leghemoglobin will function to contribute to the flavour and nutritional quality of ground beef analogue products. A typical ground beef analogue product may contain:

| Component | Meat Analogue |
|---|---|
| Protein | 10%-25% |
| Plant Oils | 0%-25% |
| Miscellaneous+ | 2% |
| Water | 50%-75% |

+Miscellaneous ingredients may include salt, flavors, vitamins, essential amino acids, etc.

LegH Prep will be added to the ground beef analogue products to deliver not more than 0.8% soy leghemoglobin protein.

## Self-limitation of the Use of Soybean Leghemoglobin Protein Product

The use of LegH Prep in ground beef analogue products above the specified use-levels is largely self-limiting based on unacceptable organoleptic properties.

## Estimated Dietary Intake

The vast majority of hemeproteins consumed in the diet are as myoglobin through consumption of meat and poultry products. Hemeprotein consumption was estimated using data from the "Retail Commodity Intakes: Mean Amounts of Retail Commodities per Individual, 2007-08. (Bowman, Martin, Clemens, Lin, & Moshfegh, 2013). For the US population, per capita mean consumption of meat and poultry products is 154 g/day and the 90th percentile intake is 308 g/day. Assuming an average myoglobin concentration for meat and poultry products of 0.5% (Yip & Dallman, 1996), the average

per capita myoglobin consumption would be 0.77 g/day and the 90th percentile intake would be 1.54 g/day.

LegH Prep will be marketed for use in ground beef analogue products that provide consumers a flavorful and nutritious alternative to meat containing products. Impossible Foods has estimated daily intakes of soy leghemoglobin protein by assuming consumers will substitute the meat analogue product for the traditional meat product on a 1-for-1 basis.

Impossible Foods has assumed it will capture 100% of the total ground beef market with soy leghemoglobin protein-containing ground beef analogue products. 100% of the total ground beef market represents approximately 500 times the volume of the current meat analogue market size based on sales estimates[1]. The Estimated Daily Intake (EDI) of soy leghemoglobin in the target ground beef analogue applications was established using the Retail Commodity Intakes: Mean Amounts of Retail Commodities per Individual, 2007-08 (Bowman, Martin, Clemens, Lin, & Moshfegh, 2013). The results of that analysis are presented below. The estimates were calculated as follows:

For beef, the mean daily consumption is 59 grams. For ground beef, the mean consumption is 25 grams (59 grams x 42%). As the highest usage case, Impossible Foods assumes capturing 100% of this market with a ground beef analogue product consisting of not more than 0.8% soy leghemoglobin. This equates to a highest intake case of 200 mg/person/day of soy leghemoglobin (25 ground beef grams/person/day x 100% market x 0.8% soy leghemoglobin).

The estimated average daily intake of soy leghemoglobin in the intended applications will be 150 mg/person/day (0.6% soy leghemoglobin) and the maximum intake will be 200 mg/person/day (0.8% soy leghemoglobin). As noted above, this base case represents capturing 500 times the existing meat and poultry analogue market.

[1] Datamonitor estimates the US meat analogue volume was 53M kg in 2009. USDA-FAS Livestock and Poultry Report, April 2014 estimates 2014 US consumption of 11B kg beef, 8.5B kg pork, and 14B kg broilers. Therefore, the current meat analogue market is less than 0.2% of the overall meat market and capturing 1% of the meat market represents 5 times the current meat analogue market in the US.

Table 2a. Summary of proposed uses of soy leghemoglobin protein in food applications based on Retail Food Commodity Intakes 2007-2008.

| Food Category to be Replaced | Mean Consumption (g/day)[2] | Anticipated Market Share Replacement (%) | Anticipated Typical Use rate (%) | Soy Leghemoglobin Estimated Typical Daily Intake (mg/person/day) | Anticipated Maximum Use Rate (%) | Soy Leghemoglobin Estimated Maximum Daily Intake (mg/person/day) |
|---|---|---|---|---|---|---|
| **Ground Beef** | 25 | 100 | 0.6 | 150 | 0.8 | 200 |

Table 2b. Summary of proposed uses of LegH Prep dry solids in food applications based on Retail Food Commodity Intakes 2007-2008.

| Food Category to be Replaced | Mean Consumption (g/day) | Anticipated Market Share Replacement (%) | Anticipated Typical Use rate (%) | LegH Prep Dry Solids Estimated Typical Daily Intake (mg/person/day) | Anticipated Maximum Use Rate (%) | LegH Prep Dry Solids Estimated Maximum Daily Intake (mg/person/day) |
|---|---|---|---|---|---|---|
| **Ground Beef** | 25 | 100 | 0.6 | 404 | 0.8 | 539 |

For the basis of safety testing, the 90$^{th}$ percentile consumption of soy leghemoglobin was calculated using 25 grams ground beef/person/day x 0.8% soy leghemoglobin/ground beef / 60 kg/person x 2. Therefore, the 90$^{th}$ percentile consumption equates to 6.67 mg/kg/day, which was used as the basis for safety testing.

## Safety of Soy Leghemoglobin

Hemeproteins are found in bacteria, protozoa, fungi, plants and animals (Everse, 2004) (Hardison, 1998). Soy plants have been shown to express three hemoglobin proteins: symbiotic, non-symbiotic and truncated (Lee, Kim, & An, 2004). Symbiotic plant hemoglobins, which evolved from non-symbiotic hemoglobins (Gupta, Hebelstrup, Mur, & Igamberdiev, 2011), are commonly referred to as leghemoglobins. Symbiotic leghemoglobins, found predominately in legume root nodules, function in the nitrogen fixation process in concert with the bacterium *Rhizobium* where they facilitate oxygen diffusion within host root tissues. LegH Prep contains this symbiotic soy leghemoglobin derived from *Pichia pastoris*.

[2] Retail Food Commodity Intakes: Mean Amounts of Retail Commodities per Individual, 2007-08. U.S. Department of Agriculture, Agricultural Research Service, Beltsville, MD and US Department of Agriculture, Economic Research Service, Washington, D.C.
http://www.ncaur.usda.gov/SP2UserFiles/Place/12355000/pdf/ficrcd/FICRCD_Intake_Tables_2007_08.pdf

Anderson et al. demonstrated that the non-symbiotic hemoglobin in soybeans was expressed in various plant tissues including stems, shoots, cotyledon, leaves, and root hair (Anderson, Jensen, Leewellyn, Dennis, & and Peacock, 1996). These soybean tissues are commonly consumed in the diet in the form of bean sprouts. Commercial production of soybean sprouts is a six (6) day process from imbibition to packaging for retail sale (Lim, 2014). Sprouted barley, which is widely used in the beverage industry (malted barley) and in the baking industry (malted barley flour), has been reported to express hemoglobin one (1) day after imbibition (Duff, Guy, Xianzhou, Durnin, & Hill, 1998). Non-symbiotic hemoglobins are expressed in the rice embryo and in the coleoptiles and seminal root of sprouted rice, which are consumed as part of the diet (Lira-Ruan, Ruiz-Kubli, & Arredondo-Peter, 2011).

Impossible Foods analyzed plant symbiotic leghemoglobins (soy, lupine), non-symbiotic plant hemoglobins (rice, corn, barley), and animal myoglobins (horse, tuna, pig) and confirmed the structural similarity (cf. Annex 1, GRASN). The three dimensional structure of soybean leghemoglobin is highly similar to the non-symbiotic hemoglobins of corn, rice, and barley as well as mammalian myoglobin.

Globin proteins bind the identical heme prosthetic group and are involved in binding or transporting oxygen. The oxygen binding mechanism of soy leghemoglobin is similar to that of animal muscle myoglobin.

**History of Safe Use**

The safety of soy protein is well established. Soybeans have been part of the human diet for more than 5000 years.

In the 2004/2005 marketing year, 229 million metric tons of soybeans were produced worldwide. Although the majority of the crop is used for animal feed, approximately 14% is used for human food in the form of traditional soyfoods, e.g. tofu, soymilk, natto, miso, bean sprouts, and as soy protein ingredients used to formulate food products as diverse as infant formula, dairy and meat alternatives, nutritional supplements and energy bars. (Golbitz & Jordan, 2006) Plant and animal hemoglobin proteins are widely consumed in the human diet where they represent a highly bioavailable source of dietary iron for human nutrition. Plant-derived hemoglobins are prevalent in our food system through malted grain products and sprouted beans (pulses).

**Regulatory Status**

The use of soy proteins is widely accepted in the United States. The US Food and Drug Administration has affirmed the safety of soy protein isolates for inclusion in many products and has approved a health claim for soy protein and the reduced risk of

coronary heart disease (21 CFR 101.82). In 2000, the US Department of Agriculture issued a ruling allowing soy protein to completely replace animal protein in the National School Lunch Program (Messina, 2006). The safety of soy protein in human food has been clearly established and affirmed by the two major food regulatory agencies in the US.

**Repeated Dose (28-Day) Toxicity Studies in CRL- Sprague-Dawley-CD® IGS Rats**

Two studies were conducted by Product Safety Laboratories (Dayton, NJ) consistent with OECD GLP Guidelines and with OECD Guidelines 407 and FDA'S Red Book for the initial study (43166) and with OECD Guideline 421 for the follow-up study (44856). Experimental and environmental conditions were the same including doses of LegH Prep (0, 250, 500, 750 mg soy leghemoglobin protein/kg bw/day), mode of administration (dietary admixture) and species and strain of rats.

In the initial study, although there were no consistent, dose-dependent, statistically significant treatment-related adverse effects reported, a NOAEL was not determined since potential perturbations on estrous cyclicity were reported at the low and high dose but not the middle dose. This lack of a dose-response suggested these effects were not treatment-related. Upon the advice of its scientific consults and as part of its products stewardship program, Impossible Foods secured the services of Dr. Karen Regan, an internationally recognized expert in reproductive toxicology, to review the results of this study and to assist in the design and execution of a follow up study, if deemed advisable. It was determined that OECD Guidelines for evaluating estrous activity (OECD 421) were most appropriate. The study was successfully executed. Dr. Regan independently completed her critical evaluation of the data and then reviewed her findings with the study pathologist who examined the tissues from the initial study. Dr. Regan and Product Safety Labs concluded that there were no test-substance related effects on reproductive macroscopic and microscopic parameters/observations, reproductive organ weights or estrous cyclicity in either study. The NOAEL was determined to be the highest dose tested, 750 mg soy leghemoglobin protein/kg bw/day. The Expert Panel concurs with these conclusions, there are no LegH Prep-related adverse effects on rat estrous cyclicity and the NOAEL is 750 mg soy leghemoglobin protein/kg bw/day.

**Allergenicity**

Soybeans are acknowledged as a commonly allergenic food. Soybeans contain several allergenic proteins (Taylor, Panda, Goodman, & Baumert, 2014). Soy leghemoglobin is not identified among the known soybean allergens. Moreover, soy leghemoglobin is expressed in the root nodules of the soy plant rather than the bean. The potential

allergenicity of soy leghemoglobin and the most abundant *Pichia pastoris* proteins (17 in total) present within LegH Prep can be assessed in the same manner as used for the novel proteins expressed in genetically engineered foods. The Codex Alimentarius Commission developed an assessment scheme for the analysis of potential allergenicity of proteins derived from biotechnology (Codex Alimentarius, 2003). This assessment is a multi-factorial approach which includes assessing the source of the protein for allergenicity, the sequence homology of the protein to known allergens, resistance to pepsin degradation and, if there is a high suspicion of allergenicity, specific serum screening. This analysis provides a likelihood of allergenic response by considering the totality of the evidence.

In its search of the biomedical literature, Impossible Foods did not find any publications implicating soy leghemoglobin or the 17 Pichia proteins in allergenicity or toxicity. Impossible Foods then enlisted Dr. Richard E. Goodman at the Food Allergy Resource and Research Program (FARRP) of the University of Nebraska to assess the potential allergenicity and toxicity of LegH Prep. Dr. Goodman conducted a comprehensive search of the biomedical literature to identify any published reports regarding possible allergenicity or toxicity associated with leghemoglobin and the Pichia proteins and any reports regarding health issues associated with human consumption. No negative reports were found.

Bioinformatics searches (amino acid sequence comparisons) were performed comparing the known sequence of soy leghemoglobin (GI:126241) and the 17 Pichai protein with known or putative allergens listed in the AllergenOnline.org, version 16 database using both FASTA full-length sequence alignments and search for 80 amino acid matches along the entire sequence looking for >35% identity. No significant alignments were found with soy leghemoglobin. Bioinformatics searches with the 17 most abundant residual *Pichia pastoris* proteins found in LegH Prep identified a few related protein sequences with sufficient similarity to exceed the Codex suggestion for potential cross reactivity (>35%). However, the sequence-related putative allergens identified in this search were not potent, common allergens, nor were any of them known to be allergenic when ingested. Moreover, comparison of the same *Pichia pastoris* proteins with all proteins in the NCBI Protein database identified far more significant matches to proteins found in commonly consumed fungi, including baker's yeast (*Saccharomyces* species). Thus, the bioinformatics searches did not reveal any similarities of concern between soy leghemoglobin and the 17 Pichia proteins and known allergens.

Dr. Goodman also tested the stability of LegH Prep in a model simulated gastric digestion study using the conditions recommended by Ofori-Anti et al. (Ofori-Anti, Ariyarathna, Chen, Lee, Pramod, & Goodman, 2008) to evaluate the pepsin stability of

novel proteins in genetically modified crops. A positive correlation exists between the stability of abundant dietary proteins in this assay and the likelihood that they will be identified as food allergens. LegH Prep was very rapidly digested by pepsin (90% in less than 2 min). No stable protein fragments were detected either. On the basis of resistance to pepsin digestion, LegH Prep shows a low potential risk of allergenicity or toxicity.

Dr. Goodman stated "My conclusion from this "weight of evidence" approach to dietary protein safety is that the LegH Prep is very unlikely to present a risk of dietary allergy or toxicity to consumers."

**Conclusions**

We, members of the Expert Panel, have individually and collectively critically evaluated the information and data summarized above and other information deemed pertinent to the safety of the proposed uses of Soy Leghemoglobin Protein Preparation (LegH Prep). We unanimously conclude that the proposed uses as a protein component in ground beef replacement (analogue) products of LegH Prep, produced consistent with current Good Manufacturing Practice (cGMP) and meeting the appropriate food grade specifications presented above, are safe and suitable.

We unanimously conclude that the proposed uses as a protein component in ground beef replacement (analogue) products of LegH Prep, produced consistent with current Good Manufacturing Practice (cGMP) and meeting the food grade specifications presented above, are Generally Recognized As Safe (GRAS) based on scientific procedures.

It is our unanimous opinion that other qualified experts would concur with these conclusions.

(b) (6)

09 August 2017

Professor Joseph F. Borzelleca, Ph.D.
Virginia Commonwealth University School of Medicine

Date

Michael W. Pariza, Ph.D.

Digitally signed by Michael W. Pariza, Ph.D.
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August 9, 2017

Professor Michael W. Pariza, Ph.D.
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August 11, 2017

Professor Steve Taylor, Ph.D.
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Date

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## 6.7 Basis for GRAS Conclusion

Impossible Foods convened a panel of independent scientists (Expert Panel), qualified by their scientific training and relevant national and international experience to evaluate the safety of food ingredients, to conduct an independent, critical and comprehensive evaluation of the available safety information on its soy leghemoglobin protein preparation (LegH Prep), and to determine if the proposed use of soy leghemoglobin as a protein component in ground beef analogue products would be Generally Recognized as Safe (GRAS) based on scientific procedures.

In June 2017, the Expert Panel, independently and collectively, critically evaluated the documents provided by Impossible Foods and other information deemed appropriate or necessary including information pertaining to the method of manufacture, product specifications, batch analyses, intended levels of use, exposure estimates, and available scientific information pertaining to the safety of soy leghemoglobin and other plant and animal hemoglobins.

The Expert Panel reviewed reports prepared by Dr. Richard E. Goodman (Food Allergy Resource and Research Program (FARRP) of the University of Nebraska) that assessed the potential allergenicity and toxicity of LegH Prep, consistent with the Codex recommendations. Dr. Goodman conducted a comprehensive search of the biomedical literature to identify any published reports regarding possible allergenicity or toxicity associated with soy leghemoglobin and *Pichia pastoris* proteins and any reports regarding health issues associated with human consumption of soy leghemoglobin and *Pichia pastoris* proteins. Dr. Goodman concluded that there is no published evidence that soy leghemoglobin or the *Pichia pastoris* proteins present in LegH Prep were associated with allergic reactions or toxicity.

Dr. Goodman conducted bioinformatics searches (amino acid sequence comparisons) that compared the known sequence of soy leghemoglobin (GI:126241), as well as the *Pichia* proteins that are greater than or equal to 1% of the total protein fraction in LegH Prep, with known or putative allergens. The bioinformatics searches did not reveal any similarities of concern between soy leghemoglobin or the *Pichia* proteins and known allergens. Bioinformatics searches also were conducted to determine if similarities existed between the amino acid sequence of soy leghemoglobin and the *Pichia* proteins and the sequences of known toxic proteins. The search results did not raise concerns of potential toxicity for soy leghemoglobin or the *Pichia* proteins present in LegH Prep.

Additionally, Dr. Goodman's laboratory tested the stability of LegH Prep in a model simulated gastric digestion study using the conditions recommended by Ofori-Anti et al. (Ofori-Anti, Ariyarathna, Chen, Lee, Pramod, & Goodman, 2008) to evaluate the pepsin stability of novel proteins in genetically modified crops. The soy leghemoglobin and the *Pichia pastoris* proteins present in the preparation were very rapidly digested by pepsin. On the basis of resistance to pepsin digestion, LegH Prep (which includes soy leghemoglobin, *Pichia* proteins as well as other components; *see* Table 1), shows a low potential risk of allergenicity or toxicity.

Impossible Foods commissioned a bacterial reverse mutation (Ames) test and an *in vitro* mammalian chromosomal aberration test using human lymphocytes to evaluate the genotoxic

potential of LegH Prep. These studies demonstrated that LegH Prep was neither mutagenic in bacterial cells nor clastogenic in human cells.

Impossible Foods commissioned a 28-day GLP feeding study in rats using the LegH Prep (containing soy leghemoglobin, *Pichia* proteins as well as other components; *see* Table 1) to determine the NOAEL for soy leghemoglobin with a max dose of 750 mg/kg/day soy leghemoglobin (43166). There were no clinically significant differences between groups in clinical observations, body weights, hematological parameters, clotting potential, or biochemical composition of the blood for both sexes. Therefore, the NOAEL for male and female rats was determined to be 750 mg/kg/day soy leghemoglobin. This represents a 112-fold safety factor above the 90$^{th}$ percentile EDI of 6.67 mg/kg/day soy leghemoglobin.

This weight of evidence approach to the safety assessment of soy leghemoglobin expressed in *Pichia pastoris* demonstrates that the LegH Prep (which contains soy leghemoglobin, *Pichia* proteins and other components; *see* Table 1), is highly unlikely to present a dietary safety risk to consumers.

Following its independent and collective evaluation of the available information, the Expert Panel unanimously concluded that the intended use of soy leghemoglobin protein preparation (LegH Prep) as an ingredient in ground beef analogue products, manufactured consistent with current Good Manufacture Practice (cGMP) and meeting the food grade specifications presented in this notification is generally recognized as safe based on scientific procedures.

## PART 7: LIST OF REFERENCES

Pursuant to 21 C.F.R. 170.255, the list of supporting data and information referenced in the GRAS notice is contained below.

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# Annex 1

The globin structural superfamily is a large, well studied family of globular proteins, present in all domains of life: archae, bacteria, and eukaryotes (PFAM PF00042). All members of the globin structural superfamily are thought to share a common ancestor (Punta et al. 2012). The globin structural fold is comprised of eight alpha helical segments and a heme co-factor, which coordinates binding and/or transfer of oxygen. Structural comparisons of animal myoglobin, plant leghemoglobin, and plant non-symbiotic hemoglobin monomers are shown in Figure 1A-H. The crystal structure for cow myoglobin does not exist, so we have included myoglobin structures from tuna, pig, and horse in this analysis. Based on their similarity to eachother (Figure 1F-H), we expect that they are highly similar to cow myoglobin. The crystal structures were superimposed over all backbone atoms using the Super algorithm in PyMOL (Delano, 2007) (Figure 1I-L) and the corresponding root mean square deviations (RMSDs) are shown in Table 1 . Comparison of proteins folds (Figure 1) and RMSD values (Table 1) illustrates that animal myoglobins, plant non-symbiotic hemoglobins, and plant leghemoglobins all adopt the same globin fold and are structurally very similar. Furthermore, animal myoglobins, plant non-symbiotic hemoglobins, and plant leghemoglobins all bind the identical heme prosthetic group, heme B (Figure 1M).

The minimum temperature of denaturation for soy leghemoglobin, determined by Impossible Foods using dynamic light scattering, is 64 degrees Celsius (Figure 2A). Dynamic light scattering measures the mean effective diameter (Stokes radius) of a protein as a function of temperature. Increased Stokes radius indicates protein denaturation and aggregation. Protein denaturation leads to dissociation of the protein polypeptide from the heme co-factor. The denaturation temperature for soy leghemoglobin is similar to equine myoglobin, which Impossible Foods determined to be 70 degrees Celsius using dynamic light scattering. Lysozyme was included as a control and displayed the expected denaturation temperature of 72 degrees Celsius. The denaturation temperature for bovine myoglobin is 74 degrees Celsius (Sepe et al. 2005). The USDA recommended cooking temperature for ground beef is 160 degrees Fahrenheit (71 degrees Celsius). Impossible Foods' meat analogue is cooked at a similar temperature. Therefore, both mammalian myoglobins and leghemoglobin are denatured when consumed in a cooked meat or meat analogue product, respectively.

Proteins within the globin family typically denature and dissociate from their heme co-factor at pH <4. For example, at pH 3.2, human myoglobin dissociates from its heme co-factor in 45 seconds (Konermann et al 1997). To monitor heme-binding of the leghemoglobin polypeptide as a function of pH, Impossible Foods monitored the absorption spectra of the Soret region (Figure 2B). At pH 7, the heme co-factor is bound to the folded leghemoglobin polypeptide, as indicated by the narrow Soret peak at ~415 nm. At pH 2, the heme co-factor has dissociated from the denatured polypeptide, as indicated by the broad Soret peak at ~380 nm. Therefore, even if consumed in a raw meat analogue product, leghemoglobin will denature and release the heme co-factor upon exposure to the low pH environment of gastric fluid.

Leghemoglobins, non-symbiotic hemoglobins, and myoglobins each contain the identical heme b co-factor (Figure 1M). Soybean leghemoglobin does not contain peptide sequences that are associated with allergenicity (Annex 8), denatures at 64 degrees Celsius (Figure 2A) and pH 2 (Figure 2B), and is completely digested by pepsin (Annex 10), leaving only the heme cofactor. Therefore, the health effects of ingesting soybean leghemoglobin should be equivalent to non-symbiotic plant hemoglobins and mammalian myoglobins, which are readily consumed in the diet.

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**Figure 1.** Plant hemoglobins and animal myoglobins adopt the same structural fold. Individual plant leghemoglobins (A-B), plant non-symbiotic hemoglobins (C-E), and animal myoglobins (F-H), are shown in ribbon representation colored in gray, heme porphyrin ring is shown in red stick representation, and iron in blue CPK representation. Superposition of individual proteins shows that the 3D structure of soybean leghemoglobin is highly similar leghemoglobins, non-symbiotic hemoglobins, and myoglobins from different species (I-L).

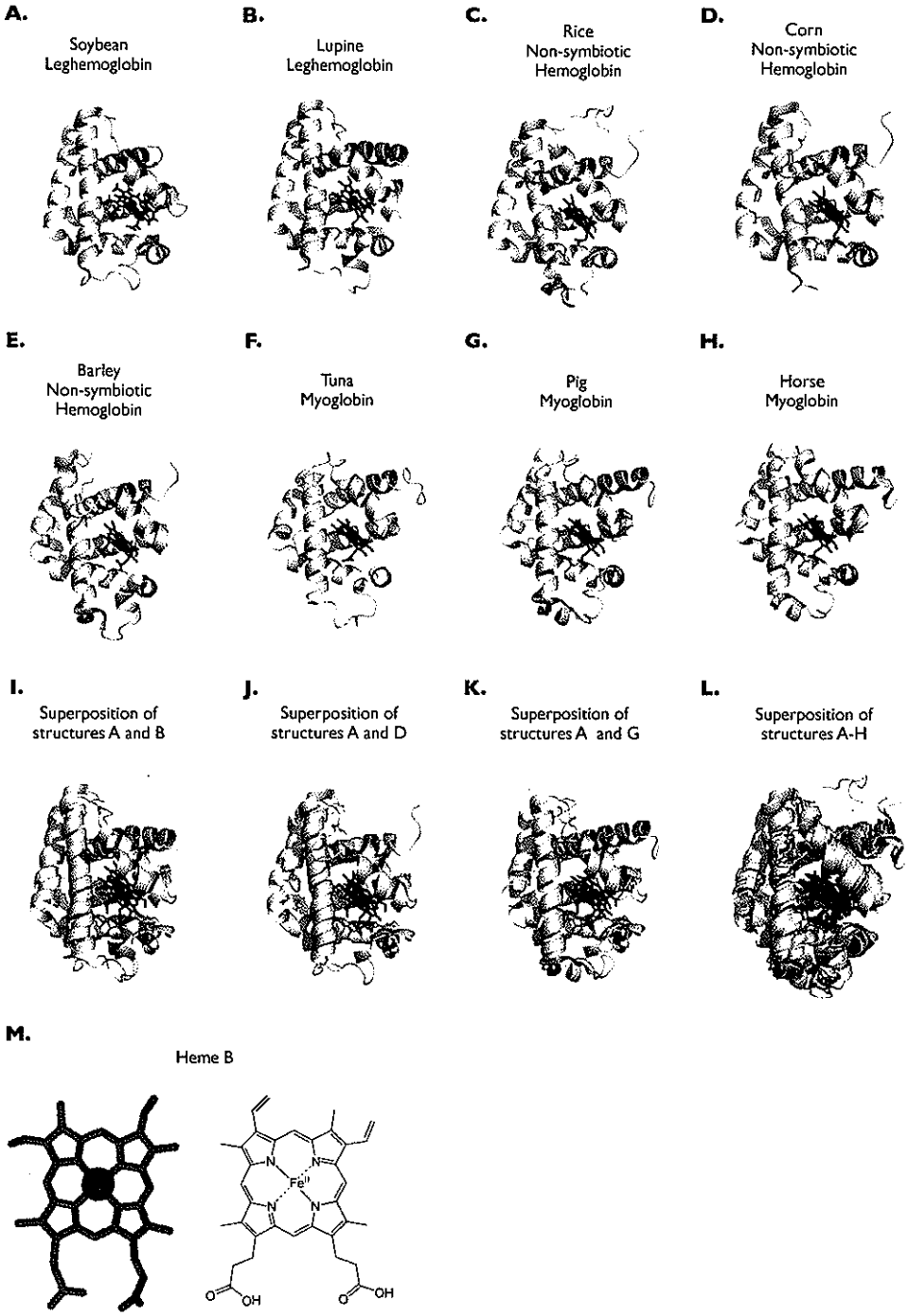
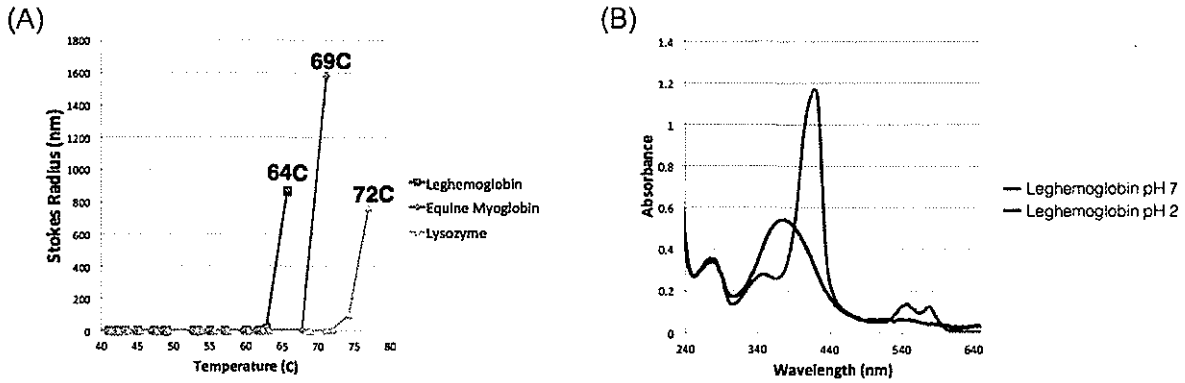


**Table 1.** Structural comparison between plant hemoglobins and animal myoglobins. Root-mean-square-deviation (RMSD) between all backbone atoms of superimposed X-ray crystallography protein structures (respective PDB codes are shown in parenthesis).

| Species | | RMSD (Å) |
|---|---|---|
| Soybean leghemoglobin (1BIN) | Horse myoglobin (1YMB) | 4.5 |
| Soybean leghemoglobin (1BIN) | Pig myoglobin (1PMB) | 4.4 |
| Soybean leghemoglobin (1BIN) | Tuna myoglobin (1MYT) | 3.6 |
| Soybean leghemoglobin (1BIN) | Barley non-symbiotic hemoglobin (2OIF) | 2.5 |
| Soybean leghemoglobin (1BIN) | Corn non-symbiotic hemoglobin (2R50) | 1.0 |
| Soybean leghemoglobin (1BIN) | Rice non-symbiotic hemoglobin (1D8U) | 1.0 |
| Soybean leghemoglobin (1BIN) | Lupine leghemoglobin (2GDM) | 0.8 |
| Soybean leghemoglobin (1BIN) | Soybean leghemoglobin (1FSL) | 0.5 |

**Figure 2.** Leghemoglobin sensitivity to temperature and pH. (A) Impossible Foods measured the melting temperature of leghemoglobin using dynamic light scattering. Equine myoglobin (Sigma, cat# M0360) and Lysozyme (Sigma, cat# L4919) were included as controls. (B) Impossible Foods monitored heme dissociation from leghemoglobin at low pH by measuring the absorption spectra of the Soret region.



# Annex 2

# Product Safety Labs

## SOY LEGHEMOGLOBIN PREPARATION: A 28-DAY DIETARY STUDY IN RATS

## PRODUCT IDENTIFICATION

Soy Leghemoglobin Preparation

## DATA REQUIREMENT

OECD Guidelines for Testing of Chemicals and Food Ingredients, Section 4 (Test No. 407): Health Effects, Repeated Dose 28-day Oral Toxicity Study in Rodents (2008)

US FDA Toxicological Principles for the Safety Assessment of Food Ingredients, Redbook 2000, IV.C. 4. a. (2007)

## STUDY NUMBER

43166

## PERFORMING LABORATORY

Product Safety Labs
2394 US Highway 130
Dayton, New Jersey 08810

## STUDY COMPLETION DATE

July 26, 2017

## STUDY DIRECTOR

Mithila Shitut, BVSc & AH, MS

## SPONSOR

Impossible Foods Inc.
525 Chesapeake Dr.
Redwood City, CA 94063

## GOOD LABORATORY PRACTICE COMPLIANCE STATEMENT

Soy Leghemoglobin Preparation

This study meets the requirements of US FDA GLP: 21 CFR Part 58, 1987 and OECD Principles of Good Laboratory Practice (as revised in 1997) published in ENV/MC/CHEM (98)17, OECD, Paris, 1998. Specific information related to the characterization of the test substance(s) as received and tested is the responsibility of the study sponsor (Section 3.B) with the following exception:

1) Chemistry analysis was not conducted in compliance with GLP regulations

Specific information related to the characterization of the test substance as received and tested is the responsibility of the study Sponsor (Section 3.A).

Study Director: (b) (6) Date: 7/26/17

Name of Signer: Mithila Shitut, BVSc & AH, MS

Name of Company: Product Safety Labs

Sponsor: (b) (6) Date: 7/26/17

Name of Signer: Rachel Fraser, PhD

Name of Company: Impossible Foods Inc.

Submitter (b) (6) Date: 7/26/17

Name of Signer: Rachel Fraser, PhD

Name of Company: Impossible Foods Inc.

## QUALITY ASSURANCE STATEMENT

The Product Safety Labs' Quality Assurance (QA) Unit has reviewed this final study report to assure the report accurately describes the methods and standard operating procedures, and that the reported results accurately reflect the raw data of the study.

QA Activities for This Study:

| QA Activity | Performed By | Date Conducted | Date Findings Reported To Study Director And Management |
|---|---|---|---|
| Protocol review | R. Krick; M. Zakrzewski | Sep 14, 2016; Nov 7 & 8, 2016 | Sep 14, 2016; Nov 8, 2016 |
| In-process inspection: *Study Schedule* | M. Zakrzewski | Sep 27, 2016 | Sep 27, 2016 |
| In-process inspection: *Diet Preparation and Sampling* | M. Zakrzewski | Sep 28, 2016 | Sep 28, 2016 |
| In-process inspection: *In-life and detailed observations* | M. Zakrzewski | Oct 19, 2016 | Oct 19, 2016 |
| In-process inspection: *Necropsy* | M. Zakrzewski | Oct 27, 2016 | Oct 27, 2016 |
| Raw data audit | M. Zakrzewski | Nov 7 & 8, 2016 | Nov 8, 2016 |
| Draft report review | M. Zakrzewski | Dec 16, 2016 | Dec 16, 2016 |

QA Statements for the chemical analysis, clinical pathology and histopathology phases of the study may be found in Appendices D, N, and T, respectively.

**Final report reviewed by:**

(b) (6)

Maryann Zakrzewski
Quality Assurance Auditor
Product Safety Labs

July 26, 2017
Date

## CERTIFICATION

We, the undersigned, declare that the methods, results and data contained in this report faithfully reflect the procedures used and raw data collected during the study.

(b) (6)

Mithila Shitut, BVSc & AH, MS
Study Director
Product Safety Labs

26 July 2017
Date

(b) (6)

Odete Mendes, DVM, PhD, DACVP, DABT
Director of Toxicology and Pathology
Product Safety Labs

26 July 2017
Date

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## STUDY INFORMATION

| | |
|---|---|
| Protocol No.: | P703.01 IMP |
| Test Substance(s): | Soy Leghemoglobin Preparation<br>Lot #: PP-PGM2-16-088-301 |
| Physical Descriptions: | Red/brown powder |
| Date Test Substance Received: | July 20, 2016 |
| PSL IDs: | 160720-5R |
| PSL Study Number: | 43166 |
| Sponsor: | Impossible Foods Inc.<br>525 Chesapeake Dr.<br>Redwood City, CA 94063 |
| Study Initiated-Completed: | September 21, 2016 – (see report cover page) |
| In-Life Study Initiated-Completed: | September 28 – October 28, 2016 |
| Notebook No.: | 16-43166: pages 1-466 |

## KEY PERSONNEL

Product Safety Labs:

| | |
|---|---|
| President: | Daniel J. Merkel, BS, MBA |
| Director of Toxicology and Pathology: | Odete Mendes, DVM, PhD, DACVP, DABT |
| Study Director: | Mithila Shitut, BVSc & AH, MS |
| Primary Scientist: | Colleen Wojenski, BS, LATG |
| Contributing Personnel: | Joshua Battaglia, BS<br>Aubrey Blue<br>Cynthia Bodnar<br>Lisa Broske-Godin, BS, RLATG<br>Stephanie DeCarlo, BS<br>Janet Dell John, BA, RLATG<br>Kathleen Quinn, BS<br>Matthew Notta, BS<br>Mark Schooley<br>Matthew Sorber, BS<br>Shannon Stevens, BS, CVT |
| Director of Quality Assurance: | Rhonda S. Krick, BS |
| Technical Writing Supervisor: | Celeste Dunn, AS |

The following individual was responsible for the ophthalmology evaluations:

| | |
|---|---|
| Ophthalmologist: | Kristina R. Vygantas, DVM, DACVO<br>319 Perrineville Road<br>Robbinsville, NJ 08691 |

The following facility was responsible for the conduct and reporting of analysis of the neat test substance and all dietary preparations:

| | |
|---|---|
| Test Substance and Dietary Analysis: | Impossible Foods Inc<br>525 Chesapeake Dr.<br>Redwood City, CA 94063 |
| Principal Investigator: | Rachel Fraser, PhD |

## KEY PERSONNEL (cont.)

The following were responsible for the clinical pathology analysis:

| | |
|---|---|
| Clinical chemistry, hematology, coagulation and urinalysis: | DuPont Haskell Global Centers for Health and Environmental Sciences<br>P.O. Box 30, Elkton Road<br>Newark, Delaware 19714 |
| Principal Investigator: | Denise Hoban, BA, MLT, ASCP |
| Clinical pathology evaluations: | Product Safety Labs<br>2394 US Highway 130<br>Dayton, New Jersey 08810 |
| Principal Investigator: | Odete Mendes, DVM, PhD, DACVP, DABT |

The following were responsible for the histological slide preparation and pathology evaluations:

| | |
|---|---|
| Histological slides preparation: | HSRL<br>Histo-Scientific Research Laboratories<br>5930 Main Street<br>Mount Jackson, VA 22842 |
| Histology Principal Investigator: | Craig Zook |
| Histological slide evaluation by: | HSRL<br>Histo-Scientific Research Laboratories<br>5930 Main Street<br>Mount Jackson, VA 22842 |
| Pathology Principal Investigator: | Daniel G. Branstetter, DVM, PhD, DACVP |
| Histopathology Peer Review | Regan Path/Tox Services, Inc,<br>1457 Township Road 853<br>Ashland, OH 44805<br>P.I. (pathology): Karen Regan, DVM, DABT, DACVP |

## 1. OBJECTIVE

The objective of this study was to evaluate the potential subchronic toxicity of Soy Leghemoglobin Preparation in male and female rats likely to arise from continuous exposure to the test substance in the diet for at least 28 days. A no-observed-adverse-effect-level (NOAEL) was also sought for each sex.

## 2. SUMMARY

A 28-day dietary toxicity study was conducted in Crl:SD CD® IGS rats to determine the potential of Soy Leghemoglobin Preparation to produce toxicity. Eighty (80) healthy rats (40 males and 40 females) were selected for the test and equally distributed into four groups (10/sex/group). Dietary test substance levels 512, 1024 and 1536 mg/kg/day corresponded to 250 mg/kg/day (Group 2), and 500 mg/kg/day (Group 3), and 750 mg/kg/day (Group 4) of active ingredient, as well as a Basal diet control (Group 1), were evaluated.

The neat test substance was measured to be stable under the conditions of storage over the course of this study. Stability of test substance in the diet was evaluated by analyzing the low, medium, and high dietary concentrations of the test substance on Days 0, 4, 7, and 10 following preparation. Test substance homogeneity in the diet was assessed at the beginning of the study by evaluating the low, medium, and high dietary levels in the top, middle, and bottom strata of the diet preparations. At the beginning, middle, and end of the study, selected diet preparation samples were analyzed to verify test substance concentration in the diets over the course of the study. Results from the homogeneity, stability, and concentration analyses of the test diets indicate that Soy Leghemoglobin Preparation was homogeneously distributed within an acceptable margin of variability, stable in the dietary matrix, and was considered to have met target concentrations in the diet for all intake levels.

The animals were examined by focal illumination and indirect ophthalmoscopy prior to initiation and again at the end of the study (Day 23), observed for viability, signs of gross toxicity and behavioral changes at least once daily during the study and weekly for a battery of detailed clinical observations. Body weight and food consumption measurements were collected throughout the study and used to calculate the mean overall daily intake of test substance. Urine and blood samples were collected on Day 22 from all study animals for urinalysis, hematology and clinical chemistry determinations. Gross necropsies and histological evaluation of selected organs and tissues were performed on all study animals.

Administered doses of 512, 1024 and 1536 mg/kg/day of test substance correspond to 250, 500 and 750 mg/kg/day of the active, respectively. The mean overall (Days 0-28) daily intake of the test substance in male rats fed dietary concentrations of 512, 1024 and 1536 mg/kg/day was 478.9, 954.7 and 1438.2 mg/kg/day respectivelly. For the same dietary concentrations, the mean overall (Days 0-28) daily intake in female rats was 497.8, 983.4, and 1470.4 mg/kg/day of test substance, respectively. The animals are considered to have received close to the targeted dose levels.

There were no mortalities, clinical observations, ophthalmology, body weight, body weight gain, food consumption, or food efficiency changes attributable to Soy Leghemoglobin Preparation administration.

There were no test substance related changes in hematology, serum chemistry or urinalysis parameters for males or females rats. Changes in coagulation paramentes were limited to a non dose-dependent increase in activated partial tromboplastin time observed in Group 3 and 4 males,

that due to its very slight magnitude and lack of correlating pathological or clinical finding this change is considered non adverse.

There were no microscopic or macroscopic findings related to the administration of the test substance, Soy Leghemoglobin Preparation, in male or female rats. There were no test substance-related changes in absolute or relative organ weight values in male rats treated with Soy Leghemoglobin Preparation. Decreases in uterine weight were observed in Group 2-4 female rats. These decreases did not correlate with adverse histopathological findings and are therefore interpreted to be non-adverse.

Under the conditions of the study and based on the toxicological endpoints evaluated, the no-adverse-effect level (NOAEL) for administration of Soy Leghemoglobin Preparation in the diet was determined to be 1536 mg/kg/day, which corresponds to 750 mg/kg/day of the active ingredient Soy Leghemoglobin for Sprague Dawley rats.

## 3. TEST SUBSTANCE

### A. Source

The test substance was provided by the Sponsor.

### B. Identification

The test substance was received on July 20, 2016, and identified using the following information provided by the Sponsor and Product Safety Labs (PSL) identification number.

Test Substance: Soy Leghemoglobin Preparation
PSL ID: 160720-5R
Lot #: PP-PGM2-16-088-301
Physical Description: Red/brown powder
Composition: Soy Leghemoglobin 48.82%
Storage Conditions: Frozen
Expiration Date: Not Applicable

Documentation of the methods of synthesis, fabrication, or derivation of the test substance is retained by the Sponsor.

### C. Analysis

The test substance, as received, was expected to be stable for the duration of the study. Stability of the neat test substance in the dietary matrix and that of the concentration of the test substance in the test diets was determined as part of this study.

### D. Hazards

Appropriate routine safety precautions were exercised in the handling of the test and control substances.

## 4. GENERAL TEST SYSTEM PARAMETERS

### A. Animal Requirements

4.A.1 Number of Animals: 80

4.A.2 Number of Groups: 4 (3 dietary levels per sex + 1 control group per sex)

4.A.3 Number of Animals per Group: 20 (10 male, 10 female)

4.A.4 Sex: Male and female; females will be nulliparous and non-pregnant.

4.A.5 Species/Strain: CRL Sprague-Dawley CD® IGS rats

4.A.6 Age/Weight: Seven to eight weeks at initiation; the weight variation did not exceed ± 20% of the mean weight for each sex.

4.A.7 Supplier: Charles River Laboratories, Inc. Rats were shipped in filtered cartons by airfreight and/or truck.

On September 22, 2016, 88 CRL Sprague-Dawley CD® IGS rats (44 males and 44 females) arrived from Charles River Laboratories, Inc., with an assigned birth date of August 6, 2016. The rats were designated by the supplier to be 6-7 weeks of age upon arrival.

### B. Test System Justification

The Sprague-Dawley® rat was the system of choice because, historically, it has been a preferred and commonly used species for dietary toxicity tests. The current state of scientific knowledge does not provide acceptable alternatives to the use of live animals to accomplish the objective of this study.

### C. Animal Husbandry

4.C.1 Housing

The animals were group housed in suspended stainless steel caging, which conforms to the size recommendations in the most recent *Guide for the Care and Use of Laboratory Animals* (Natl. Res. Council, 2011). Litter paper was placed beneath the cages and was changed at least three times per week. The animal room had a 12-hour light/dark cycle and was kept clean and vermin free.

4.C.2 Animal Room Temperature and Relative Humidity Ranges

The animal room was temperature and humidity were 19-23°C and 39-62%, respectively.

4.C.3 Acclimation

The animals were conditioned to the housing facilities for six days prior to testing. Body weights and clinical observations were recorded at least two times prior to study start.

4.C.4 Feed

2016 certified Envigo Teklad Global Rodent Diet® was stored in a dedicated temperature and humidity monitored feed storage site and was available *ad libitum* during acclimation. Test diets were prepared as described in Section 6.B using 2016 certified Envigo Teklad Global Rodent Diet® and were available *ad libitum* during the study.

4.C.5 Water

Filtered tap water was available *ad libitum*. Water analysis was conducted by Precision Analytical Services, Inc., Toms River, NJ and South Brunswick Municipal Water Supply, South Brunswick, NJ.

4.C.6 Contaminants

There were no known contaminants reasonably expected to be found in the food or water that would interfere with the results of this study. Routine analysis consisting of each lot of feed used in this study was received from Envigo Teklad, Madison, WI. Water analysis was conducted periodically and the records are kept on file at Product Safety Labs. The date(s) of the most recent analyses are reported in Appendix B.

4.C.7 Viral Screen

The animals used in this study were considered to be pathogen-free as received from the vendor (Section 4.A.). Rodent-health surveillance for study animals was monitored by designating three rats as "sentinels" for the study room (Animals 257M 10.28.16, 268M 10.28.16, and 316F 10.28.16). Sentinels were housed under the conditions of the study, on racks alongside study animals, for the duration of the study (September 28 – October 28, 2016). These animals were not a part of the study, and were clearly marked as such. A serum sample was collected from each sentinel rat for screening of common rat pathogens (Rat Parvovirus, Toolan's H-1 Virus, Kilham Rat Virus, Rat Minute Virus, Parvovirus NS-1, Rat Coronavirus, Rat Theilovirus, and Pneumocystis carinii). The serum samples were sent on ice to IDEXX BioResearch (Columbia, MO) for evaluation. Serological pathogen screening results for the sentinels 257M 10.28.16, 268M 10.28.16, and 316F 10.28.16, corresponding with this study, are reported in Appendix B. The sentinel samples were negative for all pathogens evaluated and therefore, the study animals were considered to be healthy and reasonably free of common rat pathogens.

### D. Identification

4.D.1 Cage

Each cage was identified by a cage card indicating the study number, dose level, group assignment, individual animal identification and sex of the animal.

4.D.2 Animal

Each animal was given a sequential number in addition to being uniquely identified with a Monel® self-piercing stainless steel ear tag.

## 5. EXPERIMENTAL DESIGN

### A. Route of Administration

The test substance was administered in the diet.

### B. Justification of Route of Administration

The dietary route of administration was used because it was recommended in the referenced guidelines (Section 8.C.), as human exposure may occur via this route.

### C. Control of Bias

Animals were randomly assigned to test groups, stratified by body weight.

### D. Dose Levels

Ten male and ten female test animals were randomly assigned to each of the following test groups:

| Group | No. Animals/ Group M/F | Dietary Dose Level/ Target Exposure of Active Ingredient (mg/kg/day) | Dietary Dose Level/ Target Exposure of Test Substance [a] (mg/kg/day) |
|---|---|---|---|
| 1 | 10/10 | 0 | 0 |
| 2 | 10/10 | 250 | 512 |
| 3 | 10/10 | 500 | 1024 |
| 4 | 10/10 | 750 | 1536 |

[a] Based on 48.82% active ingredient (AI, Soy Leghemoglobin) of Soy Leghemoglobin Preparationlot # PP-PGM2-16-088-301

### E. Justification of Dose Level Selection

The Sponsor, in consultation with the Study Director, and based on a 14-day palatability/toxicity study (PSL, 2016) selected target dietary dose levels of 512, 1024 and 1536 mg/kg/day that correspond to target dose levels of 250, 500 and 750 mg/kg/day of the active ingredient, Soy leghemoglobin. To maintain target dietary dose levels throughout the study, concentrations in the test diets were calculated based on the most recent group body weight and food consumption data. Alternatively, historical control values, relevant to the age and weight of the rats at corresponding intervals were used. Diets for males and females at each dietary dose level were made separately each week. A NOAEL was expected to be achieved for this study.

## 6. GENERAL PROCEDURES

### A. Selection of Animals

After acclimating to the laboratory environment for 6 days, the rats were examined for general health and weighed. Only those rats free of clinical signs of disease or injury and having a body weight range within ±20% of the mean were selected for test. Eighty (80) healthy rats (40 males; 40 females) were selected for test. The animals weighed 227-250 grams (males) and 156-198 grams (females) and were approximately 7-8 weeks of age at initiation of dosing. The rats that were used on test were randomly distributed, stratified by body weight, among the dose and control groups on the day of study start.

### B. Diet Preparation and Sampling

6.B.1 Diet Preparation

The test substance was processed as needed to decrease particle size using a grinder and then added to 2016 Envigo Teklad Global Rodent Diet® and thoroughly mixed in a high-speed mixer. Control diet was mixed under the same conditions as the diets prepared with the test substance. All diets were kept frozen following preparation, unless presented to the test animals on the same day as diet preparation. All diets were prepared approximately weekly.

6.B.2 Diet Presentation

The control and test diets were presented to their respective groups on Day 0 of the study. The diets were replaced concurrently with food consumption measurements on Days 3, 7, 10, 14, 17, 21 and 24. Additional diet may be provided as needed throughout the study to insure *ad libitum* feeding. Animals were exposed to the test diets for at least 28 days.

6.B.3 Sampling

The neat test substance and selected prepared diets (at each concentration) were sampled in duplicate.

6.B.4 Stability of Test Substance

At the initial, middle, and final diet preparation, a sample of the test substance (neat) was retained for stability. Analytical results of the initial and final stability samples were used to establish the stability of the test substance under normal laboratory conditions for the duration of the study.

6.B.5 Stability in Dietary Matrix

During the first week of the study, samples to verify the stability of the test and control substance in the dietary matrix were prepared. Samples were prepared in standard feed jars with followers and retaining rings and were stored at ambient temperature in the animal room. Samples from each dietary concentration were collected at the first presentation of the diet and after 4, 7, and 10 days and frozen until analyzed.

6.B.6 Homogeneity

Samples to evaluate homogeneity of the test and control substance distribution were collected from the initial diet preparation. Samples were taken from approximately the top, middle and bottom of the diet mixer. Basal diet control samples were collected from the middle of the mixer only. Chemical analysis verified the diets as homogeneous and of accurate concentration throughout the study.

6.B.7 Concentration Verification

Samples were collected from representative animal diets of the initial (as part of the homogeneity assessment), middle and final diet preparations during which time samples were retained and stored frozen. Samples were analyzed to verify the concentration of the test diets.

6.B.8 Sample Preservation

Upon sampling, diet preparations and neat test substance were stored frozen. Samples were considered stable from the point at which they were frozen.

6.B.9 Sample Analysis

A single duplicate of the frozen diet samples described above was sent to Impossible Foods for analysis of diet preparation and neat test substance samples. A signed, analytical report was provided to the Study Director. This report included the methodology, pertinent measurements, study results, and tabulated results. Upon completion of the report, all raw data was transferred to the Study Director to be

incorporated into the main study report. Any remaining sample material was retained at Product Safety Labs until issuance of the final report.

### C. Ophthalmologic Evaluations

During the acclimation period, the eyes of all rats being considered for study were examined by focal illumination, indirect ophthalmoscopy and, when indicated, slit-lamp microscopy. Mydriatic eye drops were administered prior to ophthalmoscopy and the eyes were examined in subdued light. Subdued light was maintained in the animal room. These procedures were repeated on all test animals prior to test termination on Day 23.

### D. Clinical Observations

All animals were observed at least twice daily for viability. Cage-side observations of all animals were performed daily during the study. All findings were recorded.

On Day 0, prior to the first treatment with the test substance, and weekly thereafter, a detailed observation was conducted while handling the animal, generally on days that the animals were weighed and food consumption measurements were taken. Potential signs noted included, but were not limited to: changes in skin, fur, eyes, and mucous membranes, occurrence of secretions and excretions and autonomic activity (e.g., lacrimation, piloerection, pupil size, unusual respiratory pattern). Likewise, changes in gait, posture and response to handling as well as the presence of clonic or tonic movements, stereotypies (e.g., excessive grooming, repetitive circling), or bizarre behavior (e.g., self-mutilation, walking backwards) were also recorded. The date and clock time of all observations and/or mortality checks were recorded.

### E. Body Weight and Body Weight Gain

Individual body weights were recorded twice during acclimation. Test animals were weighed on Day 0 (prior to study start) and weekly thereafter (intervals of 7 days ± 1). The animals were also weighed prior to sacrifice in order to calculate organ-to-body weight ratios (Amendment 1). Body weight gain was calculated for selected intervals and for the study overall.

### F. Food Consumption, Food Efficiency, and Dietary Intake of Soy Leghemoglobin Preparation

Individual food consumption was measured and recorded on Days 3, 7, 10, 14, 17, 21, 24 and at the end of the study. Food efficiency and dietary intake of the test substance (mg/kg/day) was also calculated and reported.

### G. Clinical Pathology

Clinical pathology was performed on all animals for blood chemistry and hematology of the terminal sacrifice animals at the end of the dosing phase of the study. The animals were fasted overnight prior to blood collection. Blood samples for hematology (except coagulation samples) and clinical chemistry were collected via sublingual bleeding under isoflurane anesthesia during Week 4 of the test period. Approximately 500 µL of blood was collected in a pre-calibrated tube containing $K_2EDTA$ for hematology assessments. The whole blood samples were stored under refrigeration and shipped on cold packs. Approximately 1000 µL of blood was collected into a tube containing no preservative for clinical chemistry assessments. These samples were centrifuged in a refrigerated centrifuge and the serum was transferred to a labeled tube. Serum samples were stored in a -80°C freezer and shipped frozen on dry ice. All samples were shipped to DuPont Haskell Global Centers for Health and Environmental Sciences.

The day before collection of samples for the clinical pathology evaluation, the animals were placed in metabolism cages. Animals were fasted after 3 pm (at least 15 hours prior to) and urine was collected from each animal. Urine samples were stored under refrigeration and shipped on wet ice to DuPont Haskell Global Centers for Health and Environmental Sciences.

Blood samples used to determine the prothrombin time and activated partial thromboplastin time (coagulation) were collected via the inferior vena cava under isoflurane anesthesia at terminal sacrifice. Approximately 1.8 mL of blood was collected in a pre-calibrated tube containing 3.2% sodium citrate. These samples were centrifuged in a refrigerated centrifuge and the plasma was transferred to labeled tubes. Plasma samples were stored in a -80° C freezer and shipped frozen in dry ice to DuPont Haskell Global Centers for Health and Environmental Sciences. In addition, a second blood sample was retained during the exsanguination procedure for future possible evaluation.

All blood samples were evaluated for quality by visual examination.

6.G.1 Hematology included:

erythrocyte count (RBC)
hemoglobin concentration (HGB)
hematocrit (HCT)
mean corpuscular volume (MCV)
mean corpuscular hemoglobin (MCH)
red cell distribution width (RDW)
absolute reticulocyte count (ARET)
platelet count (PLT)
total white blood cell (WBC) and differential leukocyte count
Mean corpuscular hemoglobin concentration (MCHC) was calculated.

In addition, separate, blood smears, stained with New Methylene Blue or Wright-Giemsa stain, were prepared from each animal undergoing hematological evaluation, but were not needed for examination.

6.G.2 Coagulation included:

prothrombin time (PT)
activated partial thromboplastin time (APTT)

6.G.3 Clinical chemistry included:

serum aspartate aminotransferase (AST)
serum alanine aminotransferase (ALT)
sorbitol dehydrogenase (SDH)
alkaline phosphatase (ALKP)
total bilirubin (BILI)
urea nitrogen (BUN)
blood creatinine (CREA)
total cholesterol (CHOL)
triglycerides (TRIG)
fasting glucose (GLUC)
total serum protein (TP)
albumin (ALB)
globulin (GLOB)
calcium (CALC)
inorganic phosphorus (IPHS)
sodium (NA)
potassium (K)
chloride (CL)

6.G.4 Urinalysis included:

quality (QUAL)
pH
ketone (KET)
color (COL)
glucose (UGLC)
bilirubin (UBIL)
clarity (CLAR)
specific gravity (SG)
blood (BLD)
volume (UVOL)
protein (UMTP)
urobilinogen (URO)
microscopic urine sediment examination

Any remaining serum samples were maintained frozen at approximately -80°C and discarded upon approval of the Sponsor at finalization.

## H. Terminal Sacrifice and Histopathology

### 6.H.1 Scheduled Sacrifice

At terminal sacrifice, all survivors were euthanized by exsanguination from the abdominal aorta under isoflurane anesthesia. All animals in the study were subjected to a gross necropsy, which included examination of the external surface of the body, all orifices, musculoskeletal system, and the cranial, thoracic, abdominal, and pelvic cavities, with their associated organs and tissues. All gross lesions were recorded. The following tissues were weighed wet as soon as possible after dissection to avoid drying:

| | | |
|---|---|---|
| adrenals (combined) | kidneys (combined) | testes (combined) |
| brain | liver | thymus |
| epididymides (combined) | ovaries with oviducts (combined) | uterus |
| heart | spleen | |

The following organs and tissues from all animals were preserved in 10% neutral buffered formalin for possible future histopathological examination:

| | | |
|---|---|---|
| accessory genital organs (prostate and seminal vesicles) | ileum with Peyer's patches | rectum |
| adrenals | jejunum | salivary glands (sublingual submandibular, and parotid) |
| all gross lesions | kidneys | skeletal muscle |
| aorta | larynx | skin |
| bone (femur) | liver | spinal cord – 3 levels: cervical, mid-thoracic, and lumbar |
| bone marrow (from femur & sternum) | lungs | spleen |
| brain – 3 sections including medulla/pons, cerebellar, and cerebral cortex | lymph node mandibular | sternum |
| cecum | lymph node mesenteric | stomach |
| cervix | mammary gland | thymus |
| colon | nasal turbinates | thyroid |
| duodenum | nose | trachea |
| esophagus | ovaries | urinary bladder |
| Harderian gland | oviducts | uterus |
| heart | pancreas | vagina |
| | parathyroid | |
| | peripheral nerve (sciatic) | |
| | pharynx | |
| | pituitary gland | |

The following organs and tissues from all animals were preserved in modified Davidson's fixative and then stored in ethanol for possible future histopathological examination:

| | |
|---|---|
| eyes | optic nerve |
| epididymides | testes |

Additional tissues were preserved if indicated by signs of toxicity or target organ involvement.

6.H.2 Histopathology

Histological examination was performed on the preserved organs and tissues of the animals from both the control and high dose groups (Groups 1 and 4, respectively). The fixed tissues were trimmed, processed, embedded in paraffin, sectioned with a microtome, placed on glass microscope slides, stained with hematoxylin and eosin (HE) and examined by light microscopy. Additional special stains can be added based on HE evaluation at the discretion of the study pathologist in consultation with the study director and sponsor. Slide preparation and histological assessment, by a board-certified veterinary pathologist, was performed at Histo-Scientific Research Laboratories (HSRL).

6.H.3 Histopathology Peer Review

A histopathology peer review of female reproductive organs was performed for all female rats (Ammendment 3). The peer review pathologist was Karen Regan, DVM, DABT, DACVP form Regan Path/Tox Services, Inc, 1457 Township Road 853, Ashland, OH 44805. A peer review statement will be inserted in Appendix U.

## 7. STATISTICAL ANALYSIS

Product Safety Labs performed statistical analysis of all data collected during the in-life phase of the study as well as organ weight data. DuPont Haskell Global Centers for Health and Environmental Services provided analysis of clinical pathology results to Product Safety Labs. The use of the word "significant" or "significantly" indicates a statistically significant difference between the control and the experimental groups. Significance was judged at a probability value of $p<0.05$. Male and female rats were evaluated separately.

### A. Statistical Methods (In-Life and Organ Weight Data)

Mean and standard deviations were calculated for all quantitative data. If warranted by sufficient group sizes, data within groups were evaluated for homogeneity of variances and normality by Bartlett's test (Bartlett, 1937). Where Bartlett's test indicated homogeneous variances, treated and control groups were compared using a one-way analysis of variance (ANOVA). When one-way analysis of variance was significant, a comparison of the treated groups to control by Dunnett's test (Dunnett, 1964, 1980) for multiple comparisons was performed. Where variances were considered significantly different by Bartlett's test, groups were compared using a non-parametric method (Kruskal-Wallis non-parametric analysis of variance; Kruskal and Wallis, 1952). When non-parametric analysis of variance was significant, comparison of treated groups to control was performed using Dunn's test (Dunn, 1964). Statistical analysis was performed on all quantitative data for in-life and organ weight parameters using Provantis® version 9, Tables and Statistics, Instem LSS, Staffordshire UK.

### B. Statistical Methods (Clinical Pathology)

Significance was judged at a probability value of $p < 0.05$. Males and females were analyzed separately (Provantis™ version 8, Tables and Statistics, Instem LSS, Staffordshire UK).

| | | Method of Statistical Analysis | |
|---|---|---|---|
| Parameter | Preliminary Test | If preliminary test is not significant | If preliminary test is significant |
| Clinical Pathology[a] | Levene's test for homogeneity and Shapiro-Wilk test for normality | One-way analysis of variance followed with Dunnett's test | Transforms of the data to achieve normality and variance homogeneity were used. The order of transforms attempted was log, square-root, and rank-order. If the log and square-root transforms failed, the rank-order was used. |

[a] When an individual observation is recorded as being less than a certain value, calculations are performed on half the recorded value. For example, if bilirubin is reported as <0.1, 0.05 is used for any calculations performed with that bilirubin data. When an individual observation is recorded as being greater than a certain value, calculations are performed on the recorded value. For example, if specific gravity was reported as >1.100, 1.100 is used for any calculation performed with that specific gravity data.

## 8. STUDY CONDUCT

### A. Laboratory

| | |
|---|---|
| In-life portion | Product Safety Labs<br>2394 US Highway 130<br>Dayton, NJ 08810 |
| Ophthalmology evaluation | Kristina R. Vygantas, DVM, DACVO<br>319 Perrineville Rd.<br>Robbinsville, NJ 08691 |
| Clinical chemistry, hematology, coagulation, and urinalysis | Dupont Haskell Global Centers for Health and Environmental Sciences<br>P.O. Box 30<br>Elkton Road<br>Newark, DE 19714<br>P.I.: Denise Hoban, BA, MLT, ASCP |
| Clinical pathology evaluation | Product Safety Labs<br>2394 US Highway 130<br>Dayton, NJ 08810<br>P.I.: Odete Mendes, DVM, PhD, DACVP, DABT |
| Test substance and dietary analysis | Impossible Foods Inc<br>525 Chesapeake Dr.<br>Redwood City, CA 94063<br>P.I.: Pavel Aronov, PhD |
| Histological slide preparation | Histo-Scientific Research Laboratories (HSRL)<br>5930 Main Street<br>Mount Jackson, VA 22842<br>P.I. (histology): Craig Zook |

| | |
|---|---|
| Histological slide evaluation | Histo-Scientific Research Laboratories (HSRL)<br>5930 Main Street<br>Mount Jackson, VA 22842<br>P.I. (pathology): Daniel G. Branstetter, DVM, PhD, DACVP |
| Histopathology Peer Review | Regan Path/Tox Services, Inc,<br>1457 Township Road 853<br>Ashland, OH 44805<br>P.I. (pathology): Karen Regan, DVM, DABT, DACVP |

### B. GLP Compliance

This study was conducted in compliance with the following regulations:

- U.S. FDA GLP: 21 CFR Part 58, 1987

Which is compatible with:

- OECD Principles of Good Laboratory Practice (as revised in 1997) published in ENV/MC/CHEM (98)17, OECD, Paris, 1998.

Clinical pathology assessment was conducted in compliance with U.S. FDA GLP: 21 CFR Part 58, 1987 which is compatible with OECD Good Laboratory Practices.

Analysis of the neat test substance and test substance in the dietary matrix, for homogeneity, stability, and dose concentration verification, were performed in a non-GLP certified facility.

### C. Test Procedure Guidelines

This study design was based on the following guidelines:

- OECD Guidelines for Testing of Chemicals and Food Ingredients, Section 4 (Test No. 407): Health Effects, *Repeated Dose 28-day Oral Toxicity Study in Rodents* (2008).

- US FDA Toxicological Principles for the Safety Assessment of Food Ingredients, Redbook 2000, IV.C. 4. a. (2007).

## 9. FINAL REPORT AND RECORDS TO BE MAINTAINED

The original, signed final report was sent to the Sponsor. A copy of the signed report, together with the protocol and all raw data generated at Product Safety Labs, will be maintained in the Product Safety Labs Archives. PSL will maintain these records for a period of at least five years. After this time, the Sponsor of the study will be offered the opportunity to take possession of the records or request continued archiving by PSL.

The following records are maintained:

**A.** Information on test substance includes but is not limited to the following:

| | |
|---|---|
| Storage | Dietary analysis |
| Usage | Test substance analysis |
| Disposition | |

**B.** Information on animals includes but is not limited to the following:

| | |
|---|---|
| Receipt, date of birth | Clinical observations |
| Initial health assessment | Histopathology data |
| Dosing | Individual necropsy records |
| Body weights | Organ weights |
| Food consumption | Ophthalmologic evaluations |

Hematology, clinical chemistry, coagulation, urinalysis data

All other records that would demonstrate adherence to the protocol.

Raw data related to hematology and clinical chemistry evaluations will be maintained by Product Safety Labs and/or DuPont Haskell Global Centers for Health and Environmental Sciences, Newark, DE. Prepared slides and pathology data will be maintained by Product Safety Labs and/or by HSRL, 5930 Main Street, Mount Jackson, VA, 22842. Test substance and dietary analysis data will be maintained by Impossible Foods Inc. 525 Chesapeake Dr. Redwood City, CA 94063.

## 10. PROTOCOL AND PROTOCOL AMENDMENTS

See Appendix A for the Protocol and Protocol Amendments.

## 11. RESULTS

### A. Test Substance and Diet Analysis (Table 1A-D, Appendix D)

The test substance was expected to be stable under the conditions of storage over the course of this study.

11.A.1 Analysis of Soy Leghemoglobin Preparation Neat Test Substance

Soy Leghemoglobin Preparation was found to be stable under the conditions of storage over the course of this study. Results of the stability analysis of Soy Leghemoglobin Preparation from Day 0 to Day 21, found a change of -4.30%, for an overall test substance stability of 95.70% over the course of the study, within the range of analytical variance of measured test substance.

11.A.2 Stability

Dietary stability samples collected after 10 days of storage were compared to the initial samples for overall in-room stability of the test substance in the dietary matrix. All dietary mixtures were found to be stable within an acceptable degree of variation. The results of the stability were 90.74, 96.65, and 97.77% and 99.63, 93.78, and 97.38% on Day 10 of the nominal concentrations of 250, 500, and 750 mg/kg/day Soy Leghemoglobin Preparation for Groups 2-4 males and females, respectively.

11.A.3 Homogeneity

A sampling from the top, middle, and bottom of the dietary preparations found all dietary mixtures to be homogeneously distributed within an acceptable degree of variation. Analysis of the top, middle, and bottom of the dietary preparations resulted in a relative standard deviation (RSD) of 2.92, 3.09, and 5.24% and 4.77, 5.50, and 5.57% between the strata, for concentrations of 512, 1024, and 1536 mg/kg/day Soy Leghemoglobin Preparation, which corresponds to 250, 500, and 750 mg/kg/day of active ingredient for Groups 2-4 males and females, respectively.

11.A.4 Concentration Verification

Concentration verification results for Day 0 (obtained from the homogeneity analysis) averaged 92.86, 93.13, and 103.35% and 97.28, 98.53, and 100.35% for 250, 500, and 750 mg/kg/day Soy Leghemoglobin Preparation for Groups 2-4 males and females, respectively. Day 21 resulted in 93.24, 97.05, and 94.73% and 92.80, 97.76, and 97.65% for 250, 500, and 750 mg/kg/day Soy Leghemoglobin Preparation for Groups 2-4 males and females, respectively.

Based on the stability, homogeneity, and dose concentration verification results, the animals are considered to have received the targeted dietary concentrations of Soy Leghemoglobin Preparation, with an acceptable margin of variability.

## B. Ophthalmologic Examinations (Appendix E)

Both eyes of all animals on study were examined by focal illumination, slit lamp biomicroscopy, and indirect ophthalmoscopy prior to study initiation and near termination of the study (Day 23). All animals included in the study were normal upon ophthalmic exam. Therefore, the test substance was not considered an ocular toxicant.

## C. Mortality and Clinical Observations (Tables 2 and 3, Appendices F-H, and O)

No mortalities were observed during this study. There were no clinical observations attributable to the administration of Soy Leghemoglobin Preparation.

Males

Incidental in-life clinical observations included: red staining in the litter tray of 7/10 Group 4 animals and superficial eschar of the head in 1/10 Group 4 animals.

There were no detailed clinical observations noted for any male during the study.

Females

Incidental in-life clinical observations included: slight to moderate alopecia on the left/right forelimb in 1/10 Group 2 animals.

Incidental detailed clinical observations corresponding to the daily findings included hair loss in 1/10 Group 2 animals.

The fate of all animals is presented in Appendix O.

## D. Body Weight and Body Weight Gain (Tables 4 and 5, Appendices I and J)

There were no body weight or body weight gain findings considered attributable to Soy Leghemoglobin Preparation administration.

Males

Mean body weights and mean daily bodyweight gain for the treated male rats in Groups 2-4 were comparable to the control Group 1 values throughout the study.

Females

Mean body weights for the treated female rats in Groups 2-4 were comparable to the control Group 1 values throughout the study.

Mean daily body weight gain for the treated female rats in Groups 2-4 was generally comparable to the control Group 1 values throughout the study with the exception of a transient statistically significant decrease ($p < 0.01$) in Group 2 mean daily body weight gain on Days 14-21 that was interpreted to have no toxicological relevance.

## E. Food Consumption, Food Efficiency, and Dietary Intake of Soy Leghemoglobin Preparation (Tables 6-8, Appendices K-M)

There were no food consumption or food efficiency findings considered attributable to Soy Leghemoglobin Preparation administration.

Males

Mean daily food consumption for the treated male rats in Group 2-4 was generally comparable to the control Group 1 values throughout the study with the exception of significant increases ($p <$ 0.05-0.01) in Group 3 on Days 7-14 and in Group 4 on Days 7-10, that we transient and without significant inpact on body weight and are interpreted to be non-toxicologically relevant

Mean food efficiency for the treated male rats in Group 2-4 was comparable to the control Group 1 values throughout the study.

Females

Mean daily food consumption for the treated female rats in Group 2-4 was comparable to the control Group 1 values throughout the study.

Mean food efficiency for the treated female rats in Group 2-4 was generally comparable to the control Group 1 values throughout the study, with the exception of statistically significant increases ($p < 0.01$) in Group 2 on Days 14-21 that were transient and without significant inpact on body weight and are interpreted to be non-toxicologically relevant.

Dietary Intake

Administered doses of 512, 1024 and 1536 mg/kg/day of test substance correspond to 250, 500 and 750 mg/kg/day of the active, respectively. The mean overall (Days 0-28) daily intake of the test substance in male rats fed dietary concentrations of 512, 1024 and 1536 mg/kg/day was 478.9, 954.7 and 1438.2 mg/kg/day respectivelly. For the same dietary concentrations, the mean overall (Days 0-28) daily intake in female rats was 497.8, 983.4, and 1470.4 mg/kg/day of test substance, respectively. The animals are considered to have received close to the targeted dose levels.

## F. Clinical Pathology (Tables 9-12, Appendix N)

### 11.F.1 Hematology

There were to no test substance related changes in hematology parameters for males or females rats.

Other differences in hematology values that were statistically significant are listed below. These were observed in a non-dose dependent manner and are interpreted to be within expected biological variation and are not toxicologically relevant:

- Increased Red blood cell, hemarocrit and Hemoglobin values and absolute basophil counts in Group 2 females.
- Decreased absolute reticulocyte counts in Group 3 females.

11.F.2 Coagulation

There were no test substance related changes in coagulation parameters for female rats.

A non dose dependend increase in activated partial tromboplastin time was observed in Group 3 and 4 males. Due to its very slight magnitude and lack of correlating pathological or clinical finding this change is considered non adverse.

11.F.3 Clinical Chemistry

There were no test substance related changes in serum chemistry parameters for male rats.

Decreased alkaline phosphatase was minimally decreased in a non dose dependent manner for females at all dose levels. This minimal decrease was not correlated with concurrent clinical pathology or histopathology changes and due to its limited clinical relevance is interpreted to have no toxicological significance.

Other differences in serum chemistry parameters that were statistically significant are listed below. These were observed in a non-dose dependent manner and are interpreted to be within expected biological variation and are not toxicologically relevant:

- Increased albumin and potassium values in Group 3 males.
- Decreased glucose and chloride in Groups 2 and 3 females.
- Increased globulin values in Group 3 females.
- Increased calcium in Groups 2 and 3 females.

11.F.4 Urinalysis

There were no test substance related changes in urinalysis parameters for males or female rats.

In summary, there were to no test substance related changes in hematology, serum chemistry or urinalysis parameters for males or females rats. Changes in coagulation paramenters were limited to a non dose dependent increase in activated partial tromboplastin time observed in Group 3 and 4 males, that due to its very slight magnitude and lack of correlating pathological or clinical finding this change is considered non-adverse.

## G. Sacrifice, Macroscopic Observations, and Histopathology (Tables 13-16, Appendices O-T)

There were no microscopic or macroscopic findings related to the administration of the test substance, Soy Leghemoglobin Preparation, in male or female rats. There were no test substance-related changes in absolute or relative organ weight values in male rats treated with Soy Leghemoglobin Preparation. Decreases in uterine weight were observed in Group 2-4 female rats. These decreases did not correlate with adverse histopathological findings and are therefore interpreted to be non-adverse.

11.G.1 Macroscopic

There were no early deaths among the animals submitted for histopathological evaluation.

Males

Incidental necropsy observations included: a small soft right testicle and small right epididymis in 1/10 Group 1 animals.

Females

Incidental necropsy observations included: spleen stricture in 1/10 Group 3 animals and a fluid filled uterus in 4/10 Group 1 and 1/10 Group 3 animals.

At the Day 29/30 time point, there were no macroscopic findings related to the administration of the test substance, Soy Leghemoglobin Preparation, in male or female rats. In the female rats, the presence of "fluid filled" uteri (which correlated with dilation), typically associated with normal proestrus stage of the estrous cycle, was decreased in rats treated with 512 and 1536 mg/kg/day Soy Leghemoglobin Preparation. Fluid filled uteri were noted in 4 out of 10 females at 0 mg/kg/day (Group 1 Animals 7013, 7017, 7018, and 7020), in 0 out of 10 females at 512 mg/kg/day, in 1 out of 10 females at 1024 mg/kg/day (Group 3 Animal 7053), and in 0 out of 10 females at 1536 mg/kg/day. Fluid filled uteri correlated with the proestrus stage of the estrus cycle, and higher individual uterine weights, and is a normal finding with this stage of the cycle. The decreased macroscopic incidence of fluid filled uteri in treated female rats correlated with lower incidences of proestrus, resulting in significantly decreased uterine weights in the 512 and 1536 mg/kg/day groups. Notably, the incidences of animals in metestrus in the treated groups were not dose-related.

The remaining macroscopic observations at the Day 29/30 time point were also of sporadic incidence and showed no trends/patterns to suggest a relationship to administration of Soy Leghemoglobin Preparation. These findings included testis and epididymis small and/or soft right which had a microscopic correlate of atrophy and aspermia, respectively, in control group Animal 7002; brain depressed area, which was an artifact confirmed microscopically, in Group 3 Animal 7047; and spleen stricture, with no microscopic correlate, in Group 3 Animal 7055.

11.G.2 Microscopic

At the Day 30 time point, there were no Soy Leghemoglobin Preparation-related effects.

There was a decrease in the incidence of dilated uterine lumens in the 536 and 1536 mg/kg/day rats compared to controls. The uteri were dilated in 4 out of 10 females at 0 mg/kg/day (Animals 7013, 7017, 7018, and 7020), which was consistent with proestrus/estrus. There were no females with dilated uterine lumens in the 512 and 1536 mg/kg/day rats and two out of 8 in the 1024 mg/kg/day group (Animals 7053 and 7059), which correlated with lower incidences of animals in the proestrus/estrus stage of the estrus cycle. Microscopically, 512 and 1536 mg/kg/day rats tended to be in the metestrus stage of the estrous cycle, which correlated with the lower weights and was an unusual distribution. However, the presence of both new and old corpora lutea in females from all groups indicates that these females were cycling normally and there were no treatment related effects on the estrus cycle.

All other microscopic findings at the Day 29/30 time point were unrelated to administration of Soy Leghemoglobin Preparation and can be observed in the age and strain of rats used in this study.

11.G.3 Organ Weights and Ratios

There were no test substance-related changes in absolute or relative organ weight values in male rats treated with Soy Leghemoglobin Preparation. Decreases in uterine weight were observed in Group 2-4 female rats. These decreases did not correlate with adverse histopathological findings and are therefore interpreted to be non-adverse.

Males

Mean absolute and relative organ weights for Groups 2-4 were comparable to control Group 1 values throughout the study.

Females

Mean absolute and relative organ weights for Groups 2-4 were generally comparable to control Group 1 values throughout the study with the exception of decreases in mean absolute and relative uterus weights in Groups 2-4 that were statistically significant ($p <$ 0.05-0.01) in Group 2 and Group 4 animals.

## 12. CONCLUSION

There were no mortalities, clinical observations, ophthalmology, body weight, body weight gain, food consumption, or food efficiency changes attributable to Soy Leghemoglobin Preparation administration.

There were no test substance related changes in hematology, serum chemistry or urinalysis parameters for males or females rats. Changes in coagulation paramenters were limited to a non dose dependend increase in activated partial tromboplastin time observed in Group 3 and 4 males, that due to its very slight magnitude and lack of correlating pathological or clinical finding this change is considered non adverse.

There were no microscopic or macroscopic findings related to the administration of the test substance, Soy Leghemoglobin Preparation, in male or female rats. There were no test substance-related changes in absolute or relative organ weight values in male rats treated with Soy Leghemoglobin Preparation. Decreases in uterine weight were observed in Group 2-4 female rats. These decreases did not correlate with adverse histopathological findings and are therefore interpreted to be non-adverse.

Under the conditions of the study and based on the toxicological endpoints evaluated, the no-adverse-effect level (NOAEL) for administration of Soy Leghemoglobin Preparation in the diet was determined to be 1536 mg/kg/day, which corresponds to 750 mg/kg/day of the active ingredient Soy Leghemoglobin for Sprague Dawley rats.

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## TABLE 1A: CHEMICAL ANALYSIS RESULTS

**Results for Neat Test Substance Stability Samples**

| Sampling Day | Measured Recovery (%) | % Change[1] | Overall Stability (%) |
|---|---|---|---|
| Day 0 (Initial) | 94.96% | 0.00% | 100.00% |
| Day 14 (Middle) | 95.29% | 0.35% | 100.35% |
| Day 21 (Final) | 90.88% | -4.30% | 95.70% |

[1] $\frac{\text{Final Sample} - \text{Initial Sample}}{\text{Initial Sample}} \times 100$

## TABLE 1B: CHEMICAL ANALYSIS RESULTS

**Results for Dietary Stability of Initial Samples**

| Day[1] | Group | Target Concentration Test Substance (ppm) | Measured Concentration Test Substance (ppm) | % of Target[2] |
|---|---|---|---|---|
| 0 | 1 (BO) | 0 | ND | NA |
| | 2 (M) | 4373 | 4508 | 103.08% |
| | 2 (F) | 4711 | 4645 | 98.61% |
| | 3 (M) | 8746 | 7951 | 90.91% |
| | 3 (F) | 9422 | 9034 | 95.89% |
| | 4(M) | 13118 | 12265 | 93.50% |
| | 4(F) | 14133 | 12808 | 90.62% |
| 4 | 1 (BO) | 0 | ND | NA |
| | 2 (M) | 4373 | 4207 | 96.20% |
| | 2 (F) | 4711 | 4471 | 94.90% |
| | 3 (M) | 8746 | 8238 | 94.19% |
| | 3 (F) | 9422 | 8918 | 94.65% |
| | 4(M) | 13118 | 12097 | 92.22% |
| | 4(F) | 14133 | 13191 | 93.33% |
| 7 | 1 (BO) | 0 | ND | NA |
| | 2 (M) | 4373 | 4202 | 96.09% |
| | 2 (F) | 4711 | 4468 | 94.84% |
| | 3 (M) | 8746 | 8200 | 93.76% |
| | 3 (F) | 9422 | 8728 | 92.63% |
| | 4(M) | 13118 | 12423 | 94.70% |
| | 4(F) | 14133 | 13547 | 95.85% |
| 10 | 1 (BO) | 0 | ND | NA |
| | 2 (M) | 4373 | 3968 | 90.74% |
| | 2 (F) | 4711 | 4693 | 99.63% |
| | 3 (M) | 8746 | 8453 | 96.65% |
| | 3 (F) | 9422 | 8836 | 93.78% |
| | 4(M) | 13118 | 12825 | 97.77% |
| | 4(F) | 14133 | 13762 | 97.38% |

ND = Not Detected; NA = Not Applicable

[1] Days relative to the initial diet preparation.

[2] % of Target = Measured Conc. (ppm) / Target Conc. (ppm) x 100

## TABLE 1C: CHEMICAL ANALYSIS RESULTS

**Results for Homogeneity of Dietary Preparations**

| Day[1] | Group | Sample Location | Target Concentration Test Substance (ppm) | Measured Concentration Test Substance (ppm) | % of Target[2] | Average % of Target | RSD (%) |
|---|---|---|---|---|---|---|---|
| 0 | 1 (BO) | Middle | 0 | ND | NA | NA | NA |
| | 2 (M) | Top | 4373 | 4302 | 98.38% | 95.87% | 2.92% |
| | | Middle | | 4061 | 92.86% | | |
| | | Bottom | | 4215 | 96.38% | | |
| | 2 (F) | Top | 4711 | 4853 | 103.01% | 98.01% | 4.77% |
| | | Middle | | 4583 | 97.28% | | |
| | | Bottom | | 4416 | 93.74% | | |
| | 3 (M) | Top | 8746 | 8636 | 98.74% | 95.40% | 3.09% |
| | | Middle | | 8145 | 93.13% | | |
| | | Bottom | | 8250 | 94.33% | | |
| | 3 (F) | Top | 9422 | 9669 | 102.62% | 97.71% | 5.50% |
| | | Middle | | 9284 | 98.53% | | |
| | | Bottom | | 8666 | 91.98% | | |
| | 4 (M) | Top | 13118 | 12226 | 93.20% | 97.85% | 5.24% |
| | | Middle | | 13558 | 103.35% | | |
| | | Bottom | | 12724 | 97.00% | | |
| | 4 (F) | Top | 14133 | 14567 | 103.07% | 98.64% | 5.57% |
| | | Middle | | 14183 | 100.35% | | |
| | | Bottom | | 13072 | 92.49% | | |

[1] Day relative to initial dietary preparation.

[2] % of Target = Measured Conc. (ppm) / Target Conc. (ppm) x 100.

## TABLE 1D: CHEMICAL ANALYSIS RESULTS

**Results for Concentration Verification of Dietary Preparations**

| Day[1] | Group | Target Concentration Test Substance (ppm) | Measured Concentration Test Substance (ppm) | % of Target[2] |
|---|---|---|---|---|
| 0[3] | 1 (BO) | 0 | ND | NA |
| | 2 (M) | 4373 | 4061 | 92.86% |
| | 2 (F) | 4711 | 4583 | 97.28% |
| | 3 (M) | 8746 | 8145 | 93.13% |
| | 3 (F) | 9422 | 9284 | 98.53% |
| | 4(M) | 13118 | 13558 | 103.35% |
| | 4(F) | 14133 | 14183 | 100.35% |
| 7 | 1 (BO) | 0 | ND | NA |
| | 2 (M) | 6093 | 6158 | 101.06% |
| | 2 (F) | 5824 | 5326 | 91.45% |
| | 3 (M) | 12318 | 12189 | 98.96% |
| | 3 (F) | 11664 | 11408 | 97.81% |
| | 4(M) | 18362 | 19409 | 105.70% |
| | 4(F) | 17567 | 17238 | 98.13% |
| 21 | 1 (BO) | 0 | ND | NA |
| | 2 (M) | 7407 | 6906 | 93.24% |
| | 2 (F) | 5925 | 5498 | 92.80% |
| | 3 (M) | 14727 | 14292 | 97.05% |
| | 3 (F) | 12901 | 12612 | 97.76% |
| | 4(M) | 21943 | 20786 | 94.73% |
| | 4(F) | 19281 | 18829 | 97.65% |

ND = Not Detected; NA = Not Applicable

[1] Days relative to the initial diet preparation.

[2] % of Target = Measured Conc. (ppm) / Target Conc. (ppm) x 100.

[3] As part of the homogeneity analysis.

## TABLE 2: SUMMARY OF CLINICAL OBSERVATIONS[1]

[1] Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient.
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

Day numbers relative to Start Date

Sex: Male

| | 0 mg/kg/day | 512 mg/kg/day | 1024 mg/kg/day | 1536 mg/kg/day | |
|---|---|---|---|---|---|
| Staining | | | | | |
| Number of Observations | . | . | . | | 7 |
| Number of Animals | . | . | . | | 7 |
| Days from - to | . | . | . | 13 | 13 |
| Eschar | | | | | |
| Number of Observations | . | . | . | | 2 |
| Number of Animals | . | . | . | | 1 |
| Days from - to | . | . | . | 28 | 29 |

Day numbers relative to Start Date

Sex: Female

| | 0 mg/kg/day | 512 mg/kg/day | 1024 mg/kg/day | 1536 mg/kg/day |
|---|---|---|---|---|
| Alopecia | | | | |
| Number of Observations | . | 10 | . | . |
| Number of Animals | . | 1 | . | . |
| Days from - to | . | 21 30 | . | . |

## TABLE 3: SUMMARY OF DETAILED CLINICAL OBSERVATIONS[1]

[1] Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient.
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

## TABLE 3: SUMMARY OF DETAILED CLINICAL OBSERVATIONS

### Males

### Study Days 0, 7, 14, 21, and 28

| Group | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| **Dietary Concentration (mg/kg/day)** | **0** | **512** | **1024** | **1536** |
| **Number of Animals in Group** | **10** | **10** | **10** | **10** |
| **Observations During Removal From Cage And Handling** | **Score[1]** | | | |
| Handling Reactivity | 0 | 0 | 0 | 0 |
| Vocalization | 0 | 0 | 0 | 0 |
| Palpebral Closure | 0 | 0 | 0 | 0 |
| Lacrimation | 0 | 0 | 0 | 0 |
| Eyes | 0 | 0 | 0 | 0 |
| Mucous Membranes | 0 | 0 | 0 | 0 |
| Salivation | 0 | 0 | 0 | 0 |
| Emaciation | 0 | 0 | 0 | 0 |
| Piloerection | 0 | 0 | 0 | 0 |
| Fur/Skin | 0 | 0 | 0 | 0 |
| Muscle Tone | 0 | 0 | 0 | 0 |
| Respiratory Pattern | 0 | 0 | 0 | 0 |
| **Open Field Observations** | | | | |
| Activity/Arousal | 0 | 0 | 0 | 0 |
| Convulsions | 0 | 0 | 0 | 0 |
| Tremors | 0 | 0 | 0 | 0 |
| Posture | 0 | 0 | 0 | 0 |
| Gait | 0 | 0 | 0 | 0 |
| Locomotion | 0 | 0 | 0 | 0 |
| Vocalizations | 0 | 0 | 0 | 0 |
| Defecation | 0 | 0 | 0 | 0 |
| Urination | 0 | 0 | 0 | 0 |
| Unusual Behaviors | 0 | 0 | 0 | 0 |
| **Pupillary Response** | | | | |
| Pupillary Reflex | 0 | 0 | 0 | 0 |

[1] An entry of 0 indicates that all animals in the group appeared normal when evaluated for the specified observation, or that all animals did not exhibit the specific clinical sign. An entry greater than 0 indicates the number of animals in the group that exhibited the specific clinical sign. A number in the parenthesis (if present) represents the score given for the observed clinical sign.

## TABLE 3 (cont.): SUMMARY OF DETAILED CLINICAL OBSERVATIONS

### FEMALES

### Study Days 0, 7, 14, 21, and 28

| Group | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| **Dietary Concentration (mg/kg/day)** | **0** | **512** | **1024** | **1536** |
| **Number of Animals in Group** | **10** | **10** | **10** | **10** |
| **Observations During Removal From Cage And Handling** | **Score[1]** | | | |
| Handling Reactivity | 0 | 0 | 0 | 0 |
| Vocalization | 0 | 0 | 0 | 0 |
| Palpebral Closure | 0 | 0 | 0 | 0 |
| Lacrimation | 0 | 0 | 0 | 0 |
| Eyes | 0 | 0 | 0 | 0 |
| Mucous Membranes | 0 | 0 | 0 | 0 |
| Salivation | 0 | 0 | 0 | 0 |
| Emaciation | 0 | 0 | 0 | 0 |
| Piloerection | 0 | 0 | 0 | 0 |
| Fur/Skin | 0 | 1(3) | 0 | 0 |
| Muscle Tone | 0 | 0 | 0 | 0 |
| Respiratory Pattern | 0 | 0 | 0 | 0 |
| **Open Field Observations** | | | | |
| Activity/Arousal | 0 | 0 | 0 | 0 |
| Convulsions | 0 | 0 | 0 | 0 |
| Tremors | 0 | 0 | 0 | 0 |
| Posture | 0 | 0 | 0 | 0 |
| Gait | 0 | 0 | 0 | 0 |
| Locomotion | 0 | 0 | 0 | 0 |
| Vocalizations | 0 | 0 | 0 | 0 |
| Defecation | 0 | 0 | 0 | 0 |
| Urination | 0 | 0 | 0 | 0 |
| Unusual Behaviors | 0 | 0 | 0 | 0 |
| **Pupillary Response** | | | | |
| Pupillary Reflex | 0 | 0 | 0 | 0 |

[1] An entry of 0 indicates that all animals in the group appeared normal when evaluated for the specified observation, or that all animals did not exhibit the specific clinical sign. An entry greater than 0 indicates the number of animals in the group that exhibited the specific clinical sign. A number in the parenthesis (if present) represents the score given for the observed clinical sign.

## TABLE 4: SUMMARY OF MEAN BODY WEIGHTS[1]

[1] Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient.
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

Bodyweight (g)

| Sex: Male<br>Day(s) Relative to Start Date | | 0<br>mg/kg/day<br>Group 1 | 512<br>mg/kg/day<br>Group 2 | 1024<br>mg/kg/day<br>Group 3 | 1536<br>mg/kg/day<br>Group 4 |
|---|---|---|---|---|---|
| 0 | Mean | 236.4 [1] | 236.4 | 236.7 | 236.3 |
| | SD | 6.1 | 6.1 | 7.0 | 6.7 |
| | N | 10 | 10 | 10 | 10 |
| 7 | Mean | 287.7 [1] | 289.6 | 290.9 | 292.8 |
| | SD | 14.0 | 11.1 | 14.3 | 12.2 |
| | N | 10 | 10 | 10 | 10 |
| 14 | Mean | 332.3 [1] | 337.0 | 341.6 | 339.5 |
| | SD | 16.5 | 18.4 | 24.2 | 18.6 |
| | N | 10 | 10 | 10 | 10 |
| 21 | Mean | 373.2 [1] | 376.6 | 384.5 | 379.9 |
| | SD | 22.7 | 21.4 | 31.1 | 22.7 |
| | N | 10 | 10 | 10 | 10 |
| 28 | Mean | 394.7 [1] | 398.9 | 410.2 | 405.5 |
| | SD | 28.8 | 26.4 | 37.2 | 24.4 |
| | N | 10 | 10 | 10 | 10 |

Statistical Test: Generalised Anova/Ancova Test  Transformation: Automatic

1 [1 - Automatic Transformation: Identity (No Transformation)]

Bodyweight (g)

| Sex: Female<br>Day(s) Relative to Start Date | | 0<br>mg/kg/day<br>Group 1 | 512<br>mg/kg/day<br>Group 2 | 1024<br>mg/kg/day<br>Group 3 | 1536<br>mg/kg/day<br>Group 4 |
|---|---|---|---|---|---|
| 0 | Mean | 174.1 [1] | 174.4 | 175.6 | 174.3 |
| | SD | 12.3 | 12.6 | 11.8 | 11.9 |
| | N | 10 | 10 | 10 | 10 |
| 7 | Mean | 198.3 [1] | 201.0 | 204.0 | 199.3 |
| | SD | 14.8 | 16.5 | 13.3 | 10.5 |
| | N | 10 | 10 | 10 | 10 |
| 14 | Mean | 218.8 [1] | 218.5 | 223.7 | 221.3 |
| | SD | 21.9 | 19.6 | 14.6 | 14.3 |
| | N | 10 | 10 | 10 | 10 |
| 21 | Mean | 239.2 [1] | 229.1 | 238.8 | 238.0 |
| | SD | 24.0 | 19.4 | 19.4 | 13.1 |
| | N | 10 | 10 | 10 | 10 |
| 28 | Mean | 249.8 [1] | 244.0 | 253.2 | 248.7 |
| | SD | 24.0 | 23.3 | 17.7 | 12.4 |
| | N | 10 | 10 | 10 | 10 |

Statistical Test: Generalised Anova/Ancova Test  Transformation: Automatic

1 [I - Automatic Transformation: Identity (No Transformation)]

## TABLE 5: SUMMARY OF MEAN DAILY BODY WEIGHT GAIN[1]

[1] Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient.
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

Mean Daily Body Weight Gain (g/day)

| Sex: Male<br>Day(s) Relative to Start Date | | 0 mg/kg/day Group 1 | 512 mg/kg/day Group 2 | 1024 mg/kg/day Group 3 | 1536 mg/kg/day Group 4 |
|---|---|---|---|---|---|
| 0 → 7 | Mean | 7.33 [1] | 7.60 | 7.74 | 8.07 |
| | SD | 1.35 | 0.94 | 1.40 | 1.16 |
| | N | 10 | 10 | 10 | 10 |
| 7 → 14 | Mean | 6.37 [1] | 6.77 | 7.24 | 6.67 |
| | SD | 0.77 | 1.30 | 1.49 | 1.13 |
| | N | 10 | 10 | 10 | 10 |
| 14 → 21 | Mean | 5.84 [1] | 5.66 | 6.13 | 5.77 |
| | SD | 1.15 | 0.75 | 1.12 | 0.86 |
| | N | 10 | 10 | 10 | 10 |
| 21 → 28 | Mean | 3.07 [1] | 3.19 | 3.67 | 3.66 |
| | SD | 1.06 | 0.91 | 1.10 | 0.47 |
| | N | 10 | 10 | 10 | 10 |
| 0 → 28 | Mean | 5.65 [1] | 5.80 | 6.20 | 6.04 |
| | SD | 0.84 | 0.83 | 1.14 | 0.70 |
| | N | 10 | 10 | 10 | 10 |

Statistical Test: Generalised Anova/Ancova Test  Transformation: Automatic

1 [1 - Automatic Transformation: Identity (No Transformation)]

Mean Daily Body Weight Gain (g/day)

| Sex: Female<br>Day(s) Relative to Start Date | | 0 mg/kg/day Group 1 | 512 mg/kg/day Group 2 | 1024 mg/kg/day Group 3 | 1536 mg/kg/day Group 4 |
|---|---|---|---|---|---|
| 0 → 7 | Mean | 3.46 I[1] | 3.80 | 4.06 | 3.57 |
| | SD | 1.03 | 0.96 | 0.72 | 0.61 |
| | N | 10 | 10 | 10 | 10 |
| 7 → 14 | Mean | 2.93 R[2] | 2.50 | 2.81 | 3.14 |
| | SD | 2.09 | 0.75 | 0.66 | 0.81 |
| | N | 10 | 10 | 10 | 10 |
| 14 → 21 | Mean | 2.91 I,A[3] | 1.51 DD[5] | 2.16 | 2.39 |
| | SD | 1.15 | 0.82 | 1.03 | 0.96 |
| | N | 10 | 10 | 10 | 10 |
| 21 → 28 | Mean | 1.51 L[4] | 2.13 | 2.06 | 1.53 |
| | SD | 1.03 | 0.85 | 0.63 | 0.79 |
| | N | 10 | 10 | 10 | 10 |
| 0 → 28 | Mean | 2.70 I[1] | 2.49 | 2.77 | 2.66 |
| | SD | 0.60 | 0.53 | 0.30 | 0.34 |
| | N | 10 | 10 | 10 | 10 |

Statistical Test: Generalised Anova/Ancova Test  Transformation: Automatic

1 [I - Automatic Transformation: Identity (No Transformation)]
2 [R - Automatic Transformation: Rank]
3 [I,A - Automatic Transformation: Identity (No Transformation), (All Groups) Test: Analysis of Variance $p < 0.05$]
4 [L - Automatic Transformation: Log]
5 [DD - Test: Dunnett 2 Sided $p < 0.01$]

## TABLE 6: SUMMARY OF MEAN DAILY FOOD CONSUMPTION[1]

[1] Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient.
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

Mean Daily Food Consumption (g/day)

| Sex: Male<br>Day(s) Relative to Start Date | | 0 mg/kg/day Group 1 | 512 mg/kg/day Group 2 | 1024 mg/kg/day Group 3 | 1536 mg/kg/day Group 4 |
|---|---|---|---|---|---|
| 0 → 3 | Mean | 18.73 R[1] | 18.73 | 18.80 | 19.03 |
| | SD | 3.35 | 1.98 | 2.68 | 2.99 |
| | N | 10 | 10 | 10 | 10 |
| 3 → 7 | Mean | 28.03 R[1] | 28.60 | 28.23 | 28.63 |
| | SD | 1.08 | 0.52 | 2.08 | 1.07 |
| | N | 10 | 10 | 10 | 10 |
| 0 → 7 | Mean | 24.04 R[1] | 24.37 | 24.19 | 24.51 |
| | SD | 1.67 | 0.65 | 0.94 | 1.56 |
| | N | 10 | 10 | 10 | 10 |
| 7 → 10 | Mean | 26.30 R[1] | 27.10 | 27.80 dd[2] | 27.90 d[3] |
| | SD | 1.31 | 0.81 | 1.97 | 0.78 |
| | N | 10 | 10 | 10 | 10 |
| 10 → 14 | Mean | 26.55 R[1] | 27.25 | 27.88 | 27.45 |
| | SD | 1.17 | 0.91 | 2.25 | 1.03 |
| | N | 10 | 10 | 10 | 10 |
| 7 → 14 | Mean | 26.44 R[1] | 27.19 | 27.84 d[3] | 27.64 |
| | SD | 1.16 | 0.84 | 2.12 | 0.84 |
| | N | 10 | 10 | 10 | 10 |
| 14 → 17 | Mean | 25.90 R[1] | 25.47 | 26.33 | 26.17 |
| | SD | 0.89 | 1.83 | 2.71 | 0.82 |
| | N | 10 | 10 | 10 | 10 |
| 17 → 21 | Mean | 26.38 R[1] | 26.50 | 27.10 | 26.93 |
| | SD | 0.97 | 0.77 | 2.31 | 0.86 |
| | N | 10 | 10 | 10 | 10 |
| 14 → 21 | Mean | 26.17 R[1] | 26.06 | 26.77 | 26.60 |
| | SD | 0.93 | 1.19 | 2.42 | 0.67 |
| | N | 10 | 10 | 10 | 10 |
| 21 → 24 | Mean | 21.80 R[1] | 22.07 | 22.27 | 22.47 |
| | SD | 0.77 | 1.03 | 1.61 | 0.66 |
| | N | 10 | 10 | 10 | 10 |
| 24 → 28 | Mean | 27.70 R[1] | 28.75 | 29.13 | 29.18 |
| | SD | 1.04 | 1.21 | 1.92 | 1.28 |
| | N | 10 | 10 | 10 | 10 |

Statistical Test: Generalised Anova/Ancova Test  Transformation: Automatic

1 [R - Automatic Transformation: Rank]
2 [dd - Test: Dunn 2 Sided p < 0.01]
3 [d - Test: Dunn 2 Sided p < 0.05]

Mean Daily Food Consumption (g/day)

| Sex: Male<br>Day(s) Relative to Start Date | | 0 mg/kg/day Group 1 | 512 mg/kg/day Group 2 | 1024 mg/kg/day Group 3 | 1536 mg/kg/day Group 4 |
|---|---|---|---|---|---|
| 21 → 28 | Mean | 25.17 R[1] | 25.89 | 26.19 | 26.30 |
| | SD | 0.89 | 1.10 | 1.73 | 0.83 |
| | N | 10 | 10 | 10 | 10 |
| 0 → 28 | Mean | 25.46 R[1] | 25.88 | 26.25 | 26.26 |
| | SD | 0.91 | 0.87 | 1.58 | 0.90 |
| | N | 10 | 10 | 10 | 10 |

Statistical Test: Generalised Anova/Ancova Test  Transformation: Automatic

1 [R - Automatic Transformation: Rank]

Mean Daily Food Consumption (g/day)

| Sex: Female<br>Day(s) Relative to Start Date | | 0<br>mg/kg/day<br>Group 1 | 512<br>mg/kg/day<br>Group 2 | 1024<br>mg/kg/day<br>Group 3 | 1536<br>mg/kg/day<br>Group 4 |
|---|---|---|---|---|---|
| 0 → 3 | Mean | 13.43 R[1] | 12.93 | 13.73 | 13.70 |
| | SD | 2.05 | 2.21 | 1.74 | 2.56 |
| | N | 10 | 10 | 10 | 10 |
| 3 → 7 | Mean | 21.18 R[1] | 21.23 | 21.05 | 20.18 |
| | SD | 1.24 | 1.13 | 1.31 | 0.77 |
| | N | 10 | 10 | 10 | 10 |
| 0 → 7 | Mean | 17.86 R[1] | 17.67 | 17.91 | 17.40 |
| | SD | 0.98 | 1.06 | 1.02 | 0.82 |
| | N | 10 | 10 | 10 | 10 |
| 7 → 10 | Mean | 19.33 R[1] | 18.43 | 19.30 | 18.90 |
| | SD | 2.23 | 0.54 | 2.26 | 0.96 |
| | N | 10 | 10 | 10 | 10 |
| 10 → 14 | Mean | 19.55 I[2] | 20.45 | 19.45 | 19.08 |
| | SD | 1.59 | 2.02 | 1.12 | 1.11 |
| | N | 10 | 10 | 10 | 10 |
| 7 → 14 | Mean | 19.46 R[1] | 19.59 | 19.39 | 19.00 |
| | SD | 1.83 | 1.29 | 1.52 | 1.02 |
| | N | 10 | 10 | 10 | 10 |
| 14 → 17 | Mean | 19.27 I[2] | 19.40 | 18.47 | 18.73 |
| | SD | 1.34 | 0.76 | 1.22 | 1.17 |
| | N | 10 | 10 | 10 | 10 |
| 17 → 21 | Mean | 19.88 L[3] | 20.08 | 19.35 | 19.13 |
| | SD | 1.72 | 1.18 | 1.52 | 0.64 |
| | N | 10 | 10 | 10 | 10 |
| 14 → 21 | Mean | 19.61 R[1] | 19.79 | 18.97 | 18.96 |
| | SD | 1.53 | 0.64 | 1.35 | 0.61 |
| | N | 10 | 10 | 10 | 10 |
| 21 → 24 | Mean | 15.90 I[2] | 16.23 | 15.97 | 15.63 |
| | SD | 0.74 | 0.68 | 0.34 | 0.55 |
| | N | 10 | 10 | 10 | 10 |
| 24 → 28 | Mean | 20.70 R[1] | 21.33 | 21.08 | 20.45 |
| | SD | 1.38 | 1.44 | 0.91 | 0.55 |
| | N | 10 | 10 | 10 | 10 |

Statistical Test: Generalised Anova/Ancova Test  Transformation: Automatic

1 [R - Automatic Transformation: Rank]
2 [I - Automatic Transformation: Identity (No Transformation)]
3 [L - Automatic Transformation: Log]

Mean Daily Food Consumption (g/day)

| Sex: Female<br>Day(s) Relative to Start Date | | 0<br>mg/kg/day<br>Group 1 | 512<br>mg/kg/day<br>Group 2 | 1024<br>mg/kg/day<br>Group 3 | 1536<br>mg/kg/day<br>Group 4 |
|---|---|---|---|---|---|
| 21 → 28 | Mean | 18.64 R[1] | 19.14 | 18.89 | 18.39 |
| | SD | 1.09 | 0.96 | 0.54 | 0.32 |
| | N | 10 | 10 | 10 | 10 |
| 0 → 28 | Mean | 18.89 I[2] | 19.05 | 18.79 | 18.44 |
| | SD | 1.23 | 0.81 | 1.09 | 0.61 |
| | N | 10 | 10 | 10 | 10 |

Statistical Test: Generalised Anova/Ancova Test  Transformation: Automatic

1 [R - Automatic Transformation: Rank]
2 [I - Automatic Transformation: Identity (No Transformation)]

## TABLE 7: SUMMARY OF FOOD EFFICIENCY[1,2]

[1] Food efficiency = $\frac{\text{Mean Daily Body Weight Gain}}{\text{Mean Daily Food Consumption}}$

[2] Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient.
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

Food Efficiency

| Sex: Male<br>Day(s) Relative to Start Date | | 0<br>mg/kg/day<br>Group 1 | 512<br>mg/kg/day<br>Group 2 | 1024<br>mg/kg/day<br>Group 3 | 1536<br>mg/kg/day<br>Group 4 |
|---|---|---|---|---|---|
| 0 → 7 | Mean | 0.304 [1] | 0.312 | 0.319 | 0.329 |
| | SD | 0.046 | 0.038 | 0.051 | 0.046 |
| | N | 10 | 10 | 10 | 10 |
| 7 → 14 | Mean | 0.241 [1] | 0.248 | 0.258 | 0.241 |
| | SD | 0.025 | 0.043 | 0.041 | 0.040 |
| | N | 10 | 10 | 10 | 10 |
| 14 → 21 | Mean | 0.223 [2] | 0.217 | 0.227 | 0.217 |
| | SD | 0.044 | 0.022 | 0.026 | 0.031 |
| | N | 10 | 10 | 10 | 10 |
| 21 → 28 | Mean | 0.121 [1] | 0.123 | 0.139 | 0.139 |
| | SD | 0.040 | 0.032 | 0.040 | 0.019 |
| | N | 10 | 10 | 10 | 10 |
| 0 → 28 | Mean | 0.222 [1] | 0.224 | 0.235 | 0.230 |
| | SD | 0.031 | 0.028 | 0.034 | 0.027 |
| | N | 10 | 10 | 10 | 10 |

Statistical Test: Generalised Anova/Ancova Test  Transformation: Automatic

1 [I - Automatic Transformation: Identity (No Transformation)]
2 [L - Automatic Transformation: Log]

Food Efficiency

| Sex: Female<br>Day(s) Relative to Start Date | | 0<br>mg/kg/day<br>Group 1 | 512<br>mg/kg/day<br>Group 2 | 1024<br>mg/kg/day<br>Group 3 | 1536<br>mg/kg/day<br>Group 4 |
|---|---|---|---|---|---|
| 0 → 7 | Mean | 0.193 I[1] | 0.215 | 0.226 | 0.206 |
| | SD | 0.055 | 0.052 | 0.037 | 0.038 |
| | N | 10 | 10 | 10 | 10 |
| 7 → 14 | Mean | 0.148 R[2] | 0.128 | 0.146 | 0.165 |
| | SD | 0.093 | 0.037 | 0.033 | 0.040 |
| | N | 10 | 10 | 10 | 10 |
| 14 → 21 | Mean | 0.149 I,A[3] | 0.077 DD[5] | 0.112 | 0.126 |
| | SD | 0.057 | 0.042 | 0.049 | 0.052 |
| | N | 10 | 10 | 10 | 10 |
| 21 → 28 | Mean | 0.080 L[4] | 0.111 | 0.109 | 0.083 |
| | SD | 0.052 | 0.041 | 0.033 | 0.044 |
| | N | 10 | 10 | 10 | 10 |
| 0 → 28 | Mean | 0.142 I[1] | 0.131 | 0.147 | 0.144 |
| | SD | 0.027 | 0.028 | 0.011 | 0.019 |
| | N | 10 | 10 | 10 | 10 |

Statistical Test: Generalised Anova/Ancova Test  Transformation: Automatic

1 [I - Automatic Transformation: Identity (No Transformation)]
2 [R - Automatic Transformation: Rank]
3 [I,A - Automatic Transformation: Identity (No Transformation), (All Groups) Test: Analysis of Variance $p < 0.05$]
4 [L - Automatic Transformation: Log]
5 [DD - Test: Dunnett 2 Sided $p < 0.01$]

## TABLE 8: SUMMARY OF MEAN DAILY DIETARY INTAKE OF SOY LEGHEMOGLOBIN PREPARATION[1]

[1] Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient.
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

Dietary Intake Variable (mg/kg/day)

| Sex: Male<br>Day(s) Relative to Start Date | | 0 mg/kg/day Group 1 | 512 mg/kg/day Group 2 | 1024 mg/kg/day Group 3 | 1536 mg/kg/day Group 4 |
|---|---|---|---|---|---|
| 0 → 7 | Mean | 0.0 | 485.4 | 966.5 | 1459.8 |
| | SD | 0.0 | 20.9 | 42.5 | 103.0 |
| | N | 10 | 10 | 10 | 10 |
| 7 → 14 | Mean | 0.0 | 540.5 | 1095.9 | 1631.5 |
| | SD | 0.0 | 24.5 | 53.5 | 78.9 |
| | N | 10 | 10 | 10 | 10 |
| 14 → 21 | Mean | 0.0 | 503.2 | 1007.2 | 1513.7 |
| | SD | 0.0 | 30.7 | 61.7 | 81.1 |
| | N | 10 | 10 | 10 | 10 |
| 21 → 28 | Mean | 0.0 | 495.9 | 973.0 | 1473.9 |
| | SD | 0.0 | 33.2 | 49.1 | 92.5 |
| | N | 10 | 10 | 10 | 10 |
| 0 → 28 | Mean | 0.0 | 478.9 | 954.7 | 1438.2 |
| | SD | 0.0 | 24.7 | 36.0 | 78.6 |
| | N | 10 | 10 | 10 | 10 |

Dietary Intake Variable (mg/kg/day)

| Sex: Female<br>Day(s) Relative to Start Date | | 0 mg/kg/day Group 1 | 512 mg/kg/day Group 2 | 1024 mg/kg/day Group 3 | 1536 mg/kg/day Group 4 |
|---|---|---|---|---|---|
| 0 → 7 | Mean | 0.0 | 498.0 | 995.9 | 1481.1 |
| | SD | 0.0 | 43.5 | 29.2 | 115.0 |
| | N | 10 | 10 | 10 | 10 |
| 7 → 14 | Mean | 0.0 | 541.9 | 1064.6 | 1604.6 |
| | SD | 0.0 | 49.9 | 39.2 | 116.7 |
| | N | 10 | 10 | 10 | 10 |
| 14 → 21 | Mean | 0.0 | 518.8 | 1015.1 | 1537.2 |
| | SD | 0.0 | 53.9 | 34.3 | 92.3 |
| | N | 10 | 10 | 10 | 10 |
| 21 → 28 | Mean | 0.0 | 482.4 | 994.0 | 1460.2 |
| | SD | 0.0 | 41.9 | 56.0 | 79.0 |
| | N | 10 | 10 | 10 | 10 |
| 0 → 28 | Mean | 0.0 | 497.8 | 983.4 | 1470.4 |
| | SD | 0.0 | 42.8 | 29.0 | 88.2 |
| | N | 10 | 10 | 10 | 10 |

## TABLE 9: SUMMARY OF HEMATOLOGY VALUES[1]

[1] Individual data are reported in the Clinical Pathology Report presented in Appendix N.

| Sex: Male | Day(s) Relative to Start Date | | 0 mg/kg/day Group 1 | 250 mg/kg/day Group 2 | 500 mg/kg/day Group 3 | 750 mg/kg/day Group 4 |
|---|---|---|---|---|---|---|
| RBC (x10^6/µL) | 22 | Mean | 7.72 | 7.60 | 7.61 | 7.70 |
| | | SD | 0.23 | 0.34 | 0.35 | 0.27 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | . | -1.6 | -1.5 | -0.3 |
| HGB (g/dL) | 22 | Mean | 15.6 | 15.4 | 15.5 | 15.9 |
| | | SD | 0.3 | 0.6 | 0.6 | 0.4 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | . | -1.5 | -1.0 | 1.4 |
| HCT (%) | 22 | Mean | 45.5 | 45.1 | 45.1 | 45.9 |
| | | SD | 0.9 | 1.5 | 1.7 | 0.8 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | . | -0.9 | -0.8 | 1.0 |
| MCV (fL) | 22 | Mean | 58.9 | 59.3 | 59.3 | 59.7 |
| | | SD | 1.0 | 2.3 | 1.5 | 1.9 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | . | 0.7 | 0.7 | 1.3 |
| MCH (pg) | 22 | Mean | 20.3 | 20.3 | 20.4 | 20.6 |
| | | SD | 0.5 | 0.9 | 0.5 | 0.7 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | . | 0.2 | 0.6 | 1.6 |
| MCHC (g/dL) | 22 | Mean | 34.4 | 34.2 | 34.4 | 34.5 |
| | | SD | 0.4 | 0.4 | 0.3 | 0.5 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | . | -0.5 | -0.1 | 0.4 |
| RDW (%) | 22 | Mean | 12.1 | 12.5 | 12.5 | 12.3 |
| | | SD | 0.3 | 0.5 | 0.3 | 0.5 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | . | 3.0 | 3.3 | 1.6 |
| PLT (x10^3/µL) | 22 | Mean | 1160 | 1202 | 1171 | 1227 |
| | | SD | 121 | 69 | 76 | 185 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | . | 3.6 | 1.0 | 5.8 |

General Footnote: [Statistical Test: Anova and Dunnett's test Transformation :Automatic]

| Sex: Male | Day(s) Relative to Start Date | | 0 mg/kg/day Group 1 | 250 mg/kg/day Group 2 | 500 mg/kg/day Group 3 | 750 mg/kg/day Group 4 |
|---|---|---|---|---|---|---|
| WBC (x10^3/µL) | 22 | Mean | 13.00 | 14.41 | 11.13 | 13.45 |
| | | SD | 1.33 | 2.67 | 1.82 | 4.41 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | . | 10.8 | -14.4 | 3.4 |
| ANEU (x10^3/µL) | 22 | Mean | 1.91 | 1.99 | 1.75 | 1.57 |
| | | SD | 0.67 | 0.43 | 0.43 | 0.62 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | . | 4.1 | -8.1 | -17.8 |
| ALYM (x10^3/µL) | 22 | Mean | 10.49 | 11.79 | 8.86 | 11.29 |
| | | SD | 1.17 | 2.48 | 1.70 | 4.15 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | . | 12.4 | -15.5 | 7.7 |
| AMON (x10^3/µL) | 22 | Mean | 0.31 | 0.34 | 0.28 | 0.30 |
| | | SD | 0.10 | 0.11 | 0.05 | 0.10 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | . | 10.2 | -9.8 | -1.5 |
| AEOS (x10^3/µL) | 22 | Mean | 0.12 | 0.13 | 0.11 | 0.11 |
| | | SD | 0.04 | 0.08 | 0.04 | 0.05 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | . | 4.4 | -7.2 | -7.6 |
| ABAS (x10^3/µL) | 22 | Mean | 0.09 | 0.09 | 0.07 | 0.10 |
| | | SD | 0.03 | 0.04 | 0.02 | 0.06 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | . | -5.0 | -27.0 | 6.2 |
| ALUC (x10^3/µL) | 22 | Mean | 0.08 | 0.08 | 0.06 | 0.08 |
| | | SD | 0.03 | 0.03 | 0.02 | 0.04 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | . | -8.1 | -27.0 | -2.4 |
| ARET (x10^3/µL) | 22 | Mean | 232.6 | 235.8 | 246.3 | 243.8 |
| | | SD | 31.2 | 40.7 | 24.1 | 41.1 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | . | 1.4 | 5.9 | 4.8 |

General Footnote: [Statistical Test: Anova and Dunnett's test Transformation :Automatic]

| Sex: Female | Day(s) Relative to Start Date | | 0 mg/kg/day Group 1 | 250 mg/kg/day Group 2 | 500 mg/kg/day Group 3 | 750 mg/kg/day Group 4 |
|---|---|---|---|---|---|---|
| RBC (x10^6/µL) | 22 | Mean | 7.59 | 8.01 #[1] | 7.86 | 7.63 |
| | | SD | 0.24 | 0.38 | 0.24 | 0.30 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | . | 5.6 | 3.6 | 0.6 |
| HGB (g/dL) | 22 | Mean | 15.3 | 16.2 #[1] | 15.7 | 15.5 |
| | | SD | 0.5 | 0.5 | 0.4 | 0.6 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | . | 5.7 | 2.5 | 0.9 |
| HCT (%) | 22 | Mean | 43.6 | 45.9 #[1] | 44.7 | 44.0 |
| | | SD | 1.2 | 1.2 | 1.3 | 1.7 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | . | 5.2 | 2.4 | 0.9 |
| MCV (fL) | 22 | Mean | 57.5 | 57.4 | 56.8 | 57.7 |
| | | SD | 1.1 | 2.2 | 1.2 | 2.2 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | . | -0.2 | -1.1 | 0.4 |
| MCH (pg) | 22 | Mean | 20.2 | 20.2 | 20.0 | 20.3 |
| | | SD | 0.3 | 0.7 | 0.5 | 0.7 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | . | 0.1 | -1.0 | 0.3 |
| MCHC (g/dL) | 22 | Mean | 35.2 | 35.3 | 35.2 | 35.2 |
| | | SD | 0.7 | 0.3 | 0.4 | 0.5 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | . | 0.3 | 0.1 | 0.0 |
| RDW (%) | 22 | Mean | 11.3 | 11.3 | 11.2 | 11.5 |
| | | SD | 0.4 | 0.5 | 0.3 | 0.5 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | . | 0.1 | -0.4 | 1.7 |
| PLT (x10^3/µL) | 22 | Mean | 1190 | 1176 | 1230 | 1229 |
| | | SD | 108 | 127 | 115 | 114 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | . | -1.1 | 3.4 | 3.3 |

General Footnote: [Statistical Test: Anova and Dunnett's test Transformation :Automatic]
1 [#- Test: Dunnett 2 Sided $p < 0.05$]

| Sex: Female | Day(s) Relative to Start Date | | 0 mg/kg/day Group 1 | 250 mg/kg/day Group 2 | 500 mg/kg/day Group 3 | 750 mg/kg/day Group 4 |
|---|---|---|---|---|---|---|
| WBC (x10^3/µL) | 22 | Mean | 10.08 | 11.87 | 11.59 | 10.19 |
| | | SD | 1.70 | 1.75 | 3.35 | 3.72 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | . | 17.7 | 15.0 | 1.1 |
| ANEU (x10^3/µL) | 22 | Mean | 1.48 | 1.56 | 1.68 | 1.54 |
| | | SD | 0.30 | 0.58 | 0.85 | 1.10 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | . | 5.3 | 13.9 | 4.0 |
| ALYM (x10^3/µL) | 22 | Mean | 8.15 | 9.74 | 9.29 | 8.21 |
| | | SD | 1.58 | 1.43 | 2.71 | 2.88 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | . | 19.5 | 14.0 | 0.7 |
| AMON (x10^3/µL) | 22 | Mean | 0.25 | 0.29 | 0.33 | 0.22 |
| | | SD | 0.15 | 0.06 | 0.15 | 0.14 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | . | 16.7 | 32.5 | -11.1 |
| AEOS (x10^3/µL) | 22 | Mean | 0.11 | 0.13 | 0.15 | 0.12 |
| | | SD | 0.03 | 0.04 | 0.05 | 0.06 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | . | 21.4 | 35.8 | 9.0 |
| ABAS (x10^3/µL) | 22 | Mean | 0.04 | 0.07 #[1] | 0.06 | 0.05 |
| | | SD | 0.01 | 0.03 | 0.03 | 0.04 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | . | 93.2 | 64.1 | 46.7 |
| ALUC (x10^3/µL) | 22 | Mean | 0.05 | 0.07 | 0.07 | 0.05 |
| | | SD | 0.02 | 0.02 | 0.03 | 0.04 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | . | 29.1 | 26.2 | 2.9 |
| ARET (x10^3/µL) | 22 | Mean | 205.8 | 182.4 | 169.1 #[1] | 184.2 |
| | | SD | 33.9 | 32.9 | 30.9 | 33.7 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | . | -11.3 | -17.8 | -10.5 |

General Footnote: [Statistical Test: Anova and Dunnett's test Transformation :Automatic]
1 [#- Test: Dunnett 2 Sided p < 0.05]

## TABLE 10: SUMMARY OF COAGULATION VALUES[1]

[1] Individual data are reported in the Clinical Pathology Report presented in Appendix N.

| Sex: Male | Day(s) Relative to Start Date | | 0 mg/kg/day Group 1 | 250 mg/kg/day Group 2 | 500 mg/kg/day Group 3 | 750 mg/kg/day Group 4 |
|---|---|---|---|---|---|---|
| PT (sec) | 29 | Mean | 10.7 | 10.7 | 10.6 | 10.6 |
| | | SD | 0.3 | 0.4 | 0.2 | 0.2 |
| | | N | 10 | 10 | 10 | 10 |
| APTT (sec) | 29 | Mean | 20.2 | 23.8 | 24.9 @[1] | 23.9 @[1] |
| | | SD | 2.4 | 5.3 | 6.9 | 4.8 |
| | | N | 10 | 10 | 10 | 10 |

General Footnote: [Statistical Test: Anova and Dunnett's test Transformation :Automatic]
1 [@ - Test: Dunnett Non-Parametric 2 Sided p < 0.05]

| Sex: Female | Day(s) Relative to Start Date | | 0 mg/kg/day Group 1 | 250 mg/kg/day Group 2 | 500 mg/kg/day Group 3 | 750 mg/kg/day Group 4 |
|---|---|---|---|---|---|---|
| PT (sec) | 30 | Mean | 10.0 | 9.8 | 10.0 | 9.8 |
| | | SD | 0.2 | 0.2 | 0.3 | 0.2 |
| | | N | 10 | 10 | 10 | 10 |
| APTT (sec) | 30 | Mean | 21.9 | 20.0 | 20.8 | 19.4 |
| | | SD | 2.5 | 3.1 | 5.0 | 1.9 |
| | | N | 10 | 10 | 10 | 10 |

General Footnote: [Statistical Test: Anova and Dunnett's test Transformation :Automatic]

## TABLE 11: SUMMARY OF CLINICAL CHEMISTRY VALUES[1]

[1] Individual data are reported in the Clinical Pathology Report presented in Appendix N.

| Sex: Male | Day(s) Relative to Start Date | | 0 mg/kg/day Group 1 | 250 mg/kg/day Group 2 | 500 mg/kg/day Group 3 | 750 mg/kg/day Group 4 |
|---|---|---|---|---|---|---|
| AST (U/L) | 22 | Mean | 73 | 76 | 79 | 78 |
| | | SD | 8 | 9 | 7 | 8 |
| | | N | 5 | 9 | 6 | 8 |
| | | %Diff | . | 4.0 | 7.5 | 6.9 |
| ALT (U/L) | 22 | Mean | 29 | 28 | 28 | 30 |
| | | SD | 4 | 4 | 3 | 4 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | . | -3.1 | -2.4 | 2.4 |
| SDH (U/L) | 22 | Mean | 8.2 | 8.1 | 8.4 | 8.0 |
| | | SD | 1.4 | 1.7 | 2.4 | 1.4 |
| | | N | 5 | 9 | 6 | 8 |
| | | %Diff | . | -0.8 | 2.7 | -1.9 |
| ALKP (U/L) | 22 | Mean | 183 | 216 | 216 | 205 |
| | | SD | 24 | 29 | 44 | 42 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | . | 18.6 | 18.5 | 12.3 |
| BILI (mg/dL) | 22 | Mean | 0.17 | 0.17 | 0.18 | 0.18 |
| | | SD | 0.02 | 0.02 | 0.02 | 0.02 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | . | 1.2 | 4.1 | 5.9 |
| BUN (mg/dL) | 22 | Mean | 10 | 11 | 10 | 11 |
| | | SD | 1 | 1 | 1 | 2 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | . | 4.8 | -3.8 | 1.0 |
| CREA (mg/dL) | 22 | Mean | 0.22 | 0.23 | 0.23 | 0.21 |
| | | SD | 0.01 | 0.02 | 0.02 | 0.02 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | . | 3.6 | 4.1 | -5.9 |
| CHOL (mg/dL) | 22 | Mean | 76 | 73 | 72 | 67 |
| | | SD | 16 | 27 | 14 | 12 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | . | -3.4 | -5.4 | -11.7 |

General Footnote: [Statistical Test: Anova and Dunnett's test Transformation :Automatic]

| Sex: Male | Day(s) Relative to Start Date | | 0 mg/kg/day Group 1 | 250 mg/kg/day Group 2 | 500 mg/kg/day Group 3 | 750 mg/kg/day Group 4 |
|---|---|---|---|---|---|---|
| TRIG (mg/dL) | 22 | Mean | 66 | 67 | 67 | 68 |
| | | SD | 17 | 13 | 17 | 26 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | . | 1.8 | 0.9 | 2.4 |
| GLUC (mg/dL) | 22 | Mean | 95 | 100 | 102 | 98 |
| | | SD | 12 | 9 | 13 | 8 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | . | 5.4 | 7.1 | 2.6 |
| TP (g/dL) | 22 | Mean | 6.0 | 6.1 | 6.2 | 6.0 |
| | | SD | 0.2 | 0.2 | 0.2 | 0.2 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | . | 0.7 | 2.8 | 0.2 |
| ALB (g/dL) | 22 | Mean | 3.1 | 3.2 | 3.3 #[1] | 3.2 |
| | | SD | 0.1 | 0.1 | 0.1 | 0.1 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | . | 2.2 | 4.1 | 1.9 |
| GLOB (g/dL) | 22 | Mean | 2.9 | 2.8 | 2.9 | 2.8 |
| | | SD | 0.1 | 0.2 | 0.1 | 0.2 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | . | -1.0 | 1.4 | -1.7 |
| CALC (mg/dL) | 22 | Mean | 10.4 | 10.4 | 10.4 | 10.5 |
| | | SD | 0.2 | 0.2 | 0.2 | 0.2 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | . | -0.1 | 0.1 | 0.8 |
| IPHS (mg/dL) | 22 | Mean | 8.6 | 8.7 | 8.8 | 8.6 |
| | | SD | 0.4 | 0.4 | 0.9 | 0.4 |
| | | N | 5 | 9 | 6 | 8 |
| | | %Diff | . | 0.6 | 2.1 | -0.3 |
| NA (mmol/L) | 22 | Mean | 140.5 | 142.1 | 141.1 | 141.7 |
| | | SD | 4.2 | 0.6 | 0.7 | 0.8 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | . | 1.1 | 0.4 | 0.9 |

General Footnote: [Statistical Test: Anova and Dunnett's test Transformation :Automatic]
1 [#- Test: Dunnett 2 Sided $p < 0.05$]

| Sex: Male | Day(s) Relative to Start Date | | 0 mg/kg/day Group 1 | 250 mg/kg/day Group 2 | 500 mg/kg/day Group 3 | 750 mg/kg/day Group 4 |
|---|---|---|---|---|---|---|
| K (mmol/L) | 22 | Mean | 5.03 | 5.19 | 5.55 #[1] | 5.10 |
| | | SD | 0.25 | 0.26 | 0.61 | 0.25 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | . | 3.1 | 10.4 | 1.4 |
| CL (mmol/L) | 22 | Mean | 100.8 | 102.0 | 101.6 | 101.7 |
| | | SD | 2.4 | 1.0 | 0.8 | 1.2 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | . | 1.2 | 0.8 | 0.9 |

General Footnote: [Statistical Test: Anova and Dunnett's test Transformation :Automatic]
1 [#- Test: Dunnett 2 Sided $p < 0.05$]

| Sex: Female | Day(s) Relative to Start Date | | 0 mg/kg/day Group 1 | 250 mg/kg/day Group 2 | 500 mg/kg/day Group 3 | 750 mg/kg/day Group 4 |
|---|---|---|---|---|---|---|
| AST (U/L) | 22 | Mean | 69 | 69 | 64 | 65 |
| | | SD | 6 | 10 | 8 | 6 |
| | | N | 9 | 9 | 10 | 10 |
| | | %Diff | . | -0.3 | -7.4 | -6.5 |
| ALT (U/L) | 22 | Mean | 25 | 26 | 25 | 27 |
| | | SD | 4 | 5 | 6 | 5 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | . | 2.8 | -0.4 | 5.2 |
| SDH (U/L) | 22 | Mean | 8.7 | 8.1 | 8.0 | 9.9 |
| | | SD | 2.2 | 1.2 | 0.9 | 2.5 |
| | | N | 9 | 9 | 10 | 10 |
| | | %Diff | . | -7.4 | -9.0 | 12.9 |
| ALKP (U/L) | 22 | Mean | 137 | 107 #[1] | 121 | 108 #[1] |
| | | SD | 16 | 19 | 29 | 25 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | . | -22.4 | -12.1 | -21.3 |
| BILI (mg/dL) | 22 | Mean | 0.18 | 0.19 | 0.20 | 0.19 |
| | | SD | 0.02 | 0.02 | 0.02 | 0.03 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | . | 8.4 | 10.6 | 7.8 |
| BUN (mg/dL) | 22 | Mean | 12 | 11 | 12 | 12 |
| | | SD | 2 | 1 | 2 | 1 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | . | -11.5 | -0.8 | 0.0 |
| CREA (mg/dL) | 22 | Mean | 0.28 | 0.26 | 0.27 | 0.28 |
| | | SD | 0.02 | 0.02 | 0.03 | 0.03 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | . | -6.9 | -2.9 | 1.1 |
| CHOL (mg/dL) | 22 | Mean | 85 | 95 | 98 | 94 |
| | | SD | 11 | 19 | 19 | 22 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | . | 12.2 | 15.6 | 11.2 |

General Footnote: [Statistical Test: Anova and Dunnett's test Transformation :Automatic]
1 [#- Test: Dunnett 2 Sided $p < 0.05$]

| Sex: Female | Day(s) Relative to Start Date | | 0 mg/kg/day Group 1 | 250 mg/kg/day Group 2 | 500 mg/kg/day Group 3 | 750 mg/kg/day Group 4 |
|---|---|---|---|---|---|---|
| TRIG (mg/dL) | 22 | Mean | 37 | 38 | 46 | 35 |
| | | SD | 6 | 9 | 15 | 8 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | . | 3.5 | 24.9 | -4.3 |
| GLUC (mg/dL) | 22 | Mean | 118 | 103 #[1] | 104 #[1] | 110 |
| | | SD | 15 | 10 | 10 | 14 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | . | -13.3 | -12.0 | -6.7 |
| TP (g/dL) | 22 | Mean | 6.4 | 6.7 | 6.8 | 6.7 |
| | | SD | 0.3 | 0.4 | 0.3 | 0.4 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | . | 5.1 | 5.6 | 3.7 |
| ALB (g/dL) | 22 | Mean | 3.5 | 3.7 | 3.7 | 3.6 |
| | | SD | 0.2 | 0.2 | 0.2 | 0.3 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | . | 4.0 | 4.6 | 3.4 |
| GLOB (g/dL) | 22 | Mean | 2.9 | 3.1 | 3.1 #[1] | 3.0 |
| | | SD | 0.1 | 0.2 | 0.2 | 0.1 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | . | 6.6 | 6.9 | 4.1 |
| CALC (mg/dL) | 22 | Mean | 10.5 | 10.9 #[1] | 11.0 #[1] | 10.7 |
| | | SD | 0.3 | 0.3 | 0.3 | 0.4 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | . | 3.8 | 5.1 | 1.8 |
| IPHS (mg/dL) | 22 | Mean | 7.1 | 7.8 | 7.6 | 7.1 |
| | | SD | 0.5 | 0.6 | 0.4 | 0.8 |
| | | N | 9 | 9 | 10 | 10 |
| | | %Diff | . | 9.7 | 6.5 | -0.6 |
| NA (mmol/L) | 22 | Mean | 140.3 | 140.6 | 140.3 | 140.2 |
| | | SD | 1.1 | 0.6 | 0.7 | 1.1 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | . | 0.2 | 0.0 | 0.0 |

General Footnote: [Statistical Test: Anova and Dunnett's test Transformation :Automatic]
1 [#- Test: Dunnett 2 Sided $p < 0.05$]

| Sex: Female | Day(s) Relative to Start Date | | 0 mg/kg/day Group 1 | 250 mg/kg/day Group 2 | 500 mg/kg/day Group 3 | 750 mg/kg/day Group 4 |
|---|---|---|---|---|---|---|
| K (mmol/L) | 22 | Mean | 4.56 | 4.63 | 4.72 | 4.74 |
| | | SD | 0.33 | 0.38 | 0.21 | 0.38 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | . | 1.5 | 3.5 | 4.0 |
| CL (mmol/L) | 22 | Mean | 102.6 | 101.3 #1 | 101.1 #1 | 102.1 |
| | | SD | 1.2 | 1.4 | 1.0 | 1.1 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | . | -1.3 | -1.5 | -0.5 |

General Footnote: [Statistical Test: Anova and Dunnett's test Transformation :Automatic]
1 [#- Test: Dunnett 2 Sided p < 0.05]

## TABLE 12: SUMMARY OF URINALYSIS VALUES[1]

[1] Individual data are reported in the Clinical Pathology Report presented in Appendix N.

| Sex: Male | Day(s) Relative to Start Date | | 0 mg/kg/day Group 1 | 250 mg/kg/day Group 2 | 500 mg/kg/day Group 3 | 750 mg/kg/day Group 4 |
|---|---|---|---|---|---|---|
| UVOL (mL) | 22 | Mean | 11.7 | 11.5 | 12.3 | 14.3 |
| | | SD | 8.2 | 9.8 | 7.3 | 7.7 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | . | -1.8 | 4.8 | 22.0 |
| pH | 22 | Mean | 6.5 | 6.5 | 6.6 | 6.6 |
| | | SD | 0.3 | 0.4 | 0.4 | 0.4 |
| | | N | 10 | 9 | 10 | 10 |
| | | %Diff | . | 0.0 | 0.8 | 1.5 |
| SG | 22 | Mean | 1.027 | 1.027 | 1.026 | 1.024 |
| | | SD | 0.019 | 0.015 | 0.015 | 0.019 |
| | | N | 10 | 9 | 10 | 10 |
| | | %Diff | . | 0.0 | -0.1 | -0.3 |
| URO (EU/dL) | 22 | Mean | 0.3 | 0.2 | 0.3 | 0.2 |
| | | SD | 0.3 | 0.0 | 0.3 | 0.0 |
| | | N | 10 | 9 | 10 | 10 |
| | | %Diff | . | -28.6 | 0.0 | -28.6 |
| UMTP (mg/dL) | 22 | Mean | 104 | 241 | 124 | 111 |
| | | SD | 49 | 365 | 80 | 97 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | . | 132.5 | 19.5 | 7.4 |

General Footnote: [Statistical Test: Anova and Dunnett's test Transformation :Automatic]

| Sex: Female | Day(s) Relative to Start Date | | 0 mg/kg/day Group 1 | 250 mg/kg/day Group 2 | 500 mg/kg/day Group 3 | 750 mg/kg/day Group 4 |
|---|---|---|---|---|---|---|
| UVOL (mL) | 22 | Mean | 7.8 | 6.8 | 6.5 | 6.6 |
| | | SD | 6.4 | 5.1 | 3.0 | 4.1 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | . | -12.3 | -15.9 | -14.9 |
| pH | 22 | Mean | 6.4 | 6.2 | 6.6 | 6.5 |
| | | SD | 0.4 | 0.4 | 0.6 | 0.6 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | . | -3.9 | 3.1 | 0.8 |
| SG | 22 | Mean | 1.037 | 1.035 | 1.028 | 1.030 |
| | | SD | 0.027 | 0.023 | 0.011 | 0.013 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | . | -0.2 | -0.8 | -0.6 |
| URO (EU/dL) | 22 | Mean | 0.2 | 0.2 | 0.2 | 0.3 |
| | | SD | 0.0 | 0.0 | 0.0 | 0.3 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | . | 0.0 | 0.0 | 40.0 |
| UMTP (mg/dL) | 22 | Mean | 43 | 41 | 34 | 44 |
| | | SD | 34 | 25 | 12 | 30 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | . | -3.7 | -20.0 | 3.5 |

General Footnote: [Statistical Test: Anova and Dunnett's test Transformation :Automatic]

## TABLE 13: SUMMARY OF GROSS NECROPSY OBSERVATIONS[1]

[1] Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient.
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

| Removal Reason: ALL | Male | | | | Female | | | |
|---|---|---|---|---|---|---|---|---|
| | 0 mg/kg/day Group 1 | 512 mg/kg/day Group 2 | 1024 mg/kg/day Group 3 | 1536 mg/kg/day Group 4 | 0 mg/kg/day Group 1 | 512 mg/kg/day Group 2 | 1024 mg/kg/day Group 3 | 1536 mg/kg/day Group 4 |
| Number of Animals | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Number of Completed Animals | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| **spleen** | | | | | | | | |
| Submitted | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| structure | | | | | | . | 1 | |
| **testes-combined** | | | | | | | | |
| Submitted | 10 | 10 | 10 | 10 | | | | |
| right, small, soft | 1 | . | . | | | . | . | . |
| **uterus** | | | | | | | | |
| Submitted | . | . | . | | 10 | 10 | 10 | 10 |
| fluid filled | | | | | 4 | | 1 | |
| **epididymides-combined** | | | | | | | | |
| Submitted | 10 | 10 | 10 | 10 | . | . | . | . |
| right, small | 1 | | . | | | . | . | |

## TABLE 14: SUMMARY OF MEAN TERMINAL BODY AND ORGAN WEIGHTS[1]

[1] Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient.
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

| Sex: Male | Day(s) Relative to Start Date | | 0 mg/kg/day Group 1 | 512 mg/kg/day Group 2 | 1024 mg/kg/day Group 3 | 1536 mg/kg/day Group 4 |
|---|---|---|---|---|---|---|
| Terminal BW (g) | - | Mean | 367.5 | 372.5 | 384.0 | 379.3 |
| | | SD | 25.3 | 23.8 | 33.4 | 21.4 |
| | | N | 10 | 10 | 10 | 10 |
| Adrenal Glands Wt (g) | - | Mean | 0.0654 [1] | 0.0655 | 0.0593 | 0.0672 |
| | | SD | 0.0068 | 0.0112 | 0.0116 | 0.0098 |
| | | N | 10 | 10 | 10 | 10 |
| Brain Wt (g) | - | Mean | 2.141 [1] | 2.143 | 2.186 | 2.152 |
| | | SD | 0.095 | 0.110 | 0.140 | 0.105 |
| | | N | 10 | 10 | 10 | 10 |
| Epididymides Wt (g) | - | Mean | 1.032 [1] | 1.088 | 1.035 | 1.008 |
| | | SD | 0.123 | 0.083 | 0.131 | 0.100 |
| | | N | 10 | 10 | 10 | 10 |
| Heart Wt (g) | - | Mean | 1.195 [1] | 1.254 | 1.272 | 1.219 |
| | | SD | 0.104 | 0.121 | 0.113 | 0.088 |
| | | N | 10 | 10 | 10 | 10 |
| Kidneys Wt (g) | - | Mean | 2.641 [1] | 2.678 | 2.789 | 2.800 |
| | | SD | 0.297 | 0.219 | 0.246 | 0.241 |
| | | N | 10 | 10 | 10 | 10 |
| Liver Wt (g) | - | Mean | 11.218 [1] | 11.182 | 12.317 | 12.093 |
| | | SD | 1.657 | 0.691 | 1.804 | 1.452 |
| | | N | 10 | 10 | 10 | 10 |
| Spleen Wt (g) | - | Mean | 0.831 [1] | 0.813 | 0.769 | 0.809 |
| | | SD | 0.125 | 0.107 | 0.053 | 0.105 |
| | | N | 10 | 10 | 10 | 10 |
| Testes Wt (g) | - | Mean | 3.148 [2] | 3.381 | 3.266 | 3.272 |
| | | SD | 0.531 | 0.292 | 0.251 | 0.246 |
| | | N | 10 | 10 | 10 | 10 |
| Thymus Wt (g) | - | Mean | 0.5205 [1] | 0.5661 | 0.5466 | 0.5276 |
| | | SD | 0.1595 | 0.1162 | 0.1185 | 0.1097 |
| | | N | 10 | 10 | 10 | 10 |

1 [I - Automatic Transformation: Identity (No Transformation)]
2 [R - Automatic Transformation: Rank]

| Sex: Female | Day(s) Relative to Start Date | | 0 mg/kg/day Group 1 | 512 mg/kg/day Group 2 | 1024 mg/kg/day Group 3 | 1536 mg/kg/day Group 4 |
|---|---|---|---|---|---|---|
| Terminal BW (g) | - | Mean | 229.2 | 225.6 | 236.3 | 233.8 |
| | | SD | 22.3 | 22.7 | 14.5 | 11.9 |
| | | N | 10 | 10 | 10 | 10 |
| Adrenal Glands Wt (g) | - | Mean | 0.0717 [1] | 0.0713 | 0.0664 | 0.0737 |
| | | SD | 0.0067 | 0.0089 | 0.0092 | 0.0093 |
| | | N | 10 | 10 | 10 | 10 |
| Brain Wt (g) | - | Mean | 2.007 [1] | 1.976 | 2.046 | 2.021 |
| | | SD | 0.093 | 0.099 | 0.077 | 0.049 |
| | | N | 10 | 10 | 10 | 10 |
| Heart Wt (g) | - | Mean | 0.840 [1] | 0.830 | 0.850 | 0.848 |
| | | SD | 0.092 | 0.057 | 0.034 | 0.065 |
| | | N | 10 | 10 | 10 | 10 |
| Kidneys Wt (g) | - | Mean | 1.752 [1] | 1.820 | 1.769 | 1.815 |
| | | SD | 0.164 | 0.177 | 0.140 | 0.101 |
| | | N | 10 | 10 | 10 | 10 |
| Liver Wt (g) | - | Mean | 7.156 [1] | 7.636 | 7.338 | 7.763 |
| | | SD | 0.720 | 1.037 | 0.512 | 0.548 |
| | | N | 10 | 10 | 10 | 10 |
| Ovaries with Oviducts Wt (g) | - | Mean | 0.1309 [1] | 0.1272 | 0.1231 | 0.1364 |
| | | SD | 0.0173 | 0.0172 | 0.0143 | 0.0150 |
| | | N | 10 | 10 | 10 | 10 |
| Spleen Wt (g) | - | Mean | 0.498 [1] | 0.518 | 0.507 | 0.513 |
| | | SD | 0.088 | 0.119 | 0.068 | 0.060 |
| | | N | 10 | 10 | 10 | 10 |
| Thymus Wt (g) | - | Mean | 0.4343 [1] | 0.4654 | 0.4762 | 0.5218 |
| | | SD | 0.0998 | 0.0741 | 0.0967 | 0.1127 |
| | | N | 10 | 10 | 10 | 10 |
| Uterus Wt (g) | - | Mean | 0.727 [2] | 0.457 dd[3] | 0.615 | 0.490 d[4] |
| | | SD | 0.247 | 0.061 | 0.276 | 0.057 |
| | | N | 10 | 10 | 10 | 10 |

1 [I - Automatic Transformation: Identity (No Transformation)]
2 [R - Automatic Transformation: Rank]
3 [dd - Test: Dunn 2 Sided p < 0.01]
4 [d - Test: Dunn 2 Sided p < 0.05]

## TABLE 15: SUMMARY OF MEAN ORGAN-TO-BODY WEIGHT RATIOS[1]

[1] Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient.
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

| Sex: Male | Day(s) Relative to Start Date | | 0 mg/kg/day Group 1 | 512 mg/kg/day Group 2 | 1024 mg/kg/day Group 3 | 1536 mg/kg/day Group 4 |
|---|---|---|---|---|---|---|
| Adrenal /TBW (Ratio) | - | Mean | 0.1781 [1] | 0.1766 | 0.1540 | 0.1773 |
| | | SD | 0.0165 | 0.0328 | 0.0253 | 0.0264 |
| | | N | 10 | 10 | 10 | 10 |
| Brain /TBW (Ratio) | - | Mean | 5.846 [1] | 5.766 | 5.722 | 5.682 |
| | | SD | 0.411 | 0.355 | 0.497 | 0.294 |
| | | N | 10 | 10 | 10 | 10 |
| Epididymides /TBW (Ratio) | - | Mean | 2.8075 [1] | 2.9351 | 2.7030 | 2.6712 |
| | | SD | 0.2682 | 0.3125 | 0.3143 | 0.3544 |
| | | N | 10 | 10 | 10 | 10 |
| Heart /TBW (Ratio) | - | Mean | 3.251 [1] | 3.362 | 3.315 | 3.214 |
| | | SD | 0.151 | 0.151 | 0.128 | 0.149 |
| | | N | 10 | 10 | 10 | 10 |
| Kidneys /TBW (Ratio) | - | Mean | 7.184 [1] | 7.199 | 7.274 | 7.387 |
| | | SD | 0.610 | 0.541 | 0.421 | 0.560 |
| | | N | 10 | 10 | 10 | 10 |
| Liver /TBW (Ratio) | - | Mean | 30.549 [2] | 30.052 | 31.962 | 31.893 |
| | | SD | 4.348 | 1.405 | 2.654 | 3.559 |
| | | N | 10 | 10 | 10 | 10 |
| Spleen /TBW (Ratio) | - | Mean | 2.256 [1] | 2.199 | 2.012 | 2.139 |
| | | SD | 0.255 | 0.391 | 0.184 | 0.312 |
| | | N | 10 | 10 | 10 | 10 |
| Testes /TBW (Ratio) | - | Mean | 8.549 [1] | 9.108 | 8.564 | 8.657 |
| | | SD | 1.201 | 0.971 | 0.970 | 0.885 |
| | | N | 10 | 10 | 10 | 10 |
| Thymus /TBW (Ratio) | - | Mean | 1.4134 [1] | 1.5209 | 1.4171 | 1.3939 |
| | | SD | 0.4037 | 0.3105 | 0.2319 | 0.2919 |
| | | N | 10 | 10 | 10 | 10 |

1 [I - Automatic Transformation: Identity (No Transformation)]
2 [R - Automatic Transformation: Rank]

| Sex: Female | Day(s) Relative to Start Date | | 0 mg/kg/day Group 1 | 512 mg/kg/day Group 2 | 1024 mg/kg/day Group 3 | 1536 mg/kg/day Group 4 |
|---|---|---|---|---|---|---|
| Adrenal /TBW (Ratio) | - | Mean | 0.3139 [1] | 0.3168 | 0.2812 | 0.3157 |
| | | SD | 0.0265 | 0.0336 | 0.0372 | 0.0399 |
| | | N | 10 | 10 | 10 | 10 |
| Brain /TBW (Ratio) | - | Mean | 8.801 [1] | 8.828 | 8.692 | 8.664 |
| | | SD | 0.545 | 0.852 | 0.686 | 0.492 |
| | | N | 10 | 10 | 10 | 10 |
| Heart /TBW (Ratio) | - | Mean | 3.665 [1] | 3.692 | 3.605 | 3.625 |
| | | SD | 0.189 | 0.171 | 0.178 | 0.163 |
| | | N | 10 | 10 | 10 | 10 |
| Kidneys /TBW (Ratio) | - | Mean | 7.657 [1] | 8.094 | 7.505 | 7.783 |
| | | SD | 0.412 | 0.639 | 0.657 | 0.602 |
| | | N | 10 | 10 | 10 | 10 |
| Liver /TBW (Ratio) | - | Mean | 31.278 [1] | 33.819 | 31.158 | 33.269 |
| | | SD | 2.212 | 2.693 | 2.883 | 2.772 |
| | | N | 10 | 10 | 10 | 10 |
| Ovaries with oviducts/TBW (Ratio) | - | Mean | 0.5727 [1] | 0.5635 | 0.5222 | 0.5835 |
| | | SD | 0.0669 | 0.0474 | 0.0643 | 0.0581 |
| | | N | 10 | 10 | 10 | 10 |
| Spleen /TBW (Ratio) | - | Mean | 2.171 [1] | 2.284 | 2.149 | 2.191 |
| | | SD | 0.300 | 0.384 | 0.291 | 0.206 |
| | | N | 10 | 10 | 10 | 10 |
| Thymus /TBW (Ratio) | - | Mean | 1.8863 [1] | 2.0742 | 2.0184 | 2.2362 |
| | | SD | 0.3463 | 0.3287 | 0.4067 | 0.4918 |
| | | N | 10 | 10 | 10 | 10 |
| Uterus /TBW (Ratio) | - | Mean | 3.159 [2] | 2.060 DD | 2.579 | 2.103 DD |
| | | SD | 0.949 | 0.452 | 1.063 | 0.277 |
| | | N | 10 | 10 | 10 | 10 |

1 [I - Automatic Transformation: Identity (No Transformation)]
2 [L,AA - Automatic Transformation: Log, (All Groups) Test: Analysis of Variance $p < 0.01$]
3 [DD - Test: Dunnett 2 Sided $p < 0.01$]

## TABLE 16: SUMMARY OF MEAN ORGAN-TO-BRAIN WEIGHT RATIOS[1]

[1] Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient.
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

| Sex: Male | Day(s) Relative to Start Date | | 0 mg/kg/day Group 1 | 512 mg/kg/day Group 2 | 1024 mg/kg/day Group 3 | 1536 mg/kg/day Group 4 |
|---|---|---|---|---|---|---|
| Adrenal /BrW (Ratio) | - | Mean | 0.0306 I[1] | 0.0307 | 0.0270 | 0.0312 |
| | | SD | 0.0031 | 0.0056 | 0.0043 | 0.0039 |
| | | N | 10 | 10 | 10 | 10 |
| Epididymides /BrW (Ratio) | - | Mean | 0.4813 I[1] | 0.5095 | 0.4738 | 0.4700 |
| | | SD | 0.0455 | 0.0535 | 0.0521 | 0.0573 |
| | | N | 10 | 10 | 10 | 10 |
| Heart /BrW (Ratio) | - | Mean | 0.558 R[2] | 0.585 | 0.583 | 0.566 |
| | | SD | 0.038 | 0.048 | 0.052 | 0.027 |
| | | N | 10 | 10 | 10 | 10 |
| Kidneys /BrW (Ratio) | - | Mean | 1.232 I[1] | 1.251 | 1.278 | 1.300 |
| | | SD | 0.114 | 0.100 | 0.114 | 0.078 |
| | | N | 10 | 10 | 10 | 10 |
| Liver /BrW (Ratio) | - | Mean | 5.238 I[1] | 5.228 | 5.633 | 5.614 |
| | | SD | 0.727 | 0.374 | 0.740 | 0.579 |
| | | N | 10 | 10 | 10 | 10 |
| Spleen /BrW (Ratio) | - | Mean | 0.388 I[1] | 0.380 | 0.353 | 0.376 |
| | | SD | 0.057 | 0.055 | 0.039 | 0.044 |
| | | N | 10 | 10 | 10 | 10 |
| Testes /BrW (Ratio) | - | Mean | 1.469 I[1] | 1.581 | 1.498 | 1.523 |
| | | SD | 0.235 | 0.155 | 0.123 | 0.125 |
| | | N | 10 | 10 | 10 | 10 |
| Thymus /BrW (Ratio) | - | Mean | 0.2436 I[1] | 0.2630 | 0.2502 | 0.2450 |
| | | SD | 0.0739 | 0.0472 | 0.0514 | 0.0476 |
| | | N | 10 | 10 | 10 | 10 |

1 [I - Automatic Transformation: Identity (No Transformation)]
2 [R - Automatic Transformation: Rank]

| Sex: Female | Day(s) Relative to Start Date | | 0 mg/kg/day Group 1 | 512 mg/kg/day Group 2 | 1024 mg/kg/day Group 3 | 1536 mg/kg/day Group 4 |
|---|---|---|---|---|---|---|
| Adrenal /BrW (Ratio) | - | Mean | 0.0357 I[1] | 0.0361 | 0.0325 | 0.0365 |
| | | SD | 0.0024 | 0.0043 | 0.0047 | 0.0050 |
| | | N | 10 | 10 | 10 | 10 |
| Heart /BrW (Ratio) | - | Mean | 0.418 I[1] | 0.420 | 0.416 | 0.420 |
| | | SD | 0.031 | 0.028 | 0.026 | 0.036 |
| | | N | 10 | 10 | 10 | 10 |
| Kidneys /BrW (Ratio) | - | Mean | 0.872 I[1] | 0.920 | 0.866 | 0.898 |
| | | SD | 0.056 | 0.062 | 0.080 | 0.049 |
| | | N | 10 | 10 | 10 | 10 |
| Liver /BrW (Ratio) | - | Mean | 3.566 I[1] | 3.862 | 3.592 | 3.842 |
| | | SD | 0.325 | 0.476 | 0.310 | 0.267 |
| | | N | 10 | 10 | 10 | 10 |
| Ovaries with oviducts/BrW (Ratio) | - | Mean | 0.0652 I[1] | 0.0644 | 0.0603 | 0.0676 |
| | | SD | 0.0075 | 0.0086 | 0.0079 | 0.0078 |
| | | N | 10 | 10 | 10 | 10 |
| Spleen /BrW (Ratio) | - | Mean | 0.248 I[1] | 0.261 | 0.248 | 0.254 |
| | | SD | 0.039 | 0.054 | 0.035 | 0.031 |
| | | N | 10 | 10 | 10 | 10 |
| Thymus /BrW (Ratio) | - | Mean | 0.2158 I[1] | 0.2366 | 0.2332 | 0.2583 |
| | | SD | 0.0459 | 0.0434 | 0.0489 | 0.0561 |
| | | N | 10 | 10 | 10 | 10 |
| Uterus /BrW (Ratio) | - | Mean | 0.361 R[2] | 0.232 dd[3] | 0.301 | 0.242 d[4] |
| | | SD | 0.118 | 0.033 | 0.136 | 0.028 |
| | | N | 10 | 10 | 10 | 10 |

1 [I - Automatic Transformation: Identity (No Transformation)]
2 [R - Automatic Transformation: Rank]
3 [dd - Test: Dunn 2 Sided p < 0.01]
4 [d - Test: Dunn 2 Sided p < 0.05]

# APPENDIX A: PROTOCOL AND PROTOCOL AMENDMENTS

## PRODUCT IDENTIFICATION

Soy Leghemoglobin Preparation

**Product Safety Labs**

28-Day dietary Study in rats
Protocol # P703.01 IMP
PSL ID: 160720-5R
Study No: 43166

# SOY LEGHEMOGLOBIN PREPARATION: A 28-DAY DIETARY STUDY IN RATS

## PRODUCT IDENTIFICATION

Soy Leghemoglobin Preparation

## PSL PROTOCOL NO.

P703.01 IMP

## PERFORMING LABORATORY

Product Safety Labs
2394 US Highway 130
Dayton, New Jersey 08810

## PSL STUDY NUMBER

43166

## STUDY DIRECTOR

Mithila Shitut, BVSc & AH, MS

## SPONSOR

Impossible Foods, Inc.
525 Chesapeake Dr.
Redwood City, CA 94063

**Product Safety Labs**

28-Day dietary Study in rats
Protocol # P703.01 IMP
PSL ID: 160720-5R
Study No: 43166

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**Product Safety Labs**

28-Day dietary Study in rats
Protocol # P703.01 IMP
PSL ID: 160720-5R
Study No: 43166

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# Product Safety Labs



## 1. TITLE OF STUDY: SOY LEGHEMOGLOBIN PREPARATION: A 28-DAY DIETARY STUDY IN RATS

## 2. OBJECTIVE

The objective of this study is to evaluate the potential subchronic toxicity of Soy Leghemoglobin Preparation in male and female rats continuously exposed to the test substance in the diet for at least 28 days. A no-observed-adverse-effect-level (NOAEL) is sought for each sex.

## 3. STUDY DIRECTOR

Mithila Shitut
Study Director
Tel: 732-438-5100 x1558
Email: MithilaShitut@ProductSafetyLabs.com

## 4. NAME AND ADDRESS OF THE TESTING FACILITY

Product Safety Labs (PSL)
2394 US Highway 130
Dayton, NJ 08810
Tel: 732 438 5100

## 5. SPONSOR

Impossible Foods, Inc.
525 Chesapeake Dr.
Redwood City, CA 94063

## 6. SPONSOR REPRESENTATIVE

Rachel Fraser
Impossible Foods, Inc.
525 Chesapeake Dr.
Redwood City, CA 94063
Email: rachel.fraser@impossiblefoods.com

## 7. DATES

Proposed In-Life Start Date: 9/28/16

Proposed Experimental Termination Date: 10/28/16

## 8. TEST SUBSTANCE

### 8.A Source

The test substance will be provided by the Sponsor.

### 8.B Identification

The test substance will be identified using the following information provided by the Sponsor and Product Safety Labs (PSL) identification number.

Test Substance: Soy Leghemoglobin Preparation
PSL ID: 160720-5R
Lot #: PP-PGM2-16-088-301
Physical Description: Red/brown powder
Composition: Soy Leghemoglobin 48.82%
Storage Conditions: Frozen
Expiration Date: Not Applicable

Documentation of the methods of synthesis, fabrication, or derivation of the test substance is retained by the Sponsor.

### 8.C Analysis

The test substance, as received, is expected to be stable for the duration of the study. Stability of the test substance in the dietary matrix and that of the concentration of the test substance in the test diets will be determined as part of this study.

### 8.D Hazards

Appropriate routine safety precautions will be exercised in the handling of the test substance unless otherwise indicated by the Sponsor.

## 9. GENERAL TEST SYSTEM PARAMETERS

### 9.A Animal Requirements

9.A.1 Number of Animals: 80

9.A.2 Number of Groups: 4 (3 dietary levels per sex + 1 control group per sex)

9.A.3 Number of Animals per Group: 20 (10 male, 10 female)

9.A.4 Sex: Male and female; females will be nulliparous and non-pregnant.

9.A.5 Species/Strain: CRL Sprague-Dawley CD® IGS rats

9.A.6 Age/Weight: Seven to eight weeks at initiation; the weight variation will not exceed ± 20% of the mean weight for each sex.

9.A.7 Supplier: Charles River Laboratories, Inc. Rats will be shipped in filtered cartons by airfreight and/or truck.

### 9.B Test System Justification

The Sprague-Dawley® rat is the system of choice because, historically, it has been a preferred and commonly used species for dietary toxicity tests. The current state of scientific knowledge does not provide acceptable alternatives to the use of live animals to accomplish the objective of this study.

## 9.C Husbandry

### 9.C.1 Housing

The animals will be group housed in suspended stainless steel cages, which conform to the size recommendations in the latest *Guide for the Care and Use of Laboratory Animals*[1]. Litter paper placed beneath the cage will be changed at least three times/week. The animal room will have a 12-hour light/dark cycle and will be kept clean and vermin free. Environmental controls are set to maintain temperature and relative humidity ranges of 21 ± 2°C and 30-70%, respectively. Observed ranges will be documented in the raw data.

### 9.C.2 Acclimation

The animals will be conditioned to the housing facilities for at least five days prior to testing. Body weights and clinical observations will be recorded at least two times prior to study start.

### 9.C.3 Feed

2016 Certified Envigo Teklad Global Rodent Diet® will be stored in a dedicated temperature and humidity monitored feed storage site and will be available *ad libitum* during acclimation. Test diets will be prepared as described in Section 11.B using 2016 certified Envigo Teklad Global Rodent Diet® and will be available *ad libitum* during the study.

### 9.C.4 Water

Filtered tap water will be available *ad libitum* from individual bottles attached to the cages or from an automatic watering access system. Water analysis is conducted by Precision Analytical Services, Inc., Toms River, NJ and South Brunswick Municipal Water Supply, South Brunswick, NJ.

### 9.C.5 Contaminants

There are no known contaminants reasonably expected to be found in the food or water that would interfere with the results of this study. Routine analysis consisting of each lot of feed used in this study will be received from Envigo Teklad, Madison, WI. Water analysis is conducted periodically and the records are kept on file at Product Safety Labs. The date(s) of the most recent analyses will be reported in the final report.

### 9.C.6 Viral Screen

Serum samples from naive rats housed in the same room as test animals, as part of PSL's sentinel health monitoring program, will be evaluated for the absence of viruses near the end of the in-life portion of the study (PSL SOP #755).

[1] National Research Council. (2011). *Guide for the Care and Use of Laboratory Animals (8th ed.)*. Washington, DC: The National Academies Press.

### 9.D Identification

9.D.1 Cage

Each cage will be identified by a cage card indicating at least the study number, dose level, group assignment, individual animal identification and sex of the animals.

9.D.2 Animal

Each animal will be given a sequential number in addition to being uniquely identified with a Monel® self-piercing stainless steel ear tag.

## 10. EXPERIMENTAL DESIGN

### 10.A Route of Administration

The test substance will be administered in the diet.

### 10.B Justification of Route of Administration

The dietary route of administration will be used because it is recommended in the referenced guidelines (Section 14.C.), and because human exposure may occur via this route.

### 10.C Control of Bias

Animals will be randomly assigned to test groups according to PSL SOP # 714.

### 10.D Dose Levels

Ten male and ten female test animals will be randomly assigned to each of the following test groups:

| Group | No. Animals/ Group M/F | Dietary Dose Level/ Target Exposure of Active Ingredient (mg/kg/day) | Dietary Dose Level/ Target Exposure of Test Substance [a] (mg/kg/day) |
|---|---|---|---|
| 1 | 10/10 | 0 | 0 |
| 2 | 10/10 | 250 | 512 |
| 3 | 10/10 | 500 | 1024 |
| 4 | 10/10 | 750 | 1536 |

[a]Based on 48.82% active ingredient (AI, Soy Leghemoglobin) of Soy Leghemoglobin Preparationlot # PP-PGM2-16-088-301

### 10.E Justification of Dose Level Selection

The Sponsor, in consultation with the Study Director, and based on a 14-day palatability/toxicity study (43167[1]) selected target dietary dose levels of 512, 1024 and 1536 mg/kg/day that correspond to target dose levels of 250, 500 and 750 mg/kg/day of the active ingredient, Soy leghemoglobin. To maintain target dietary dose levels throughout the study, concentrations in the test diets will be calculated based on the most recent group body weight and food consumption data. Alternatively, historical control values, relevant to the age and weight of the rats at

[1] Product Safety Labs (2016). Soy Leghemoglobin Preparation, Purified Soy Leghemoglobin Preparation and Bovine Erythrocytes: A 14-day dietary toxicity/palatability study in rats (In Draft).

corresponding intervals will be used. Diets for males and females at each dietary dose level will be made separately each week. A NOAEL is expected to be achieved for this study.

## 11. GENERAL PROCEDURES

### 11.A Selection of Animals

Eighty (80) healthy rats (forty males; forty females) will be used on test. Animals will be selected for this study on the basis of adequate body weight gain, absence of clinical signs of disease or injury, and a body weight within ±20% of the mean within a sex. Selected rats will be distributed by randomization according to stratification by body weight so that there will be no statistically significant difference among group body weight means within a sex.

### 11.B Diet Preparation and Sampling

11.B.1 Diet Preparation (PSL SOP #605)

The test substance will be processed as needed to decrease particle size using a grinder and then added to 2016 Envigo Teklad Global Rodent Diet® and thoroughly mixed in a high-speed mixer. Control diet will be mixed under the same conditions as the diets prepared with the test substance. All diets will be kept frozen following preparation, unless presented to the test animals on the same day as diet preparation. All diets will be prepared approximately weekly.

11.B.2 Diet Presentation

The control and test diets will be presented to their respective groups on Day 0 of the study. The diets will be replaced concurrently with food consumption measurements on Days 3, 7, 10, 14, 17, 21 and 24. Additional diet may be provided as needed throughout the study to insure *ad libitum* feeding. Animals will be exposed to the test diets for at least 28 days.

11.B.3 Sampling (PSL SOP #607)

The neat test substance and selected prepared diets (at each concentration), will be sampled in duplicate.

11.B.4 Stability of Test Substance

At the initial, middle, and final diet preparation, a sample of the test substance (neat) will be retained for stability. Analytical results of the initial and final stability samples will be used to establish the stability of the test substance under normal laboratory conditions for the duration of the study.

11.B.5 Stability in Dietary Matrix

During the first week of the study, samples to verify the stability of the test and control substance in the dietary matrix will be prepared. Samples will be prepared in standard feed jars with followers and retaining rings and will be stored at ambient temperature in the animal room. Samples from each dietary concentration will be collected at the first presentation of the diet and after 4, 7, and 10 days and frozen until analyzed.

11.B.6 Homogeneity

Samples to evaluate homogeneity of the test and control substance distribution will be collected from the initial diet preparation. Samples will be taken from approximately the top, middle and bottom of the diet mixer. Basal diet control samples will be collected

from the middle of the mixer only. Chemical analysis will verify the diets as homogeneous and of accurate concentration throughout the study.

11.B.7 Concentration Verification

Samples will be collected from representative animal diets of the initial (as part of the homogeneity assessment), middle and final diet preparations during which time samples will be retained and stored frozen. Samples will be analyzed to verify the concentration of the test diets.

11.B.8 Sample Preservation

Upon sampling, diet preparations and neat test substance will be stored frozen. Samples will be considered stable from the point at which they are frozen.

11.B.9 Sample Analysis

A single duplicate of the frozen diet samples described above will be sent to Impossible Foods for analysis of diet preparation and neat test substance samples. A signed, analytical report will be provided to the Study Director. This report will include the methodology, pertinent measurements, study results, and tabulated results. Upon completion of the report, all raw data will be transferred to the Study Director to be incorporated into the main study report. Any remaining sample material will be retained at Product Safety Labs until issuance of the final report.

## 11.C Analytical Chemistry

11.C.1 Sample Storage

Upon receipt, all samples will be stored and maintained frozen (approximately -20°C) prior to analysis.

11.C.2 Method Validation

Prior to sample analysis, the suitability of the methods will be demonstrated. Method validation will include, but it not limited to determination of linearity, precision, and accuracy.

11.C.3 Reference Substance

Aliquots of the neat test substance will serve as the reference standard.

11.C.4 Chemical Analysis

Analytical test methodology will be validated by Impossible Foods personnel. Samples will be analyzed in replicate. A detailed description of the analytical test method(s) will be documented. Any remaining sample material will be retained until the issuance of the final report.

11.C.5 Data Reporting

Data will be captured on standard raw data sheets and as instrument output, as necessary, and summarized in tabular form.

11.C.6 Analytical Report and Records to be Maintained

A signed, analytical report will be provided to the Study Director. This report will include the methodology, pertinent measurements, study results, and tabulated results. Upon completion of the report, all raw data will be transferred to the Study Director. The analytical report will be incorporated into the main study report.

### 11.D Ophthalmologic Evaluations

During the acclimation period, the eyes of all rats being considered for study will be examined by focal illumination, indirect ophthalmoscopy and, when indicated, slit-lamp microscopy. Mydriatic eye drops will be administered prior to ophthalmoscopy and the eyes will be examined in subdued light. Subdued light will be maintained in the animal room according to PSL SOP #737. These procedures will be repeated on all surviving test animals prior to test termination.

### 11.E Clinical Observations

All animals will be observed at least twice daily for viability. Cage-side observations of all animals will be performed daily during the study. All findings will be recorded.

On Day 0, prior to the first treatment with the test substance, and approximately weekly thereafter, a detailed observation will be conducted (PSL SOP #726) while handling the animal, generally on days that the animals are weighed and food consumption measurements are taken. Potential signs noted should include, but not be limited to: changes in skin, fur, eyes, and mucous membranes, occurrence of secretions and excretions and autonomic activity (e.g., lacrimation, piloerection, pupil size, unusual respiratory pattern). Likewise, changes in gait, posture and response to handling as well as the presence of clonic or tonic movements, stereotypes (e.g., excessive grooming, repetitive circling), or bizarre behavior (e.g., self-mutilation, walking backwards) should also be recorded. The date and clock time of all observations and/or mortality checks will be recorded.

The Study Director will be promptly notified of severe/remarkable clinical observations and will be advised when an animal is found in a moribund condition and may authorize euthanasia and necropsy as necessary to avoid the loss of quality data. All such authorizations will be recorded in the raw data.

### 11.F Body Weight and Body Weight Gain

Individual body weights will be recorded at least two times during acclimation. Test animals will be weighed on Day 0 (prior to study start) and approximately weekly thereafter (intervals of 7 days ± 1). Decedents need not be weighed. Body weight gain will be calculated for selected intervals and for the study overall.

### 11.G Food Consumption, Food Efficiency, and Dietary Intake of Soy Leghemoglobin Preparation

Individual food consumption will be measured and recorded on Days 3, 7, 10, 14, 17, 21, 24 and at the end of the study. Food efficiency and dietary intake of the test substance (mg/kg/day) will also be calculated and reported.

### 11.H Clinical Pathology

Clinical pathology will be performed on all surviving animals for blood chemistry and hematology of the terminal sacrifice animals once toward the end of the dosing phase of the study. The animals will be fasted overnight prior to blood collection. Blood samples for hematology (except coagulation samples) and clinical chemistry will be collected via sublingual bleeding under isoflurane anesthesia during approximately Week 4 of the test period. Approximately 500 µL of blood will be collected in a pre-calibrated tube containing $K_2EDTA$ for hematology assessments. The whole blood samples will be stored under refrigeration and shipped on cold packs. Approximately 1000 µL of blood will be collected into a tube containing

no preservative for clinical chemistry assessments. These samples will be centrifuged in a refrigerated centrifuge and the serum will be transferred to a labeled tube. Serum samples will be stored in a -80°C freezer and shipped frozen on dry ice. All samples will be shipped to DuPont Haskell Global Centers for Health and Environmental Sciences.

The day before collection of samples for the clinical pathology evaluation, the animals will be placed in metabolism cages. Animals will be fasted after 3 pm (at least 15 hours prior to) and urine will be collected from each animal. Urine samples will be stored under refrigeration and shipped on cold packs or wet ice to DuPont Haskell Global Centers for Health and Environmental Sciences.

Blood samples used to determine the prothrombin time and activated partial thromboplastin time (coagulation) will be collected via the inferior vena cava under isoflurane anesthesia at terminal sacrifice. Approximately 1.8 mL of blood will be collected in a pre-calibrated tube containing 3.2% sodium citrate. These samples will be centrifuged in a refrigerated centrifuge and the plasma will be transferred to labeled tubes. Plasma samples will be stored in a -80°C freezer and shipped frozen in dry ice to DuPont Haskell Global Centers for Health and Environmental Sciences. In addition, a second blood sample will be retained during the exsanguination procedure for future possible evaluation if treatment related effects are identified. Details of this evaluation will be added by amendment.

All blood samples will be evaluated for quality by visual examination.

11.H.1 Hematology: Will include:

| | |
|---|---|
| erythrocyte count (RBC) | hemoglobin concentration (HGB) |
| hematocrit (HCT) | mean corpuscular volume (MCV) |
| mean corpuscular hemoglobin (MCH) | red cell distribution width (RDW) |
| absolute reticulocyte count (ARET) | platelet count (PLT) |

total white blood cell (WBC) and differential leukocyte count

Mean corpuscular hemoglobin concentration (MCHC) will be calculated.

In addition, separate, blood smears, stained with New Methylene Blue or Wright-Giemsa stain, will be prepared from each animal undergoing hematological evaluation and will be examined, if required, to substantiate or clarify the results of hematology findings.

11.H.2 Coagulation: Will include:

prothrombin time (PT)
activated partial thromboplastin time (APTT)

11.H.3 Clinical chemistry: Will include:

| | |
|---|---|
| serum aspartate amino transferase (AST) | serum alanine aminotransferase (ALT) |
| sorbitol dehydrogenase (SDH) | alkaline phosphatase (ALKP) |
| total bilirubin (BILI) | urea nitrogen (BUN) |
| blood creatinine (CREA) | total cholesterol (CHOL) |
| triglycerides (TRIG) | fasting glucose (GLUC) |
| total serum protein (TP) | albumin (ALB) |
| globulin (GLOB) | calcium (CALC) |
| inorganic phosphorus (IPHS) | sodium (NA) |
| potassium (K) | chloride (CL) |

11.H.4 Urinalysis: Will include:

| | | |
|---|---|---|
| quality (QUAL) | pH | ketone (KET) |
| color (COL) | glucose (UGLC) | bilirubin (UBIL) |
| clarity (CLAR) | specific gravity (SG) | blood (BLD) |
| volume (UVOL) | protein (UMTP) | urobilinogen (URO) |
| microscopic urine sediment examination | | |

Any remaining serum samples will be maintained frozen at approximately -80°C and discarded upon approval of the Sponsor at finalization.

## 11.I Terminal Sacrifice and Histopathology

### 11.I.1 Scheduled Sacrifice

At terminal sacrifice, all survivors will be euthanized by exsanguination from the abdominal aorta under isoflurane anesthesia. All animals in the study (including decedents) will be subjected to a gross necropsy, which will include examination of the external surface of the body, all orifices, musculoskeletal system, and the cranial, thoracic, abdominal, and pelvic cavities, with their associated organs and tissues. All gross lesions will be recorded. The following tissues (of all animals sacrificed by design) will be weighed wet as soon as possible after dissection to avoid drying:

| | | |
|---|---|---|
| adrenals (combined) | kidneys (combined) | spleen |
| brain | liver | thymus |
| epididymides (combined) | ovaries with oviducts (combined) | uterus |
| heart | testes (combined) | |

The following organs and tissues from all animals will be preserved in 10% neutral buffered formalin for possible future histopathological examination:

| | | |
|---|---|---|
| accessory genital organs (prostate and seminal vesicles) | ileum with Peyer's patches | rectum |
| adrenals | jejunum | salivary glands (sublingual submandibular, and parotid) |
| all gross lesions | kidneys | skeletal muscle |
| aorta | larynx | skin |
| bone (femur) | liver | spinal cord - 3 levels: cervical, mid- thoracic, and lumbar |
| bone marrow (from femur & sternum) | lungs | spleen |
| brain – 3 sections including medulla/pons, cerebellar, and cerebral cortex | lymph node mandibular | sternum |
| cecum | lymph node mesenteric | stomach |
| cervix | mammary gland | thymus |
| colon | nasal turbinates | thyroid |
| duodenum | nose | trachea |
| esophagus | ovaries | urinary bladder |
| Harderian gland | oviducts | uterus |
| heart | pancreas | vagina |
| | parathyroid | |
| | peripheral nerve (sciatic) | |
| | pharynx | |
| | pituitary gland | |

The following organs and tissues from all animals will be preserved in modified Davidson's fixative and then stored in ethanol for possible future histopathological examination:

| | |
|---|---|
| eyes | optic nerve |
| epididymides | testes |

Additional tissues will be preserved if indicated by signs of toxicity or target organ involvement.

11.L2 Unscheduled Sacrifice

Any rat that dies or is sacrificed because of a moribund condition will be examined for the cause of death or moribund condition on the day the observation is made. Rats will be evaluated for gross lesions. Organs and tissues will be excised, weighed (except for animals found dead), and preserved as described for those animals sacrificed by design.

11.L3 Histopathology

Histological examination will be performed on the preserved organs and tissues of the animals from both the control and high dose groups (Groups 1 and 4, respectively) as well as from any animal that dies during the course of the study. In addition, gross lesions of potential toxicological significance noted in any test groups at the time of terminal sacrifice will also be examined. These examinations may be extended to other tissues and organs from the low and intermediate groups at the request of Pathologist in consultation with the Study Director and Sponsor to further investigate changes observed in the high dose group. The fixed tissues will be trimmed, processed, embedded in paraffin, sectioned with a microtome, placed on glass microscope slides, stained with hematoxylin and eosin (HE) and examined by light microscopy. Additional special stains can be added based on HE evaluation at the discretion of the study pathologist in consultation with the study director and sponsor. Slide preparation and histological assessment, by a board-certified veterinary pathologist, will be performed at Histo-Scientific Research Laboratories (HSRL).

## 12. STATISTICAL ANALYSIS

Product Safety Labs will perform statistical analysis of all data collected during the in-life phase of the study as well as organ weight data, if applicable. The use of the word "significant" or "significantly" indicates a statistically significant difference between the control and the experimental groups. Significance will be judged at a probability value of $p < 0.05$. Male and female rats will be evaluated separately.

### 12.A Statistical Methods (In-Life and Organ Weight Data):

Mean and standard deviations will be calculated for all quantitative data. If warranted by sufficient group sizes, data within groups will be evaluated for homogeneity of variance[1] and normality. Where homogeneous variance and normal distribution is observed, treatment and control groups will be compared using a one-way analysis of variance (ANOVA). When one-way analysis of variance is significant, a comparison of treated groups to control for multiple comparisons will be performed (e.g. Dunnett's test)[2,3]. Where variance is considered significantly

[1] Bartlett, MS. (1937). Properties of sufficiency and statistical tests. *Proceedings of the Royal Statistical Society Series A*, 160: 268-282.
[2] Dunnett, C.W. (1964). New tables for multiple comparisons with a control. *Biometrics*. 20(3), 482-491.
[3] Dunnett, C.W. (1980). Pairwise multiple comparisons in the unequal variance case. *J. Amer. Statist. Assoc.*, 75, 796-800.

different, groups will be compared using a non-parametric method (e.g. Kruskal-Wallis non-parametric analysis of variance) [1]. When non-parametric analysis of variance is significant, a comparison of treated groups to control will be performed (e.g. Dunn's test) [2].

If warranted by sufficient group sizes, the incidence of clinical observations may be evaluated through sequential application of a trend test[3]. Other procedures will be used if appropriate, and will be described in the final report.

Statistical analysis will be conducted using one or more of the following software applications: Provantis® version 9, Tables and Statistics, Instem LSS, Staffordshire UK; INSTAT or Prism Biostatistics, Graph Pad Software, San Diego, CA; Statview, version 5, SAS Institute Inc.; and SigmaStat, version 2. Other statistical methods will be used if appropriate, at the time of analysis, and described in the final report.

### 12.B Statistical Methods (Clinical Pathology)

Significance will be judged at a probability value of $p < 0.05$. Males and females will be analyzed separately (Provantis™ version 8, Tables and Statistics, Instem LSS, Staffordshire UK).

| | | Method of Statistical Analysis | |
|---|---|---|---|
| Parameter | Preliminary Test | If preliminary test is not significant | If preliminary test is significant |
| Clinical Pathology* | Levene's[4] test for homogeneity and Shapiro-Wilk[5] test for normality | One-way analysis of variance followed with Dunnett's test | Transforms of the data to achieve normality and variance homogeneity will be used. The order of transforms attempted will be log, square root, and rank-order. If the log and square root transforms fail, the rank-order will be used. |

* When an individual observation is recorded as being less than a certain value, calculations are performed on half the recorded value. For example, if bilirubin is reported as <0.1, 0.05 is used for any calculations performed with that bilirubin data. When an individual observation is recorded as being greater than a certain value, calculations are performed on the recorded value. For example, if specific gravity was reported as >1.100, 1.100 is used for any calculation performed with that specific gravity data.

Other statistical methods will be used if appropriate, at the time of analysis. The statistical methods used will be described in the final report.

## 13. FINAL REPORT

A signed study report will be provided to the Sponsor. This report will include, but not be limited to, the following information:

- individual animal data (and averages where appropriate) for actual concentration of test substance received; time of observation of each abnormal sign and its subsequent course;
- body weights, food consumption and food efficiency values;
- ophthalmological assessments;

[1] Kruskal, W.H., & Wallis, W.A. (1952). Use of ranks in one-criterion variance analysis. *J. Amer. Statist. Assoc.*, 47, 583-621.
[2] Dunn, O.J. (1964). Multiple contrasts using rank sums. *Technometrics*, 6, 241-252.
[3] Agresti, A (2013). *Categorical Data Analysis* (3rd Edition). John Wiley & Sons, Inc. Hoboken, NJ.
[4] Levene, H. (1960). Robust tests for equality of variances. In: I. Olkin et al (Eds), *Contributions to probability and statistics* (pp. 278-292). Palo Alto, CA: Stanford University Press.
[5] Shapiro, S.S. & Wilk, M.B. (1965). An analysis of variance test for normality (complete samples). *Biometrika*, 52(3-4), 591-611.

- hematology, clinical chemistry, coagulation, and urinalysis results;
- organ weights, organ to body weight and organ to brain weight ratios;
- necropsy and pathology findings;
- test substance and dose preparation analysis;
- a compliance statement signed by the Study Director that states that the report accurately reflects the raw data obtained during the performance of the study and that all applicable GLP regulations were followed in the conduct of the study;
- a Quality Assurance statement summarizing QA activities performed for the study.

## 14. STUDY CONDUCT

### 14.A Laboratory

| | |
|---|---|
| In-life portion | Product Safety Labs<br>2394 US Highway 130<br>Dayton, NJ 08810 |
| Ophthalmology evaluation | Kristina R. Vygantas, DVM, DACVO<br>319 Perrineville Rd.<br>Robbinsville, NJ 08691 |
| Clinical chemistry, hematology, coagulation, and urinalysis | Dupont Haskell Global Centers for Health and Environmental Sciences<br>P.O. Box 30<br>Elkton Road<br>Newark, DE 19714<br>P.I.: Denise Hoban, BA, MLT, ASCP |
| Clinical pathology evaluation | Product Safety Labs<br>2394 US Highway 130<br>Dayton, NJ 08810<br>P.I.: Odete Mendes, DVM, PhD, DACVP, DABT |
| Test substance and dietary analysis | Impossible Foods, Inc<br>525 Chesapeake Dr.<br>Redwood City, CA 94063<br>Prospective P.I.: Rachel Fraser, PhD |
| Histological slide preparation | Histo-Scientific Research Laboratories (HSRL)<br>5930 Main Street<br>Mount Jackson, VA 22842<br>P.I. (histology): Craig Zook |
| Histological slide evaluation | Histo-Scientific Research Laboratories (HSRL)<br>5930 Main Street<br>Mount Jackson, VA 22842<br>Prospective P.I.(s) (pathology): David Garlick, DVM, DACVP<br>Laura E. Elcock, DVM, PhD, DACVP<br>Elizabeth H. Hutto, DVM, PhD, DACVP<br>Daphne Vasconcelos, DVM, PhD, DACVP, DABT<br>Allen Singer, DVM, DACVP, DABT |

### 14.B GLP Compliance

This study will be conducted in compliance with the following regulations:

- U.S. FDA GLP: 21 CFR Part 58, 1987

Which is compatible with:

- OECD Principles of Good Laboratory Practice (as revised in 1997) published in ENV/MC/CHEM (98)17, OECD, Paris, 1998.

Clinical pathology evaluation will be conducted in compliance with U.S. FDA GLP: 21 CFR Part 58, 1987 which is compatible with OECD Good Laboratory Practices.

Analytical chemistry will be performed in conformance with GLP principles in a non-GLP facility.

### 14.C Test Procedure Guidelines

This study design is based on the following guidelines:

- OECD Guidelines for Testing of Chemicals and Food Ingredients, Section 4 (Part 407): Health Effects, Repeated Dose 28-Day Oral Toxicity Study in Rodents (2008).
- US FDA Toxicological Principles for the Safety Assessment of Food Ingredients, Redbook 2000, IV.C. 4. a. *Subchronic Toxicity Studies with Rodents* (2007).

## 15. QUALITY ASSURANCE

The Quality Assurance Unit (QAU) of PSL has reviewed this protocol for GLP compliance and will conduct in-process inspections of selected procedures during the study. The final report will be audited for agreement with the raw data records and for compliance with the protocol and PSL SOPs.

In addition, PSL QAU will function as lead QA for this study and will monitor QA activities at DuPont Haskell Global Centers for Health and Environmental Sciences and HSRL. For portions of the study conducted by a subcontractor, the QAU for that facility will conduct necessary critical phase inspections and audit respective results and reports for the study phase according to the SOPs of that facility.

The QA Units from DuPont Haskell Global Centers for Health and Environmental Sciences and HSRL will send all GLP audit reports to the Study Director, Study Director's management, and PSL QAU as soon as they are issued.

## 16. RECORDS TO BE MAINTAINED

The original signed report will be sent to the Sponsor. A copy of the signed report, together with the protocol and all raw data generated at Product Safety Labs, will be maintained in the Product Safety Labs Archives. PSL will maintain these records for a period of at least five years. After this time, the Sponsor of the study will be offered the opportunity to take possession of the records or will be charged an archiving fee for continued archiving by PSL.

The following records will be maintained:

A. Information on test substance will include but not be limited to the following:

| | |
|---|---|
| Storage | Dietary analysis |
| Usage | Test substance analysis |
| Disposition | |

B. Information on animals will include, but not be limited to the following:

| | |
|---|---|
| Receipt, date of birth | Clinical observations |
| Initial health assessment | Histopathology data |
| Dosing | Individual necropsy records |
| Body weights | Organ weights |
| Food consumption | Ophthalmologic evaluations |

Hematology, clinical chemistry, coagulation, urinalysis data

C. All other records that would demonstrate adherence to the protocol.

Raw data related to hematology and clinical chemistry evaluations will be maintained by Product Safety Labs and/or DuPont Haskell Global Centers for Health and Environmental Sciences, Newark, DE. Prepared slides and pathology data will be maintained by Product Safety Labs and/or by HSRL, 5930 Main Street, Mount Jackson, VA, 22842. Test substance and dietary analysis data will be maintained by Impossible Foods, Inc. 525 Chesapeake Dr. Redwood City, CA 94063.

## 17. PROTOCOL AMENDMENTS AND DEVIATIONS

All amendments to this protocol and the reasons therefore shall be documented, signed by the Study Director, dated and maintained with the raw data and protocol. Any deviations from this protocol will be recorded in the raw data and documented in the final report.

## 18. DISPOSITION OF TEST SUBSTANCE

A reserve sample of the test substance and records of sample disposition will be maintained at Product Safety Labs. All remaining test substance will be retained for at least one year from receipt, unless otherwise specified by the Sponsor. All remaining test substance will be returned to the Sponsor unless otherwise directed.

# Product Safety Labs

28-Day dietary Study in rats
Protocol # P703.01 IMP
PSL ID: 160720-5R
Study No: 43166

**19. PROTOCOL APPROVAL**

(b) (6)

Signature: _____
Rachel Fraser, PhD
Sponsor Representative
Impossible Foods, Inc.
Date: 9/16/16

(b) (6)

Signature: _____
Mithila Shitut, BVSc & AH, MS
Study Director
Product Safety Labs
Date: 9/21/16

(b) (6)

Signature: _____
Odete Mendes, DVM, PhD, DACVP, DABT
Director of Toxicology and Pathology
Product Safety Labs
Date: 16 Sep 16

**20. PROTOCOL REVIEW:**

(b) (6)

Signature: _____
Rhonda S. Krick, BS
Quality Assurance Director
Product Safety Labs
Date: Sep 16, 2016

New Issue: 09/16/16

# Product Safety Labs

## PROTOCOL AMENDMENT

SOY LEGHEMOGLOBIN PREPARATION:
A 28-DAY DIETARY STUDY IN RATS

**PROTOCOL NO.:** P703.01 IMP **AMENDMENT NO.:** 1

**STUDY NO.:** 43166 **PSL Sample IDs:** 160720-5R

PROTOCOL SECTION (**change from**): **11.F Body Weight and Body Weight Gain**

Individual body weights will be recorded at least two times during acclimation. Test animals will be weighed on Day 0 (prior to study start) and approximately weekly thereafter (intervals of 7 days ± 1). Decedents need not be weighed. Body weight gain will be calculated for selected intervals and for the study overall.

PROTOCOL SECTION (**change to**): **11.F Body Weight and Body Weight Gain**

Individual body weights will be recorded at least two times during acclimation. Test animals will be weighed on Day 0 (prior to study start) and approximately weekly thereafter (intervals of 7 days ± 1). **The animals will also be weighed prior to sacrifice in order to calculate organ to body weight ratios.** Decedents need not be weighed. Body weight gain will be calculated for selected intervals and for the study overall.

**REASON:** Terminal body weight was not included in the protocol.

**EFFECTIVE DATE:** September 28, 2016

(b) (6)

Mithila Shitut, BVSc & AH, MS
Study Director
Product Safety Labs

9/28/16
Date

# Product Safety Labs

## PROTOCOL AMENDMENT

SOY LEGHEMOGLOBIN PREPARATION:
A 28-DAY DIETARY STUDY IN RATS

**PROTOCOL NO.:** P703.01 IMP

**AMENDMENT NO.:** 2

**STUDY NO.:** 43166

**PSL NO.:** 160720-5R

**PROTOCOL SECTION:** 14.A. Laboratory

**Change from:**

| | |
|---|---|
| Histological slide evaluation | Histo-Scientific Research Laboratories (HSRL)<br>5930 Main Street<br>Mount Jackson, VA 22842<br>Prospective P.I.(s) (pathology): David Garlick, DVM, DACVP<br>Laura E. Elcock, DVM, PhD, DACVP<br>Elizabeth H. Hutto, DVM, PhD, DACVP<br>Daphne Vasconcelos, DVM, PhD, DACVP, DABT<br>Allen Singer, DVM, DACVP, DABT |

**Change to:**

| | |
|---|---|
| Histological slide evaluation<br>**(Change in bold)** | Histo-Scientific Research Laboratories (HSRL)<br>5930 Main Street<br>Mount Jackson, VA 22842<br>Prospective P.I.(s) (pathology): David Garlick, DVM, DACVP<br>Laura E. Elcock, DVM, PhD, DACVP<br>Elizabeth H. Hutto, DVM, PhD, DACVP<br>Daphne Vasconcelos, DVM, PhD, DACVP, DABT<br>Allen Singer, DVM, DACVP, DABT<br>**Daniel G. Branstetter, DVM, PhD, DACVP** |

**EFFECTIVE DATE:** November 1, 2016

(b) (6)

Mithila Shitut, BVSc & AH, MS
Study Director
Product Safety Labs

12/23/16
Date

# Product Safety Labs

## PROTOCOL AMENDMENT

SOY LEGHEMOGLOBIN PREPARATION:
A 28-DAY DIETARY STUDY IN RATS

**PROTOCOL NO.:** P703.01 IMP

**AMENDMENT NO.:** 3

**STUDY NO.:** 43166

**PSL NO.:** 160720-5R

**PROTOCOL SECTION:** 11.I

**Add to section 11.I.**

11.I.4 Histopathology Peer Review

A histopathology peer review of female reproductive organs will be performed for all female rats. The peer review pathologist will be Karen Regan, DVM, DABT, DACVP form Regan Path/Tox Services, Inc, 1457 Township Road 853, Ashland, OH 44805. A peer review statement will be inserted in the final study report.

**EFFECTIVE DATE:** June 1, 2017

(b) (6)

Mithila Shitut, BVSc & AH, MS
Study Director
Product Safety Labs

June 1, 2017
Date

# APPENDIX B: FEED, WATER, AND SEROLOGY ANALYSES

## PRODUCT IDENTIFICATION

Soy Leghemoglobin Preparation

# APPENDIX B (cont.): FEED

2016C

ENVIGO

Teklad Certified Global 16% Protein Rodent Diet

| | |
|---|---|
| Lot Number | 2016C-080216MA |
| Date of Manufacture | 08/02/16 |
| Report Date | 08/16/16 |

| Analysis | Result (%) |
|---|---|
| **Proximate Analysis** | |
| Protein | 16.40 |
| Fat | 3.83 |
| Fiber | 2.96 |
| Moisture | 10.33 |
| Ash | 4.74 |
| Calcium | 0.94 |
| Phosphorus | 0.63 |

***Laboratory Diet Certification Report***

The following data is a consolidation of results obtained from one or more independent testing laboratories. The actual laboratory results are available upon request.

(b) (6)

I have reviewed this document
2016.08.16
12:37:20 -05'00'

| Analysis | Result | Units | Established Maximum Concentration |
|---|---|---|---|
| **Heavy Metals** | | | |
| Arsenic | 0.13 | ppm | 1.00 |
| Cadmium | < 0.10 | ppm | 0.50 |
| Lead | < 0.20 | ppm | 1.50 |
| Mercury | < 0.05 | ppm | 0.20 |
| Selenium | 0.22 | ppm | 0.50 |
| **Mycotoxins** | | | |
| Aflatoxin B1, B2, G1, G2 | < 5.00 | ppb | 5.00 |
| **Chlorinated Hydrocarbons** | | | |
| Aldrin | < 0.01 | ppm | 0.03 |
| Lindane | < 0.01 | ppm | 0.05 |
| Chlordane | < 0.01 | ppm | 0.05 |
| DDT & related substances | < 0.03 | ppm | 0.15 |
| Dieldrin | < 0.02 | ppm | 0.03 |
| Endrin | < 0.02 | ppm | 0.03 |
| Heptachlor | < 0.01 | ppm | 0.03 |
| Heptachlor Epoxide | < 0.01 | ppm | 0.03 |
| Toxaphene | < 0.10 | ppm | 0.15 |
| PCB's | < 0.10 | ppm | 0.15 |
| a-BHC | < 0.01 | ppm | 0.05 |
| b-BHC | < 0.01 | ppm | 0.05 |
| d-BHC | < 0.01 | ppm | 0.05 |
| Hexachlorobenzene | < 0.01 | ppm | 0.03 |
| Mirex | < 0.01 | ppm | 0.02 |
| Methoxychlor | < 0.05 | ppm | 0.50 |
| **Organophosphates** | | | |
| Thimet | < 0.15 | ppm | 0.50 |
| Diazinon | < 0.14 | ppm | 0.50 |
| Disulfaton | < 0.15 | ppm | 0.50 |
| Methyl Parathion | < 0.14 | ppm | 0.50 |
| Malathion | < 0.14 | ppm | 0.50 |
| Parathion | < 0.12 | ppm | 0.50 |
| Thiodan | < 0.02 | ppm | 0.50 |
| Ethion | < 0.14 | ppm | 0.50 |
| Trithion | < 0.15 | ppm | 0.50 |

Teklad Global Diets is a trademark of Envigo & Envigo 2012

Envigo Teklad Diets + Madison WI + + tekladinfo@envigo.com (800) 483-5523

## APPENDIX B (cont.): WATER

In June 2015, water was analyzed for contaminants.

LABORATORY: PRECISION ANALYTICAL SERVICES, INC.
2161 Whitesville Road
Toms River, NJ 08755

Results of water analysis for possible contaminants were acceptable within regulatory standards.

Specialists in Drinking Water Testing Technologies ■ Residential ■ Industrial ■ Municipal

1184 WHITESTONE ROAD FORT RIVER, NJ 08785 PHONE 732-914-1515 FAX 732-914-1518

## CERTIFICATE OF ANALYSIS

Customer : Product Safety Labs
2394 Route 130
Dayton, NJ 08810

Project ID : 2nd Quarter
PAS Project ID P16-3141

Matrix : Drinking Water
Report Date : 6/28/2016

| PAS Sample ID | Client ID | Analyses | Results | Units | PQL | MDL | MCL | Method | Date Sampled | Date Analyzed |
|---|---|---|---|---|---|---|---|---|---|---|
| P16-3141-01 | Room #7 | Copper | ND | mg/L | 0.05 | 0.0185 | 1.30 | SM 3111 B | 6/21/16 11:20 | 6/27/16 18:33 |
| P16-3141-01 | Room #7 | Zinc | ND | mg/L | 0.025 | 0.0092 | 5.00 | SM 3111 B | 6/21/16 11:20 | 6/28/16 13:34 |
| P16-3141-01 | Room #7 | Lead | ND | mg/L | 0.002 | 0.000462 | 0.005 | SM 3113 B | 6/21/16 11:20 | 6/23/16 15:15 |
| P16-3141-01 | Room #7 | E. Coli / Colilert | Absent | Pres/Abs | 1 Col/100mL | 1 Col/100mL | 0 Col/100mL | SM 9223 B | 6/21/16 11:20 | 6/21/16 16:55 |
| P16-3141-01 | Room #7 | Total Coliform / Colilert | Absent | Pres/Abs | 1 Col/100mL | 1 Col/100mL | 0 Col/100mL | SM 9223 B | 6/21/16 11:20 | 6/21/16 16:55 |
| | | | | | | | | | | |
| P16-3141-02 | Room #10 | Copper | ND | mg/L | 0.05 | 0.0185 | 1.30 | SM 3111 B | 6/21/16 11:25 | 6/27/16 16:35 |
| P16-3141-02 | Room #10 | Zinc | ND | mg/L | 0.025 | 0.0092 | 5.00 | SM 3111 B | 6/21/16 11:25 | 6/28/16 13:36 |
| P16-3141-02 | Room #10 | Lead | ND | mg/L | 0.002 | 0.000462 | 0.005 | SM 3113 B | 6/21/16 11:25 | 6/23/16 15:19 |
| P16-3141-02 | Room #10 | E. Coli / Colilert | Absent | Pres/Abs | 1 Col/100mL | 1 Col/100mL | 0 Col/100mL | SM 9223 B | 6/21/16 11:25 | 6/21/16 16:55 |
| P16-3141-02 | Room #10 | Total Coliform / Colilert | Absent | Pres/Abs | 1 Col/100mL | 1 Col/100mL | 0 Col/100mL | SM 9223 B | 6/21/16 11:25 | 6/21/16 16:55 |
| | | | | | | | | | | |
| P16-3141-03 | Room #29, Pressure Station | Copper | ND | mg/L | 0.05 | 0.0185 | 1.30 | SM 3111 B | 6/21/16 11:35 | 6/27/16 16:38 |
| P16-3141-03 | Room #29, Pressure Station | Zinc | ND | mg/L | 0.025 | 0.0092 | 5.00 | SM 3111 B | 6/21/16 11:35 | 6/28/16 13:39 |
| P16-3141-03 | Room #29, Pressure Station | Lead | ND | mg/L | 0.002 | 0.000462 | 0.005 | SM 3113 B | 6/21/16 11:35 | 6/23/16 15:24 |
| P16-3141-03 | Room #29, Pressure Station | E. Coli / Colilert | Absent | Pres/Abs | 1 Col/100mL | 1 Col/100mL | 0 Col/100mL | SM 9223 B | 6/21/16 11:35 | 6/21/16 16:55 |
| P16-3141-03 | Room #29, Pressure Station | Total Coliform / Colilert | Absent | Pres/Abs | 1 Col/100mL | 1 Col/100mL | 0 Col/100mL | SM 9223 B | 6/21/16 11:35 | 6/21/16 16:55 |
| | | | | | | | | | | |
| P16-3141-04 | Sipper Bottle | Total Coliform | ND | Col/100mL | 1 Col/100mL | 1 Col/100mL | 0 Col/100mL | SM 9222 B | 6/21/16 11:40 | 6/22/16 11:10 |
| P16-3141-05 | Sipper Top | Total Coliform | NC Interference *** | Col/100mL | 1 Col/100mL | 1 Col/100mL | 0 Col/100mL | SM 9222 B | 6/21/16 11:40 | 6/22/16 11:20 |

Except for the parameters tested, PAS makes no representation as to the fitness or quality of the water sample taken.

*** Non Coliform Bacteria growth was found to be Confluent and may interfere with the growth of Total Coliform Bacteria. The result is invalidated and retesting is required. (A)

NC = Non-Coliform Bacteria
MCL = Maximum Contaminant Level
PQL = Practical Quantitation Limit
MDL = Minimum Detection Limit
ND = Analyzed for but not detected
B = Compound found in blank and sample
E = Concentration exceeds calibration range
J = Estimated result
* = Federal Action Level

All samples are analyzed in accordance with New Jersey Department of Environmental Protection protocols.

Mark D. Feldstein, Lab Director

(A) SCP 508 Dev. testing not repeated on Sipper top CM 7/6/16
Room 13 faucet not analyzed due to room being out of service (b) (6) 7/7/16

Animals are no longer given water from unfilter source (Nonresistant)
Missing sampling at room 13 has no impact.
Sipper bottle tested OK, no need to test sipper top (tube)
(b) (6) 7/7/16

OK (b) (6)
07/07/16
MZ 07/07/16

## APPENDIX B (cont.): SEROLOGY

In October 2016, serology from sentinel animals residing in Room #15, which also housed the study animals, was obtained from collected blood serum for a battery of common viral and microbiologic pathogens.

The sentinel animals along with the test animals were in Room #34 from September 28, 2016, through October 28, 2016, for the duration of the study. Blood samples were collected on October 28, 2016.

LABORATORY: IDEXX BioResearch
4011 Discovery Drive
Columbia, MO 65201

Results of the serology analyses for sentinel animals corresponding with this study are reported as samples 257M 10.28.16, 268M 10.28.16, and 316F 10.28.16. All samples were negative for microbial antibodies.

IDEXX BioResearch

**FINAL REPORT OF LABORATORY EXAMINATION**

**4011 Discovery Drive, Columbia, MO 65201**
**1-800-669-0825 1-573-499-5700**
**idexxbioresearch@idexx.com www.idexxbioresearch.com**

**IDEXX BioResearch Case # 30789-2016**

**Received: 11/15/2016**
**Completed: 11/16/2016**

**Submitted By**

Mithila Shitut
Product Safety Labs
2394 US Highway 130
Dayton, NJ 08810

Phone: 732-438-5100 ext. 1558
Email: MithilaShitut@productsafetylabs.com

**Specimen Description**

Species: rat
Description: Opti-Spot strip(s)
Number of Specimens/Animals: 3

**Purchase Order #: P1602593UDC1**

| Client ID | Investigator | Room # | Strain/Breed | Sex | Age | Study Number |
|---|---|---|---|---|---|---|
| 257M 10.28.16 | Mithila Shitut | 15 | CD/CRL | M | 3m | 43166 |
| 288M 10.28.16 | Mithila Shitut | 15 | CD/CRL | M | 3m | 43166 |
| 316F 10.28.16 | Mithila Shitut | 15 | CD/CRL | F | 3m | 43166 |

**Services/Tests Performed:** Primary Serology Profile

**Serologic evaluation for antibodies to:** H1, KRV, RCV/SDAV, RMV, RPV, RTV

**Summary:** All test results were negative.

If you have questions, please call our toll free number at 1-800-669-0825 or e-mail us at idexxbioresearch@idexx.com.

**SEROLOGY SUMMARY**

| | 257M 10 26 16 | 268M 10 26 16 | 318F 10 26 16 |
|---|---|---|---|
| RPV | - | - | - |
| RMV | - | - | - |
| KRV | - | - | - |
| H1 | - | - | - |
| RCV/SDAV | - | - | - |
| RTV | - | - | - |
| Rat IgG | N | N | N |

**Legend:** + = positive - = negative blank = test not performed EQ = equivocal HE = hemolysis precluded testing I = insufficient W = weak positive WB = Western Blot confirmatory analysis pending NS = non-specific reactivity N = normal IgG L = less than normal IgG

Page 2 of 2

IDEXX BioResearch Case # 30789-2016

IDEXX BioResearch

**FINAL REPORT OF LABORATORY EXAMINATION**

4011 Discovery Drive, Columbia, MO 65201
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**IDEXX BioResearch Case # 30789-2016**

**Received: 11/15/2016**
**Completed: 11/16/2016**

**SEROLOGY DETAILS**

| | Baseline | 257M 10 28 16 | 203M 10 28 16 | 316F 10 28 16 |
|---|---|---|---|---|
| **RPV** | | | | |
| RPV purified virus | MFI > 2.000 | - | - | - |
| NS1[1] | MFI > 3.750 | - | - | - |
| **RMV** | | | | |
| RMV VP2 recombinant | MFI > 2.000 | - | - | - |
| NS1[1] | MFI > 3.750 | - | - | - |
| **KRV** | | | | |
| KRV purified virus | MFI > 2.500 | - | - | - |
| NS1[1] | MFI > 3.750 | - | - | - |
| **H1** | | | | |
| H1 purified virus | MFI > 1.750 | - | - | - |
| NS1[1] | MFI > 3.750 | - | - | - |
| **RCV/SDAV** | | | | |
| RCV/SDAV purified virus | MFI > 3.750 | - | - | - |
| RCV/SDAV Spike | MFI > 3.750 | - | - | - |
| **RTV** | | | | |
| RTV purified virus | MFI > 2.000 | - | - | - |
| TMEV purified virus | MFI > 2.000 | - | - | - |

NS1[1]: NS1 protein is highly conserved among rodent parvoviruses and thus serves as a generic assay for parvovirus seroconversion.

Legend: + = positive - = negative blank = test not performed EQ = equivocal HE = hemolysis precluded testing I = insufficient W = weak positive WB = Western Blot confirmatory analysis pending NS = non-specific reactivity N = normal IgG L = less than normal IgG

Positive MFI results are reported as "+" followed by a number from 1 to 33 in thousands rounded off to the nearest thousand.

If you have questions, please call our toll free number at 1-800-669-0825 or e-mail us at idexxbioresearch@idexx.com

# APPENDIX C: CERTIFICATES OF ANALYSIS

## PRODUCT IDENTIFICATION

Soy Leghemoglobin Preparation

**Product Safety Labs**

# CERTIFICATE OF ANALYSIS

**Product:** Soy Leghemoglobin Preparation

**Lot #:** PP-PGM2-16-088-301

**PSL Reference No.:** 160720-5R

**Date of Analysis:** August 16, 2016

**Result:**

**Soy Leghemoglobin – 48.82%**

Approval: (b) (6) 9/17/16
David Shuling
Analytical Services
Product Safety Labs
Date

QA Release: (b) (6) Sep 14, 2016
Rhonda Krick, B.S.
Quality Assurance
Product Safety Labs
Date

***This material was analyzed in compliance with Good Laboratory Practice (40 CFR 160) standards. Data are reported in PSL GLP Study No. 43682***

PRODUCT SAFETY LABS
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# APPENDIX D: CHEMICAL ANALYSIS

## PRODUCT IDENTIFICATION

Soy Leghemoglobin Preparation

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**Project Title:**
Analysis of Samples from Study:
Soy Leghemoglobin Preparation: A 28-DAY DIETARY STUDY IN RATS

**Sponsor**
Impossible Foods, Inc.
525 Chesapeake Dr.
Redwood City, CA 94063

## ANALYTICAL REPORT

**Test Substance:**
160720-5R

**Author:**
Pavel A. Aronov, PhD

**Analytical Report Completion Date:**
December 7, 2016

**Performing Laboratory:**

Analytical Services:
Impossible Foods
525 Chesapeake Dr.
Redwood City, CA, 94063

**Project Identification Number:**
Impossible Foods Study Number IF-43166

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## GOOD LABORATORY PRACTICE COMPLIANCE STATEMENT

Soy Leghemoglobin Preparation

This analysis was conducted in a non-GLP certified facility. Method validation and sample analysis were performed and documented according to GLP. Characterization of reference substance was documented according to GLP.

(b) (6)

Principal Investigator: _____ Date: 12/7/2016

Name of Signer: Pavel A. Aronov, PhD

Name of Company: Impossible Foods

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**SIGNATURE**

Soy Leghemoglobin Preparation

I, the undersigned, declare that the methods, results and data contained in this report faithfully reflect the procedures used and raw data collected during the study.

(b)
(6)

Pavel A. Aronov, PhD
Principal Scientist
Impossible Foods

12/7/2016
Date

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## STUDY INFORMATION

| | |
|---|---|
| Protocol No.: | IF-43166 |
| Test Substance: | Soy Leghemoglobin Preparation<br>Lot/Batch #: PP-PGM2-16-088-301 |
| Physical Description: | Red/Brown Powder |
| Date Test Substance Received: | October 11, 2016 and October 25, 2016 |
| PSL Reference Nos.: | 160720-5R |
| PSL Study Number: | 43166 |
| Sponsor: | Impossible Foods, Inc. |
| Dates of Analysis: | |
| Analytical Principal Investigator: | Pavel A. Aronov, PhD |
| Primary Chemists: | Puja Agrawal, MS |
| | Rachel Fraser, PhD |

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## 1. SUMMARY

This report presents the dietary mixture and test substance analysis phase of PSL Study Number 43166: Soy Leghemoglobin Preparation: A 28-DAY DIETARY STUDY IN RATS. Samples were collected at various intervals for neat test substance stability (NT), stability in the dietary mixture (SA), homogeneity (HO), and concentration verification (CV) and transferred to the Analytical laboratory of Impossible Foods. This method was validated in terms of linearity, specificity, precision, and accuracy. All samples were received frozen and were maintained frozen prior to extraction.

Samples (BO = Both Male and Female diets, MA = Male diet, FE = Female diet):

Neat test substance for Stability: Week 1, Week 3, and Week 4

NT 1 A
NT 2 A
NT 3 A

Dietary mixture samples for Stability (Days 0, 4, 7 and 10):

| | | |
|---|---|---|
| SA0 1A BO | SA7 17A FE | SA0 6A MA |
| SA4 8A BO | SA10 24A FE | SA4 13A MA |
| SA7 15A BO | SA0 4A MA | SA7 20A MA |
| SA10 22A BO | SA4 11A MA | SA10 27A MA |
| SA0 2A MA | SA7 18A MA | SA0 7A FE |
| SA4 9A MA | SA10 25A MA | SA4 17A FE |
| SA7 16A MA | SA0 5A FE | SA7 21A FE |
| SA10 23A MA | SA4 12A FE | SA10 28A FE |
| SA0 3A FE | SA7 19A FE | |
| SA4 10A FE | SA10 26A FE | |

Initial (Day 0) Dietary Samples for Concentration Verification: and Homogeneity (T = top, M = middle, B = bottom):

| | |
|---|---|
| HO 1 A M BO | HO 11 A T FE |
| HO 2 A T MA | HO 12 A M FE |
| HO 3 A M MA | HO 13 A B FE |
| HO 4 A B MA | HO 14 A T MA |
| HO 5 A T FE | HO 15 A M MA |
| HO 6 A M FE | HO 16 A B MA |
| HO 7 A B FE | HO 17 A T FE |
| HO 8 A T MA | HO 18 A M FE |
| HO 9 A M MA | HO 19 A B FE |
| HO 10 A B MA | |

Intermediate (Day 7) Dietary Samples for Concentration Verification:

| | |
|---|---|
| CV 1 A BO | CV 4 A MA |
| CV 2 A MA | CV 5 A FE |
| CV 3 A FE | CV 6 A MA |

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CV 7 A FE

Final (Day 21) Dietary Samples for Concentration Verification:

CV 8 A BO
CV 9 A MA
CV 10 A FE
CV 11 A MA
CV 12 A FE
CV 13 A MA
CV 14 A FE

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## 2. PROCEDURE FOR THE DETERMINATION OF SOY LEGHEMOGLOBIN PREPARATION BY HIGH PERFORMANCE LIQUID CHROMATOGRAPHY (HPLC)

### A. Reference Standard

Note: The neat test substance was used as the reference standard. No purity correction was applied. Results were reported as test substance concentration (versus active ingredient concentration).

Name: Soy Leghemoglobin Preparation
Lot/Batch #: PP-PGM2-16-088-301
PSL No.: 160720-5R
Purity: 48.82%
Exp. Date: March 2017
Supplied by: Impossible Foods, Inc

### B. Method Validation

Linearity, system suitability, specificity, precision, and accuracy (spike recovery) determinations were performed prior to analysis.

Stock Standard Solution: A standard solution was prepared by weighing 0.1 grams of reference standard into a 50 mL polypropylene tube, diluting with 25 g of Lysis Reagent, shaking for 60 minutes, and mixing well.

2.B.1 Detector Linearity: The linearity of detector response was assessed using reference substance solutions targeted to bracket the expected concentrations for the analyte.

Linearity Standard Preparation: Five standard solutions with concentrations ranging from approximately 0.125 to 2 mg/mL (LIN 1 - LIN 5) were prepared by preparing individual dilutions of the stock standard solution in Lysis Reagent by weight and mixing well. Linearity solution shelf life is 3 days at 4C or 12 months at -80C.

Linear regression of the analyte peak gave coefficients of determination ($R^2$) of 0.9977 - 1.0000, which were considered acceptable.

2.B.2 System Suitability: Five replicate injections of the mid-point linearity solution (LIN 3-1) produced relative standard deviations for this study of 0.2% - 1.5% for peak response and 0.0% - 0.2% for retention time.

2.B.3 Specificity: Specificity was demonstrated by the absence of significant interferences in replicate linearity (LIN 1-A) and control feed samples (HO 1 AM-1). Background was <5% of the lowest standard signal.

2.B.4 Accuracy (Spike recovery) and Precision:

Duplicate QC stock solutions were prepared by weighing approximately 0.5 gram of a control sample (HO 1 AM) into separate 50 mL polypropylene centrifuge tubes, pipetting 1.25 mL (QC Low) or 2.5 mL (QC High) of STD1 stock standard solution, and adding 8.75 mL (QC High) or 7.5 mL (QC High) of Lysis Reagent into each tube. Each mixture was capped and placed in a mechanical shaker for 60 minutes. The solutions were allowed to settle for 30 minutes and filtered using a 0.2µm 96-well filter

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plates. Filtrate was collected in 96-well conical bottom plate for HPLC analysis.

Chromatography of the working QC solutions demonstrated accuracy (% recovery) to be 88.2% - 97.7% for QC Low and 87.2 – 92.6% for QC High. The %RSD was 0.3% - 3.7% for QC Low and 0.6% - 1.2% for QC High for precision.

## C. Analysis by High Performance Liquid Chromatography (HPLC)

2.C.1 Standard Preparation: The linearity solutions were injected with every sequence and were used for interpolation of assay results. An example result is shown in 2.B.1.

Note: All diet samples were removed from the freezer and allowed to equilibrate to room temperature before weighing.

2.C.2 Test Sample Preparation for Neat Test Substance: Samples were prepared in triplicate. Approximately 0.1 g of the test substance was weighed into 50 mL polypropylene centrifuge tubes, diluted with 25 g lysis reagent, and placed in a mechanical shaker for 60 minutes. Secondary dilutions were performed as necessary. Samples were mixed well and filtered using a 0.2µm 96-well filter plates. Filtrate was collected in 96-well conical bottom plate for HPLC analysis. Filtrate shelf life is 3 days at 4C or 12 months at -80C.

2.C.3 Sample Preparation for Dietary Samples: Each sample was prepared in triplicate. Approximately 0.5 g of a sample was weighed into a 50 mL polypropylene centrifuge tube and diluted with Lysis Reagent as necessary (higher concentration samples had a higher dilution). The solution was capped and placed in a mechanical shaker for 60 minutes. The solutions were allowed to settle for 30 minutes and filtered using a 0.2µm 96-well filter plates. Filtrate was collected in 96-well conical bottom plate for HPLC analysis. Filtrate shelf life is 3 days at 4C or 12 months at -80C.

2.C.4 Analysis: At the beginning of the analysis, the instrument was equilibrated until it gave a stable, consistent baseline. The standards and samples were injected at consistent time intervals in order to maintain a steady baseline. A solvent blank and standards were run; all samples were injected in singlet.

2.C.5 Calculations: Results were determined as follows:

$$\text{Calculated Conc (mg/g)} = \frac{\text{Peak Area - Intercept}}{\text{Slope}}$$

$$\text{Dose Conc (ppm)} = \frac{\text{Calc. Conc. (mg/g)} \times \text{Extraction Buffer Wt. (g)} \times 1000}{\text{Sample weight (g)}}$$

$$\text{Theoretical Spike Conc. (mg/g)} = \frac{\text{Wt. of Std. (g)}}{\text{Extraction Buffer Wt. (g)}} \times \text{Std. Conc. (mg/g)}$$

Final Conc (mg/g) = Theoretical Spike Conc (mg/g) x Wt of Sample Aliquot (g) / Final Wt (g)

$$\text{\% Recovery} = \frac{\text{Calc. Conc. (mg/g)}}{\text{Final Conc. (mg/g)}} \times 100$$

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$$\% \text{ Signal / Background} = \frac{\text{Avg. LIN 1-A area response}}{\text{Avg. Control area response}} \times 100$$

% Target = Dose Conc. (ppm) / Corrected Dose Level (ppm) x 100

## 3. RESULTS

A summary of the analytical chemistry results is presented in Table 1A-D. HPLC operating conditions are presented in Table 2. The analytical method passed all validation parameters (linearity, system suitability, specificity, precision, and accuracy) and results are reported in Table 3. Detailed results of stability analysis, homogeneity analysis, and concentration verification are presented in Tables 4-5. Chromatograms are maintained in the raw data but were not included in this report.

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## TABLE 1A: CHEMICAL ANALYSIS RESULTS

**Results for Neat Test Substance Stability Samples**

| Sampling Day | Measured Recovery (%) | % Change[1] | Overall Stability (%) |
|---|---|---|---|
| Day 0 (Initial) | 94.96% | 0.00% | 100.00% |
| Day 14 (Middle) | 95.29% | 0.35% | 100.35% |
| Day 21 (Final) | 90.88% | -4.30% | 95.70% |

[1] $\frac{\text{Final Sample} - \text{Initial Sample}}{\text{Initial Sample}} \times 100$

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## TABLE 1B: CHEMICAL ANALYSIS RESULTS

**Results for Dietary Stability of Initial Samples**

| Day[1] | Group | Target Concentration (ppm) | Measured Concentration (ppm) | % of Target[2] |
|---|---|---|---|---|
| 0 | 1 (BO) | 0 | ND | NA |
| | 2 (M) | 4373 | 4508 | 103.08% |
| | 2 (F) | 4711 | 4645 | 98.61% |
| | 3 (M) | 8746 | 7951 | 90.91% |
| | 3 (F) | 9422 | 9034 | 95.89% |
| | 4(M) | 13118 | 12265 | 93.50% |
| | 4(F) | 14133 | 12808 | 90.62% |
| 4 | 1 (BO) | 0 | ND | NA |
| | 2 (M) | 4373 | 4207 | 96.20% |
| | 2 (F) | 4711 | 4471 | 94.90% |
| | 3 (M) | 8746 | 8238 | 94.19% |
| | 3 (F) | 9422 | 8918 | 94.65% |
| | 4(M) | 13118 | 12097 | 92.22% |
| | 4(F) | 14133 | 13191 | 93.33% |
| 7 | 1 (BO) | 0 | ND | NA |
| | 2 (M) | 4373 | 4202 | 96.09% |
| | 2 (F) | 4711 | 4468 | 94.84% |
| | 3 (M) | 8746 | 8200 | 93.76% |
| | 3 (F) | 9422 | 8728 | 92.63% |
| | 4(M) | 13118 | 12423 | 94.70% |
| | 4(F) | 14133 | 13547 | 95.85% |
| 10 | 1 (BO) | 0 | ND | NA |
| | 2 (M) | 4373 | 3968 | 90.74% |
| | 2 (F) | 4711 | 4693 | 99.63% |
| | 3 (M) | 8746 | 8453 | 96.65% |
| | 3 (F) | 9422 | 8836 | 93.78% |
| | 4(M) | 13118 | 12825 | 97.77% |
| | 4(F) | 14133 | 13762 | 97.38% |

NA = Not Applicable; ND = Not Detected

[1] Days relative to the initial diet preparation.

[2] % of Target = Measured Conc. (ppm) / Target Conc. (ppm) x 100

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## TABLE 1C: CHEMICAL ANALYSIS RESULTS

**Results for Homogeneity of Dietary Preparations**

| Day[1] | Group | Sample Location | Target Concentration (ppm) | Measured Concentration (ppm) | % of Target[2] | Average % of Target | RSD (%) |
|---|---|---|---|---|---|---|---|
| 0 | 1 (BO) | Middle | 0 | ND | NA | NA | NA |
| | 2 (M) | Top | 4373 | 4302 | 98.38% | 95.87% | 2.92% |
| | | Middle | | 4061 | 92.86% | | |
| | | Bottom | | 4215 | 96.38% | | |
| | 2 (F) | Top | 4711 | 4853 | 103.01% | 98.01% | 4.77% |
| | | Middle | | 4583 | 97.28% | | |
| | | Bottom | | 4416 | 93.74% | | |
| | 3 (M) | Top | 8746 | 8636 | 98.74% | 95.40% | 3.09% |
| | | Middle | | 8145 | 93.13% | | |
| | | Bottom | | 8250 | 94.33% | | |
| | 3 (F) | Top | 9422 | 9669 | 102.62% | 97.71% | 5.50% |
| | | Middle | | 9284 | 98.53% | | |
| | | Bottom | | 8666 | 91.98% | | |
| | 4 (M) | Top | 13118 | 12226 | 93.20% | 97.85% | 5.24% |
| | | Middle | | 13558 | 103.35% | | |
| | | Bottom | | 12724 | 97.00% | | |
| | 4 (F) | Top | 14133 | 14567 | 103.07% | 98.64% | 5.57% |
| | | Middle | | 14183 | 100.35% | | |
| | | Bottom | | 13072 | 92.49% | | |

NA = Not Applicable; ND = Not Detected

[1] Day relative to initial dietary preparation.

[2] % of Target = Measured Conc. (ppm) / Target Conc. (ppm) x 100.

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## TABLE 1D: CHEMICAL ANALYSIS RESULTS

**Results for Concentration Verification of Dietary Preparations**

| Day[1] | Group | Target Concentration (ppm) | Measured Concentration (ppm) | % of Target[2] |
|---|---|---|---|---|
| 0[3] | 1 (BO) | 0 | ND | NA |
| | 2 (M) | 4373 | 4061 | 92.86% |
| | 2 (F) | 4711 | 4583 | 97.28% |
| | 3 (M) | 8746 | 8145 | 93.13% |
| | 3 (F) | 9422 | 9284 | 98.53% |
| | 4(M) | 13118 | 13558 | 103.35% |
| | 4(F) | 14133 | 14183 | 100.35% |
| 7 | 1 (BO) | 0 | ND | NA |
| | 2 (M) | 6093 | 6158 | 101.06% |
| | 2 (F) | 5824 | 5326 | 91.45% |
| | 3 (M) | 12318 | 12189 | 98.96% |
| | 3 (F) | 11664 | 11408 | 97.81% |
| | 4(M) | 18362 | 19409 | 105.70% |
| | 4(F) | 17567 | 17238 | 98.13% |
| 21 | 1 (BO) | 0 | ND | NA |
| | 2 (M) | 7407 | 6906 | 93.24% |
| | 2 (F) | 5925 | 5498 | 92.80% |
| | 3 (M) | 14727 | 14292 | 97.05% |
| | 3 (F) | 12901 | 12612 | 97.76% |
| | 4(M) | 21943 | 20786 | 94.73% |
| | 4(F) | 19281 | 18829 | 97.65% |

NA = Not Applicable; ND = Not Detected

[1] Days relative to the initial diet preparation.

[2] % of Target = Measured Conc. (ppm) / Target Conc. (ppm) x 100

[3] As part of the homogeneity analysis.

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**TABLE 2: HPLC OPERATING CONDITIONS**

| | | | |
|---|---|---|---|
| Instrument | | Agilent 1100 Series HPLC System, with DAD | |
| Column | | Waters Acquity xBridge BEH125 SEC, 7.8 x 150 mm ID 3.5µm | |
| Flow rate (mL/min) | | 0.86 | |
| Injection Volume (µL) | | 25 | |
| Wavelength (nm) | | 405 | |
| Column Temperature (°C) | | Ambient | |
| Tray Temperature (°C) | | 4 | |
| Run time (min) | Flow rate (ml/min) | HPLC-Grade Water (%) | 50 mM Potassium Phosphate pH 7.4, 5 mM Sodium Chloride (%) |
| 0-14.00 min | 0.86 | 0 | 100 |
| 14.01-19.00 min | 0.86 | 100 | 0 |
| 19.01 to 30.00 min | 0.86 | 0 | 100 |

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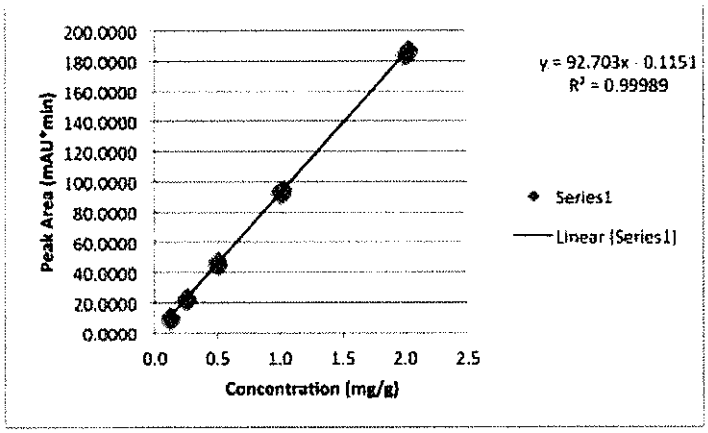
## TABLE 3: METHOD VALIDATION RESULTS

Linearity

(Analyzed on 11/17/2016)

| Sample ID | Peak Area | Theoretical Concentration (mg/g) |
|---|---|---|
| Lin 1 | 10.5743 | 0.1236 |
| | 10.7110 | 0.1239 |
| Lin 2 | 23.4604 | 0.2572 |
| | 22.9334 | 0.2509 |
| Lin 3 | 47.5942 | 0.5066 |
| | 46.4874 | 0.4962 |
| Lin 4 | 94.8130 | 1.0224 |
| | 93.6001 | 0.9964 |
| Lin 5 | 187.6864 | 2.0265 |
| | 184.2777 | 1.9985 |
| | Slope: | 92.7032 |
| | Intercept: | -0.1151 |
| | Correlation Coefficient (r): | 0.9999 |



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## TABLE 3 (cont.): METHOD VALIDATION RESULTS

System Suitability

(Analyzed on 11/17/2016)

| Sample ID | Theoretical Conc. (mg/g) | Retention time (min) | Peak Area |
|---|---|---|---|
| LIN 3-1 | 0.4962 | 4.1680 | 45.1002 |
| | | 4.1682 | 44.9289 |
| | | 4.1687 | 44.7097 |
| | | 4.1703 | 44.3757 |
| | | 4.1688 | 44.2105 |
| Average | | 4.1688 | 44.6650 |
| STDEV | | 0.0009 | 0.3713 |
| %RSD | | 0.0% | 0.8% |

Accuracy and Precision

(Analyzed on 11/17/2016)

| Sample Name | Theoretical Conc. (mg/g) | Peak Area | Calculated Conc. (mg/g) | % Recovery | Average % Recovery (SD / %RSD) |
|---|---|---|---|---|---|
| QC Low | 0.5012 | 45.1037 | 0.4878 | 97.3% | 97.0% (0.3% / 0.3%) |
| | | 44.9771 | 0.4864 | 97.0% | |
| | 0.5062 | 45.4857 | 0.4919 | 97.2% | |
| | | 45.2369 | 0.4892 | 96.6% | |
| QC High | 1.0082 | 87.1050 | 0.9409 | 93.3% | 92.6% (0.7% / 0.8%) |
| | | 86.7802 | 0.9373 | 93.0% | |
| | 1.0086 | 86.1798 | 0.9309 | 92.3% | |
| | | 85.6498 | 0.9252 | 91.7% | |
| y = 92.7032 - 0.1151 | | | | | |

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**TABLE 3 (cont.): METHOD VALIDATION RESULTS**

Specificity (Analyzed on 10/17/2016)

| | Peak Area | Specificity |
|---|---|---|
| LIN 1-A | 11.1192 | NA |
| | 11.7481 | |
| HO 1 AM-1 | ND | |
| HO 1 AM-2 | ND | |
| HO 1 AM-3 | ND | |

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## TABLE 4: NEAT TEST SUBSTANCE STABILITY ANALYSIS

Analyzed on 10/27/2016

| Day[1] | Sample Name | Sample Weight (g) | Final Conc. (mg/g) | Peak Area | Calculated Conc. (mg/g) | % Recovery | Avg. % Recovery | SD / %RSD |
|---|---|---|---|---|---|---|---|---|
| 0 | NT 1 A | 0.1017 | 0.4974 | 45.3436 | 0.4738 | 95.25% | 94.96% | 0.0036 / 0.38% |
| | | 0.0998 | 0.4888 | 44.2652 | 0.4622 | 94.55% | | |
| | | 0.1011 | 0.4960 | 45.1470 | 0.4717 | 95.08% | | |
| 14 | NT 2 A | 0.1026 | 0.5017 | 45.6401 | 0.4770 | 95.08% | 95.29% | 0.0053 / 0.55% |
| | | 0.1031 | 0.5016 | 45.5543 | 0.4760 | 94.91% | | |
| | | 0.1008 | 0.4886 | 44.8581 | 0.4686 | 95.89% | | |
| 21 | NT 3 A | 0.1039 | 0.5087 | 43.0057 | 0.4487 | 88.20% | 90.88% | 0.0245 / 2.70% |
| | | 0.1031 | 0.5132 | 45.6832 | 0.4774 | 93.02% | | |
| | | 0.1047 | 0.5181 | 45.3258 | 0.4736 | 91.41% | | |
| y = 93.1257 + 1.2237 | | | | | | | | |

[1] Days relative to the initial diet preparation.

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**TABLE 5: DIETARY MIXTURE SAMPLE ANALYSIS**

Study Day 0 (HO BO MA Analyzed on 10/17/2016, HO FE Analyzed on 10/19/2016)

| Sample ID | Sample Wt. (g) | Lysis Reagent Wt. (g) | Dose Level (ppm) | Peak Area | Calc. Conc. (mg/g) | Dose Conc. (ppm) | Average (ppm) | %RSD | % Target | % Target Average | %Target between the strata (Avg. / RSD) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| HO 1 A M-1 | 0.5071 | 5.0400 | 0 | ND | NA | NA | NA | NA | NA | NA | NA |
| HO 1 A M-2 | 0.5011 | 5.0178 | | ND | NA | NA | | | NA | | |
| HO 1 A M-3 | 0.5091 | 5.0551 | | ND | NA | NA | | | NA | | |
| HO 2 A T-1 | 0.5221 | 5.0605 | 4373 | 44.2192 | 0.4500 | 4449 | 4302 | 3.09% | 101.75% | 98.38% | 95.87% 2.92% |
| HO 2 A T-2 | 0.5264 | 5.0073 | | 42.4804 | 0.4406 | 4190 | | | 95.83% | | |
| HO 2 A T-3 | 0.5051 | 5.0814 | | 40.9036 | 0.4241 | 4267 | | | 97.57% | | |
| HO 3 A M-1 | 0.5071 | 5.0840 | | 39.6148 | 0.4110 | 4111 | 4061 | 1.88% | 94.02% | 92.86% | |
| HO 3 A M-2 | 0.5298 | 5.0759 | | 40.0607 | 0.4148 | 3973 | | | 90.85% | | |
| HO 3 A M-3 | 0.5076 | 5.0688 | | 39.6398 | 0.4104 | 4098 | | | 93.71% | | |
| HO 4 A B-1 | 0.4943 | 5.0630 | | 38.3794 | 0.3970 | 4066 | 4215 | 4.99% | 92.98% | 96.38% | |
| HO 4 A B-2 | 0.5022 | 5.0455 | | * | * | 3535 | | | * | | |
| HO 4 A B-3 | 0.5122 | 5.0625 | | 42.4020 | 0.4397 | 4363 | | | 99.78% | | |
| HO 5 A T-1 | 0.5277 | 5.0770 | 4711 | 47.3590 | 0.4880 | 4695 | 4853 | 2.87% | 99.65% | 103.01% | 98.01% 4.77% |
| HO 5 A T-2 | 0.5022 | 5.0689 | | 47.6758 | 0.4912 | 4958 | | | 105.23% | | |
| HO 5 A T-3 | 0.4967 | 5.0461 | | 46.8567 | 0.4829 | 4906 | | | 104.13% | | |
| HO 6 A M-1 | 0.5033 | 5.0046 | | 45.7853 | 0.4720 | 4693 | 4581 | 3.04% | 99.63% | 97.28% | |
| HO 6 A M-2 | 0.5150 | 5.0555 | | 43.7026 | 0.4509 | 4426 | | | 95.95% | | |
| HO 6 A M-3 | 0.4991 | 4.9870 | | 44.9224 | 0.4633 | 4629 | | | 98.26% | | |
| HO 7 A B-1 | 0.4997 | 5.0360 | | 43.7868 | 0.4517 | 4553 | 4416 | 3.25% | 96.64% | 93.74% | |
| HO 7 A B-2 | 0.4896 | 5.0504 | | 40.0276 | 0.4136 | 4267 | | | 90.57% | | |
| HO 7 A B-3 | 0.5034 | 5.0170 | | 40.0629 | 0.4444 | 4429 | | | 94.02% | | |
| BO and MA: y = 94.0599x + 1.0415 FE: y = 98.6434x + 0.7744 | | | | | | | | | | | |

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**TABLE 5 (cont.) INDIVIDUAL SAMPLE ANALYSES**

Study Day 0 Cont. (HO BO MA Analyzed on 10/17/2016, HO FE Analyzed on 10/19/2016)

| Sample ID | Sample Wt. (g) | Lysis Reagent Wt. (g) | Dose Level (ppm) | Peak Area | Calc. Conc. (mg/g) | Dose Conc. (ppm) | Average (ppm) | %RSD | % Target | % Target Average | %Target between the strata (Avg. / RSD) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| HO 8 A T-1 | 0.5044 | 10.1502 | 8746 | 31.1902 | 0.3205 | 6430 | 6814 | 4.97% | 73.53% | 77.91% | 80.45% / 4.06% |
| HO 8 A T-2 | 0.5037 | 10.1210 | | 33.2054 | 0.3420 | 6871 | | | 78.56% | | |
| HO 8 A T-3 | 0.5127 | 10.0918 | | 35.0665 | 0.3617 | 7120 | | | 81.41% | | |
| HO 9 A M-1 | 0.5240 | 10.0177 | | 34.0848 | 0.3533 | 6786 | 6898 | 4.55% | 77.72% | 79.31% | |
| HO 9 A M-2 | 0.5212 | 10.0362 | | 34.1460 | 0.3520 | 6777 | | | 77.49% | | |
| HO 9 A M-3 | 0.5177 | 10.1304 | | 36.3414 | 0.3732 | 7242 | | | 83.49% | | |
| HO 10 A B-1 | 0.5118 | 10.1298 | | 32.2761 | 0.3352 | 7625 | 7335 | 7.08% | 87.18% | 84.09% | |
| HO 10 A B-2 | 0.5021 | 10.0857 | | 30.3189 | 0.3250 | 7607 | | | 87.09% | | |
| HO 10 A B-3 | 0.5089 | 10.1426 | | 34.3700 | 0.3552 | 6754 | | | 77.23% | | |
| HO 11 A T-1 | 0.5995 | 10.1081 | 8022 | 39.6039 | 0.4093 | 8133 | 8491 | 5.67% | 88.44% | 90.12% | 87.55% / 4.32% |
| HO 11 A T-2 | 0.5068 | 10.0792 | | 39.3279 | 0.4065 | 8092 | | | 85.88% | | |
| HO 11 A T-3 | 0.5053 | 10.0604 | | 44.0646 | 0.4546 | 9050 | | | 96.03% | | |
| HO 12 A M-1 | 0.5223 | 10.0051 | | 43.6492 | 0.4500 | 8678 | 8427 | 3.70% | 92.10% | 89.44% | |
| HO 12 A M-2 | 0.4906 | 10.0448 | | 40.3411 | 0.4148 | 8535 | | | 90.58% | | |
| HO 12 A M-3 | 0.5129 | 10.0411 | | 39.8731 | 0.4121 | 8067 | | | 85.62% | | |
| HO 13 A B-1 | 0.5200 | 10.0188 | | 41.4069 | 0.4276 | 8239 | 7830 | 5.83% | 87.44% | 83.09% | |
| HO 13 A B-2 | 0.5021 | 10.0327 | | 39.2093 | 0.3952 | 7912 | | | 83.98% | | |
| HO 13 A B-3 | 0.5066 | 10.0596 | | 35.6704 | 0.3695 | 7347 | | | 77.88% | | |
| HO 14 A T-1 | 0.5172 | 15.0007 | 43118 | 30.1833 | 0.3099 | 6027 | 6776 | 9.66% | 68.70% | 74.34% | 77.54% / 5.57% |
| HO 14 A T-2 | 0.5146 | 15.1356 | | 34.7101 | 0.3579 | 10328 | | | 80.23% | | |
| HO 14 A T-3 | 0.5112 | 15.0063 | | 32.2906 | 0.3319 | 9782 | | | 74.57% | | |
| HO 15 A M-1 | 0.5116 | 15.1496 | | 33.8696 | 0.3488 | 10228 | 10309 | 0.88% | 78.73% | 78.98% | |
| HO 15 A M-2 | 0.5113 | 15.0406 | | 34.3389 | 0.3529 | 10388 | | | 79.19% | | |
| HO 15 A M-3 | 0.4942 | 15.1132 | | 32.4473 | 0.3339 | 10211 | | | 77.88% | | |
| HO 16 A B-1 | 0.5085 | 15.0909 | | 33.7001 | 0.3472 | 10369 | 10417 | 1.80% | 79.20% | 79.41% | |
| HO 16 A B-2 | 0.4912 | 15.1231 | | 32.6994 | 0.3366 | 10362 | | | 79.09% | | |
| HO 16 A B-3 | 0.5233 | 15.2106 | | 35.4266 | 0.3626 | 10626 | | | 81.00% | | |

BO (to MA) y = 90.0996x + 1041b FE y = 98.0434x - 0.7746

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**TABLE 5 (cont.) INDIVIDUAL SAMPLE ANALYSES**

Study Day 0 Cont. (HO BO MA Analyzed on 10/17/2016, HO FE Analyzed on 10/19/2016)

| Sample ID | Sample Wt. (g) | Lysis Reagent Wt. (g) | Dose Level (ppm) | Peak Area | Calc. Conc. (mg/g) | Dose Conc. (ppm) | Average (ppm) | %RSD | % Target | % Target Average | % Target between the strata |
|---|---|---|---|---|---|---|---|---|---|---|---|
| HO 17 A T-1 | 0.5172 | 15.0543 | | 38.2878 | 0.3060 | 11529 | | | 82.51% | | |
| HO 17 A T-2 | 0.5150 | 15.0814 | | 38.3201 | 0.3063 | 11529 | 11384 | 2.21% | 81.76% | 80.55% | |
| HO 17 A T-3 | 0.4937 | 15.0079 | | 35.3673 | 0.3064 | 11603 | | | 78.49% | | |
| HO 18 A M-1 | 0.5256 | 15.1448 | | 36.6825 | 0.3798 | 11357 | | | 78.94% | | |
| HO 18 A M-2 | 0.5000 | 15.1290 | 14133 | 34.5508 | 0.3579 | 10830 | 11197 | 3.47% | 76.65% | 79.22% | 79.37% / 1.39% |
| HO 18 A M-3 | 0.4911 | 15.1298 | | 36.3798 | 0.3767 | 11604 | | | 82.11% | | |
| HO 19 A B-1 | 0.5117 | 15.1035 | | 38.9280 | 0.4025 | 11892 | | | 84.14% | | |
| HO 19 A B-2 | 0.5081 | 15.0779 | | 34.5300 | 0.3578 | 10788 | 11074 | 6.89% | 76.33% | 78.33% | |
| HO 19 A B-3 | 0.4928 | 15.0228 | | 33.3371 | 0.3458 | 10542 | | | 74.59% | | |

BO and MA: y = 94.11599x + 1.0416 FE: y = 98.6334x - 0.7748

NA = Not Applicable; ND = Not Detected

* Excluded due to non-trending result

Cells shaded in gray were re-analyzed on 11/8/2016 and 11/9/2016 due to low signal.

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**TABLE 5 (cont.) INDIVIDUAL SAMPLE ANALYSES**

Day 0 Preparation (HO MA Analyzed on 11/8/2016, HO TE Analyzed on 11/9/2016)

| Sample ID | Sample Wt. (g) | Lysis Reagent Wt. (g) | Dose Level (ppm) | Peak Area | Calc. Conc. (mg/g) | Dose Conc. (ppm) | Average (ppm) | % RSD | % Target | % Target Average | % Target between the strata (Avg. / RSD) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| HO 8 A T-1 | 0.5044 | 10.1302 | 8746 | 41.3494 | 0.4309 | 8671 | 8636 | 5.00% | 99.14% | 98.74% | 95.673 / 2.973 |
| HO 8 A T-2 | 0.5037 | 10.1210 | | 43.1624 | 0.4503 | 9049 | | | 103.46% | | |
| HO 8 A T-3 | 0.5127 | 10.0918 | | 39.9595 | 0.4160 | 8187 | | | 93.61% | | |
| HO 9 A M-1 | 0.5240 | 10.0477 | | 41.6205 | 0.4338 | 8318 | 8145 | 4.46% | 95.11% | 93.13% | |
| HO 9 A M-2 | 0.5212 | 10.0362 | | 38.5959 | 0.4014 | 7726 | | | 88.17% | | |
| HO 9 A M-3 | 0.5177 | 10.1304 | | 41.1521 | 0.4288 | 8390 | | | 95.93% | | |
| HO 10 A B-1 | 0.5118 | 10.3298 | | 41.2484 | 0.4298 | 8507 | 8321 | 7.08% | 97.26% | 95.14% | |
| HO 10 A B-2 | 0.4921 | 10.0857 | | 41.1725 | 0.4290 | 8792 | | | 100.53% | | |
| HO 10 A B-3 | 0.5289 | 10.3426 | | 38.4385 | 0.3996 | 7663 | | | 87.62% | | |
| HO 11 A T-1 | 0.4995 | 10.1681 | 9422 | 43.5444 | 0.4759 | 9688 | 9669 | 5.18% | 102.81% | 102.62% | 97.71% / 5.50% |
| HO 11 A T-2 | 0.5064 | 10.0792 | | 43.5856 | 0.4502 | 9139 | | | 97.60% | | |
| HO 11 A T-3 | 0.5053 | 10.0604 | | 48.8580 | 0.5113 | 10180 | | | 108.04% | | |
| HO 12 A M-1 | 0.5222 | 10.0624 | | 47.0973 | 0.4926 | 9492 | 9284 | 3.24% | 100.34% | 98.53% | |
| HO 12 A M-2 | 0.4936 | 10.0948 | | 43.8598 | 0.4578 | 9421 | | | 99.99% | | |
| HO 12 A M-3 | 0.5129 | 10.0411 | | 43.7416 | 0.4566 | 8938 | | | 94.87% | | |
| HO 13 A B-1 | 0.5200 | 10.0188 | | 44.8442 | 0.4684 | 9025 | 8866 | 3.77% | 95.78% | 94.08% | |
| HO 13 A B-2 | 0.5021 | 10.0527 | | 41.1713 | 0.4290 | 8598 | | | 91.15% | | |
| HO 13 A B-3 | 0.5066 | 10.0596 | | 40.5455 | 0.4222 | 8385 | | | 88.99% | | |
| HO 14 A T-1 | 0.5172 | 15.0607 | 13118 | 40.3516 | 0.4202 | 12235 | 13260 | 7.06% | 93.27% | 101.08% | 100.48% / 3.20% |
| HO 14 A T-2 | 0.5146 | 15.1351 | | 45.7743 | 0.4784 | 14070 | | | 107.26% | | |
| HO 14 A T-3 | 0.5112 | 15.0663 | | 43.7994 | 0.4572 | 13474 | | | 102.72% | | |
| HO 15 A M-1 | 0.5116 | 15.1486 | | 44.9781 | 0.4698 | 13912 | 13558 | 2.31% | 106.05% | 103.35% | |
| HO 15 A M-2 | 0.5113 | 15.0496 | | 43.7589 | 0.4568 | 13444 | | | 102.49% | | |
| HO 15 A M-3 | 0.4942 | 15.1132 | | 41.7757 | 0.4355 | 13317 | | | 101.51% | | |
| HO 16 A B-1 | 0.5085 | 15.0809 | | 40.9314 | 0.4264 | 12604 | 12724 | 0.95% | 96.08% | 97.00% | |
| HO 16 A B-2 | 0.4912 | 15.1231 | | 40.0750 | 0.4172 | 12846 | | | 97.93% | | |
| HO 16 A B-3 | 0.5233 | 15.2106 | | 41.9863 | 0.4377 | 12723 | | | 96.99% | | |
| y = 99.1257x + 1.2237 | | | | | | | | | | | |

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**TABLE 5 (cont.) INDIVIDUAL SAMPLE ANALYSES**

Study Day 0 Cont. (HO MA Analyzed on 11/8/2016, HO FE Analyzed on 11/9/2016)

| Sample ID | Sample Wt. (g) | Lysis Reagent Wt. (g) | Dose Level (ppm) | Peak Area | Calc. Conc. (mg/g) | Dose Conc. (ppm) | Average (ppm) | %RSD | % Target | % Target Average | %Target between the strata |
|---|---|---|---|---|---|---|---|---|---|---|---|
| HO 17 A T-1 | 0.5171 | 15.0543 | | 47.8680 | 0.5009 | 14582 | | | 103.18% | | |
| HO 17 A T-2 | 0.5150 | 14.9814 | | 47.9792 | 0.5021 | 14605 | 14567 | 0.32% | 103.34% | 103.07% | |
| HO 17 A T-3 | 0.4957 | 15.0079 | | 45.8705 | 0.4794 | 14515 | | | 102.70% | | |
| HO 18 A M-1 | 0.5156 | 15.1428 | | 46.9848 | 0.4914 | 14434 | | | 102.13% | | |
| HO 18 A M-2 | 0.5000 | 15.1290 | 14133 | 44.1394 | 0.4608 | 13944 | 14181 | 1.71% | 98.66% | 100.35% | 98.64% / 4.52% |
| HO 18 A M-3 | 0.4911 | 15.1299 | | 44.0586 | 0.4600 | 14171 | | | 100.27% | | |
| HO 19 A B-1 | 0.5112 | 15.1035 | | 41.3844 | 0.4635 | 13693 | | | 96.89% | | |
| HO 19 A B-2 | 0.5001 | 15.0779 | | 41.5615 | 0.4332 | 13060 | 13672 | 4.71% | 92.40% | 92.49% | |
| HO 19 A B-3 | 0.4928 | 15.0228 | | 39.2956 | 0.4088 | 12463 | | | 98.18% | | |
| y = 93.1257x + 1.2237 | | | | | | | | | | | |

Cells shaded in gray were re-analyzed on 12/05/2016 due to high %RSD.

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**TABLE 5 (cont.) INDIVIDUAL SAMPLE ANALYSES**

Day 0 Preparation (SA BO MA Analyzed on 10/21/2016, SA FE Analyzed on 10/24/2016)

| Sample ID | Sample Wt. (g) | Lysis Reagent Wt. (g) | Dose Level (ppm) | Peak Area | Calc. Conc. (mg/mL) | Dose Conc. (ppm) | Average (ppm) | %RSD | % Target | % Target Average |
|---|---|---|---|---|---|---|---|---|---|---|
| SA 0- 1 A-1 | 0.4880 | 4.9002 | 0 | ND | NA | NA | NA | NA | NA | NA |
| SA 0- 1 A-2 | 0.5069 | 4.9984 | | ND | NA | NA | | | NA | |
| SA 0- 1 A-3 | 0.5263 | 4.9085 | | ND | NA | NA | | | NA | |
| SA 4- 8 A-1 | 0.5051 | 5.0002 | | ND | NA | NA | NA | NA | NA | NA |
| SA 4- 8 A-2 | 0.4835 | 4.9194 | | ND | NA | NA | | | NA | |
| SA 4- 8 A-3 | 0.4863 | 4.9915 | | ND | NA | NA | | | NA | |
| SA 7- 15 A-1 | 0.4909 | 4.9244 | | ND | NA | NA | NA | NA | NA | NA |
| SA 7- 15 A-2 | 0.5123 | 4.9587 | | ND | NA | NA | | | NA | |
| SA 7- 15 A-3 | 0.4881 | 4.9250 | | ND | NA | NA | | | NA | |
| SA 10- 22 A-1 | 0.5285 | 4.9491 | | ND | NA | NA | NA | NA | NA | NA |
| SA 10- 22 A-2 | 0.5050 | 4.9289 | | ND | NA | NA | | | NA | |
| SA 10- 22 A-3 | 0.5115 | 4.9702 | | ND | NA | NA | | | NA | |
| [illegible] | [illegible] | [illegible] | 4373 | [illegible] | [illegible] | [illegible] | [illegible] | [illegible] | [illegible] | [illegible] |
| [illegible] | [illegible] | [illegible] | | [illegible] | [illegible] | [illegible] | | | [illegible] | |
| [illegible] | [illegible] | [illegible] | | [illegible] | [illegible] | [illegible] | | | [illegible] | |
| SA 4- 9 A-1 | 0.4850 | 4.9178 | | 39.5467 | 0.4139 | 4206 | 4207 | 5.21% | 96.19% | 96.20% |
| SA 4- 9 A-2 | 0.4937 | 4.9806 | | 37.7823 | 0.3953 | 3988 | | | 91.20% | |
| SA 4- 9 A-3 | 0.5068 | 4.9570 | | 43.1991 | 0.4525 | 4426 | | | 101.21% | |
| SA 7- 16 A-1 | 0.4979 | 4.9781 | | 39.3080 | 0.4114 | 4113 | 4202 | 2.80% | 94.06% | 96.09% |
| SA 7- 16 A-2 | 0.5015 | 4.9487 | | 40.2228 | 0.4211 | 4155 | | | 95.02% | |
| SA 7- 16 A-3 | 0.5176 | 4.9378 | | 43.3992 | 0.4546 | 4337 | | | 99.17% | |
| SA 10- 23 A-1 | 0.5019 | 5.0154 | | 39.1195 | 0.4096 | 4093 | 3968 | 1.36% | 93.61% | 90.74% |
| SA 10- 23 A-2 | 0.5042 | 4.9900 | | 38.4988 | 0.4024 | 3983 | | | 91.04% | |
| SA 10- 23 A-3 | 0.5045 | 5.0001 | | 36.9239 | 0.3863 | 3828 | | | 87.54% | |
| BO and MA: y = 94.7074x + 0.3440 FE: y = 94.3268x + 0.4283 | | | | | | | | | | |

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**TABLE 5 (cont.) INDIVIDUAL SAMPLE ANALYSES**

Day 0 Preparation Cont. (SA BO MA Analyzed on 10/21/2016, SA FF Analyzed on 10/24/2016)

| Sample ID | Sample Wt. (g) | Lysis Reagent Wt. (g) | Dose Level (ppm) | Peak Area | Calc. Conc. (mg/g) | Dose Conc. (ppm) | Average (ppm) | %RSD | % Target | % Target Average |
|---|---|---|---|---|---|---|---|---|---|---|
| SA 0- 1 A-1 | 0.5200 | 5.0218 | 4711 | 46.3028 | 0.4863 | 4697 | 4645 | 1.93% | 99.70% | 98.61% |
| SA 0- 1 A-2 | 0.5102 | 4.9989 | | 44.1541 | 0.4636 | 4542 | | | 96.41% | |
| SA 0- 1 A-3 | 0.4980 | 5.0609 | | 44.0296 | 0.4622 | 4697 | | | 99.71% | |
| SA 4- 10 A-1 | 0.4907 | 4.9944 | | 42.3142 | 0.4441 | 4524 | 4471 | 1.74% | 96.03% | 94.90% |
| SA 4- 10 A-2 | 0.5008 | 4.9927 | | 41.8842 | 0.4395 | 4381 | | | 93.01% | |
| SA 4- 10 A-3 | 0.5016 | 5.0280 | | 42.8306 | 0.4495 | 4506 | | | 95.65% | |
| SA 7- 17 A-1 | 0.5180 | 5.0039 | | 42.8733 | 0.4500 | 4347 | 4468 | 2.44% | 92.27% | 94.84% |
| SA 7- 17 A-2 | 0.5057 | 5.0416 | | 42.9561 | 0.4509 | 4498 | | | 95.49% | |
| SA 7- 17 A-3 | 0.5296 | 5.0191 | | 45.5214 | 0.4781 | 4558 | | | 96.75% | |
| SA 10- 24 A-1 | 0.5134 | 4.9918 | | 46.1824 | 0.4851 | 4716 | 4693 | 5.01% | 100.11% | 99.63% |
| SA 10- 24 A-2 | 0.5069 | 4.9900 | | 47.5544 | 0.4993 | 4916 | | | 104.35% | |
| SA 10- 24 A-3 | 0.4980 | 5.0624 | | 41.7004 | 0.4375 | 4448 | | | 94.41% | |
| SA 0- 4 A-1 | 0.5215 | 10.1290 | 8746 | 37.6733 | 0.3942 | 7656 | 7448 | 4.55% | 87.53% | 85.16% |
| SA 0- 4 A-2 | 0.4894 | 10.0942 | | 35.4055 | 0.3702 | 7633 | | | 87.27% | |
| SA 0- 4 A-3 | 0.5177 | 10.0877 | | 34.7136 | 0.3629 | 7057 | | | 80.69% | |
| SA 4- 11 A-1 | 0.4929 | 10.0817 | | 36.1465 | 0.3780 | 7732 | 7478 | 2.95% | 88.41% | 85.50% |
| SA 4- 11 A-2 | 0.5228 | 10.0884 | | 36.3528 | 0.3802 | 7337 | | | 83.89% | |
| SA 4- 11 A-3 | 0.5142 | 10.0894 | | 35.8883 | 0.3755 | 7364 | | | 84.20% | |
| SA 7- 18 A-1 | 0.5121 | 10.0562 | | 34.9482 | 0.3654 | 7175 | 7270 | 1.80% | 82.04% | 83.12% |
| SA 7- 18 A-2 | 0.5158 | 10.0539 | | 37.0816 | 0.3880 | 7419 | | | 84.83% | |
| SA 7- 18 A-3 | 0.5091 | 10.0922 | | 34.8172 | 0.3640 | 7216 | | | 82.50% | |
| SA 10- 25 A-1 | 0.5099 | 10.1027 | | 37.3867 | 0.3911 | 7811 | 7518 | 6.90% | 89.31% | 85.96% |
| SA 10- 25 A-2 | 0.5153 | 10.1106 | | 33.7151 | 0.3524 | 6919 | | | 79.11% | |
| SA 10- 25 A-3 | 0.5203 | 10.1068 | | 38.4896 | 0.4028 | 7824 | | | 89.46% | |

BO and MA: y = 94.7074x + 0.5440 FF: y = 94.3268x + 0.4283

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**TABLE 5 (cont.) INDIVIDUAL SAMPLE ANALYSES**

Day 0 Preparation Cont. (SA BO MA Analyzed on 10/21/2016, SA FE Analyzed on 10/24/2016)

| Sample ID | Sample Wt. (g) | Lysis Reagent Wt. (g) | Dose Level (ppm) | Peak Area | Calc. Conc. (mg/g) | Dose Conc. (ppm) | Average (ppm) | %RSD | % Target | % Target Average |
|---|---|---|---|---|---|---|---|---|---|---|
| SA 0-5 A-1 | 0.4950 | 10.1258 | 9422 | 38.1442 | 0.3998 | 8179 | 7207 | 11.70% | 86.81% | 76.49% |
| SA 0-5 A-2 | 0.5198 | 10.1349 | | 33.1859 | 0.3473 | 6771 | | | 71.80% | |
| SA 0-5 A-3 | 0.5016 | 10.0224 | | 31.9203 | 0.3339 | 6671 | | | 70.80% | |
| SA 4-12 A-1 | 0.5175 | 10.1398 | | 39.5094 | 0.4149 | 8121 | 8102 | 1.77% | 86.19% | 85.99% |
| SA 4-12 A-2 | 0.4992 | 9.9998 | | 39.2047 | 0.4111 | 8235 | | | 87.40% | |
| SA 4-12 A-3 | 0.5180 | 10.1180 | | 38.8221 | 0.4070 | 7950 | | | 84.38% | |
| SA 7-19 A-1 | 0.5289 | 10.0854 | | 39.8415 | 0.4178 | 7932 | 7910 | 0.77% | 84.40% | 83.95% |
| SA 7-19 A-2 | 0.5055 | 10.1003 | | 37.4367 | 0.3923 | 7839 | | | 83.20% | |
| SA 7-19 A-3 | 0.4968 | 10.0567 | | 37.4159 | 0.3921 | 7938 | | | 84.25% | |
| SA 10-26 A-1 | 0.4976 | 10.1201 | | 37.6717 | 0.3948 | 8030 | 7940 | 3.05% | 85.23% | 84.27% |
| SA 10-26 A-2 | 0.5080 | 10.1127 | | 36.7736 | 0.3853 | 7666 | | | 81.36% | |
| SA 10-26 A-3 | 0.4899 | 10.1092 | | 37.5669 | 0.3937 | 8125 | | | 86.23% | |
| SA 0-6 A-1 | 0.4990 | 15.1400 | 13118 | 30.9083 | 0.3227 | 9792 | 10075 | 3.21% | 74.64% | 76.80% |
| SA 0-6 A-2 | 0.4985 | 15.0032 | | 31.8216 | 0.3324 | 10033 | | | 76.26% | |
| SA 0-6 A-3 | 0.5033 | 15.1767 | | 33.1028 | 0.3459 | 10430 | | | 79.51% | |
| SA 4-13 A-1 | 0.5146 | 15.0626 | | 34.7374 | 0.3632 | 10650 | 11021 | 3.08% | 81.03% | 84.01% |
| SA 4-13 A-2 | 0.4911 | 15.1141 | | 34.9166 | 0.3650 | 11239 | | | 85.64% | |
| SA 4-13 A-3 | 0.5140 | 15.1230 | | 36.3677 | 0.3806 | 11197 | | | 85.36% | |
| SA 7-20 A-1 | 0.5032 | 15.0859 | | 34.7190 | 0.3630 | 10880 | 10279 | 6.25% | 82.94% | 78.36% |
| SA 7-20 A-2 | 0.5224 | 15.0782 | | 34.3166 | 0.3587 | 10354 | | | 78.91% | |
| SA 7-20 A-3 | 0.4979 | 15.1023 | | 30.1275 | 0.3166 | 9603 | | | 73.20% | |
| SA 10-27 A-1 | 0.5184 | 15.1230 | | 34.6099 | 0.3618 | 10254 | 10501 | 0.74% | 80.45% | 80.74% |
| SA 10-27 A-2 | 0.5080 | 15.0712 | | 34.4422 | 0.3600 | 10681 | | | 81.43% | |
| SA 10-27 A-3 | 0.5138 | 15.0849 | | 34.3165 | 0.3587 | 10539 | | | 80.34% | |

BO and MA: y = 94.7074x + 0.3440 FE: y = 94.3288x + 0.4283

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**TABLE 5 (cont.) INDIVIDUAL SAMPLE ANALYSES**

Day 0 Preparation Cont. (SA BO MA Analyzed on 10/21/2016, SA FE Analyzed on 10/24/2016)

| Sample ID | Sample Wt. (g) | Lysis Reagent Wt. (g) | Dose Level (ppm) | Peak Area | Calc. Conc. (mg/g) | Dose Conc. (ppm) | Average (ppm) | %RSD | % Target | % Target Average |
|---|---|---|---|---|---|---|---|---|---|---|
| SA 0-7 A-1 | 0.5155 | 15.0169 | 14133 | 32.8172 | 0.3434 | 10003 | 10175 | 1.88% | 70.77% | 72.00% |
| SA 0-7 A-2 | 0.4956 | 15.0274 | | 32.7200 | 0.3423 | 10380 | | | 73.45% | |
| SA 0-7 A-3 | 0.5265 | 15.0927 | | 33.8056 | 0.3538 | 10143 | | | 71.77% | |
| SA 4-14 A-1 | 0.5104 | 15.0924 | | 31.6599 | 0.3311 | 9621 | 9698 | 1.12% | 68.07% | 68.62% |
| SA 4-14 A-2 | 0.5122 | 15.0737 | | 31.9091 | 0.3337 | 9822 | | | 69.50% | |
| SA 4-14 A-3 | 0.4935 | 15.1440 | | 30.0940 | 0.3145 | 9651 | | | 68.29% | |
| SA 7-21 A-1 | 0.5144 | 15.1119 | | 31.4225 | 0.3286 | 9650 | 9717 | 7.30% | 68.30% | 68.76% |
| SA 7-21 A-2 | 0.5004 | 15.1011 | | 28.6912 | 0.2996 | 9042 | | | 63.98% | |
| SA 7-21 A-3 | 0.4928 | 15.0646 | | 32.6949 | 0.3421 | 10457 | | | 73.99% | |
| SA 10-28 A-1 | 0.5035 | 15.0944 | | 32.1489 | 0.3363 | 10081 | 9712 | 5.80% | 71.33% | 68.72% |
| SA 10-28 A-2 | 0.4988 | 15.1463 | | 31.4624 | 0.3290 | 9990 | | | 70.69% | |
| SA 10-28 A-3 | 0.5003 | 15.0951 | | 28.7629 | 0.3004 | 9063 | | | 64.13% | |
| BO and MA: y = 94.7074x + 0.3440 FE: y = 94.3268x + 0.4283 | | | | | | | | | | |

NA = Not Applicable; ND = Not Detected

Cells shaded in light gray were re-analyzed on 11/16/2016 and 11/29/2016 due to low signal

Cells shaded in dark gray were re-analyzed on 12/05/2016 due to high %RSD.

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**TABLE 5 (cont.) INDIVIDUAL SAMPLE ANALYSES**

Day 0 Preparation (SA MA Analyzed on 11/29/2016, SA FE Analyzed on 11/16/2016)

| Sample ID | Sample Wt. (g) | Lysis Reagent Wt. (g) | Dose Level (ppm) | Peak Area | Calc. Conc. (mg/mL) | Dose Conc. (ppm) | Average (ppm) | %RSD | % Target | % Target Average |
|---|---|---|---|---|---|---|---|---|---|---|
| SA 0-4 A-1 | 0.5148 | 10.0272 | 8746 | 36.6329 | 0.3959 | 7710 | 7686 | 5.80% | 88.16% | 87.88% |
| SA 0-4 A-2 | 0.5072 | 10.0153 | | 33.7418 | 0.3690 | 7222 | | | 82.58% | |
| SA 0-4 A-3 | 0.5260 | 10.0553 | | 39.3638 | 0.4250 | 8124 | | | 92.90% | |
| SA 4-11 A-1 | 0.5165 | 10.0120 | | 34.5090 | 0.3752 | 7299 | 7441 | 4.17% | 82.88% | 85.08% |
| SA 4-11 A-2 | 0.5129 | 10.0727 | | 36.7481 | 0.3971 | 7798 | | | 89.16% | |
| SA 4-11 A-3 | 0.5183 | 9.9986 | | 34.8752 | 0.3771 | 7275 | | | 83.18% | |
| SA 7-18 A-1 | 0.5092 | 10.0576 | | 34.9911 | 0.3771 | 7452 | 7595 | 2.35% | 85.21% | 86.85% |
| SA 7-18 A-2 | 0.5045 | 10.0593 | | 36.1730 | 0.3910 | 7795 | | | 89.13% | |
| SA 7-18 A-3 | 0.5119 | 10.0360 | | 35.5720 | 0.3845 | 7539 | | | 86.20% | |
| SA 10-25 A-1 | 0.5229 | 9.9713 | | 39.8556 | 0.4302 | 8204 | 7847 | 4.36% | 93.80% | 89.72% |
| SA 10-25 A-2 | 0.5085 | 9.9885 | | 35.4250 | 0.3830 | 7523 | | | 86.02% | |
| SA 10-25 A-3 | 0.4999 | 10.0507 | | 35.9512 | 0.3886 | 7813 | | | 89.33% | |
| SA 0-5 A-1 | 0.4950 | 10.1258 | 9422 | 38.6294 | 0.4407 | 9014 | 9054 | 0.27% | 95.67% | 95.89% |
| SA 0-5 A-2 | 0.5198 | 10.1349 | | 40.6642 | 0.4630 | 9027 | | | 95.81% | |
| SA 0-5 A-3 | 0.5016 | 10.0224 | | 39.7995 | 0.4535 | 9061 | | | 96.17% | |
| SA 4-12 A-1 | 0.5175 | 10.1298 | | 39.8534 | 0.4541 | 9089 | 8918 | 1.60% | 94.31% | 94.65% |
| SA 4-12 A-2 | 0.4992 | 9.9998 | | 39.7481 | 0.4529 | 9073 | | | 96.30% | |
| SA 4-12 A-3 | 0.5180 | 10.1180 | | 39.4864 | 0.4501 | 8792 | | | 93.31% | |
| SA 7-19 A-1 | 0.5289 | 10.0654 | | 40.2252 | 0.4582 | 8719 | 8728 | 1.44% | 92.54% | 92.61% |
| SA 7-19 A-2 | 0.5055 | 10.1001 | | 37.7203 | 0.4307 | 8806 | | | 91.34% | |
| SA 7-19 A-3 | 0.4968 | 10.0567 | | 38.3455 | 0.4376 | 8857 | | | 94.01% | |
| SA 10-26 A-1 | 0.4976 | 10.1201 | | 38.3853 | 0.4380 | 9008 | 8898 | 1.57% | 94.54% | 93.78% |
| SA 10-26 A-2 | 0.5083 | 10.1127 | | 38.2140 | 0.4361 | 8677 | | | 92.09% | |
| SA 10-26 A-3 | 0.4899 | 10.1092 | | 37.8841 | 0.4325 | 8925 | | | 94.72% | |

MA: y = 95.7869x - 0.4936 FE: y = 91.1622x - 1.5430

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**TABLE 5 (cont.) INDIVIDUAL SAMPLE ANALYSES**

Day 0 Preparation Cont. (SA MA Analyzed on 11/29/2016, SA FE Analyzed on 11/16/2016)

| Sample ID | Sample Wt. (g) | Lysis Reagent Wt. (g) | Dose Level (ppm) | Peak Area | Calc. Conc. (mg/mL) | Dose Conc. (ppm) | Average (ppm) | %RSD | % Target | % Target Average |
|---|---|---|---|---|---|---|---|---|---|---|
| SA 0-6 A-1 | 0.5092 | 15.0268 | 11118 | 34.4515 | 0.3726 | 10996 | 11206 | 1.65% | 83.82% | 85.41% |
| SA 0-6 A-2 | 0.5060 | 15.1160 | | 34.9543 | 0.3777 | 11285 | | | 86.02% | |
| SA 0-6 A-3 | 0.5181 | 15.1013 | | 35.9908 | 0.3890 | 11339 | | | 86.44% | |
| SA 4-13 A-1 | 0.5003 | 15.0537 | | 36.5576 | 0.3951 | 11887 | 12097 | 1.98% | 90.62% | 92.22% |
| SA 4-13 A-2 | 0.5029 | 15.0858 | | 37.4660 | 0.4047 | 12141 | | | 92.55% | |
| SA 4-13 A-3 | 0.5181 | 15.1276 | | 38.8934 | 0.4200 | 12262 | | | 93.48% | |
| SA 7-20 A-1 | 0.5012 | 15.1843 | | 36.7537 | 0.3971 | 12032 | 12423 | 2.81% | 91.72% | 94.70% |
| SA 7-20 A-2 | 0.5129 | 15.2045 | | 39.1280 | 0.4225 | 12524 | | | 95.47% | |
| SA 7-20 A-3 | 0.5024 | 15.1361 | | 39.0795 | 0.4219 | 12712 | | | 96.91% | |
| SA 10-27 A-1 | 0.5102 | 15.1588 | | 37.6042 | 0.4062 | 12069 | 12825 | 7.05% | 92.01% | 97.77% |
| SA 10-27 A-2 | 0.5016 | 15.1416 | | 42.4640 | 0.4589 | 13826 | | | 105.40% | |
| SA 10-27 A-3 | 0.5031 | 15.1237 | | 38.7567 | 0.4185 | 12581 | | | 95.90% | |
| SA 0-7 A-1 | 0.5155 | 15.0169 | 14133 | 36.3203 | 0.4153 | 12099 | 12808 | 1.86% | 85.61% | 90.62% |
| SA 0-7 A-2 | 0.4956 | 15.0274 | | 38.3350 | 0.4374 | 13264 | | | 93.85% | |
| SA 0-7 A-3 | 0.5265 | 15.0927 | | 39.9905 | 0.4556 | 13060 | | | 92.41% | |
| SA 4-14 A-1 | 0.5194 | 15.0924 | | 40.0184 | 0.4561 | 13254 | 13191 | 1.98% | 93.78% | 93.33% |
| SA 4-14 A-2 | 0.5122 | 15.0737 | | 40.0108 | 0.4558 | 13415 | | | 94.92% | |
| SA 4-14 A-3 | 0.4935 | 15.1440 | | 36.7888 | 0.4205 | 12903 | | | 91.30% | |
| SA 7-21 A-1 | 0.5144 | 15.1119 | | 40.2469 | 0.4584 | 13467 | 13547 | 5.94% | 95.29% | 95.85% |
| SA 7-21 A-2 | 0.5004 | 15.1011 | | 37.0899 | 0.4237 | 12786 | | | 90.47% | |
| SA 7-21 A-3 | 0.4928 | 15.0646 | | 41.3654 | 0.4707 | 14588 | | | 101.81% | |
| SA 10-28 A-1 | 0.5035 | 15.0944 | | 40.7745 | 0.4642 | 13916 | 13762 | 1.79% | 98.47% | 97.38% |
| SA 10-28 A-2 | 0.4988 | 15.1463 | | 41.4408 | 0.4715 | 14318 | | | 101.31% | |
| SA 10-28 A-3 | 0.5033 | 15.0951 | | 37.8941 | 0.4326 | 13053 | | | 92.36% | |
| MA: y = 93.7869x - 0.4936 FE: y = 91.1622x + 5430 | | | | | | | | | | |

Cells shaded in gray were re-analyzed on 12/1/2016 due to low signal

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**TABLE 5 (cont.) INDIVIDUAL SAMPLE ANALYSES**

Day 0 Preparation (SA MA Analyzed on 12/01/2016)

| Sample ID | Sample Wt. (g) | Lysis Reagent Wt. (g) | Dose Level (ppm) | Peak Area | Calc. Conc. (mg/mL) | Dose Conc. (ppm) | Average (ppm) | %RSD | % Target | % Target Average |
|---|---|---|---|---|---|---|---|---|---|---|
| [illegible] | [illegible] | [illegible] | 8746 | [illegible] | [illegible] | [illegible] | [illegible] | [illegible] | [illegible] | [illegible] |
| [illegible] | [illegible] | [illegible] | | [illegible] | [illegible] | [illegible] | | | [illegible] | |
| [illegible] | [illegible] | [illegible] | | [illegible] | [illegible] | [illegible] | | | [illegible] | |
| SA 4-11-A-1 | 0.5165 | 10.0120 | | 37.2215 | 0.4109 | 7971 | 8238 | 4.34% | 91.16% | 94.19% |
| SA 4-11-A-2 | 0.5129 | 10.0127 | | 39.9241 | 0.4402 | 8545 | | | 98.84% | |
| SA 4-11-A-3 | 0.5180 | 9.9986 | | 38.0522 | 0.4196 | 8095 | | | 92.56% | |
| SA 7-18-A-1 | 0.5002 | 10.0536 | | 37.1047 | 0.4084 | 8067 | 8200 | 2.41% | 92.24% | 93.76% |
| SA 7-18-A-2 | 0.5045 | 10.0591 | | 38.3301 | 0.4227 | 8428 | | | 96.36% | |
| SA 7-18-A-3 | 0.5119 | 10.0360 | | 37.4938 | 0.4135 | 8106 | | | 92.68% | |
| SA 10-25-A-1 | 0.5229 | 9.9713 | | 41.8285 | 0.4611 | 8793 | 8453 | 4.16% | 100.54% | 96.65% |
| SA 10-25-A-2 | 0.5085 | 9.9885 | | 37.3032 | 0.4125 | 8103 | | | 92.64% | |
| SA 10-25-A-3 | 0.4999 | 10.0307 | | 38.1735 | 0.4210 | 8463 | | | 96.77% | |
| SA 0-6-A-1 | 0.5092 | 15.0268 | 13110 | 37.0226 | 0.4094 | 12031 | 12263 | 1.57% | 91.85% | 93.50% |
| SA 0-6-A-2 | 0.5091 | 15.1160 | | 37.7147 | 0.4150 | 12425 | | | 94.71% | |
| SA 0-6-A-3 | 0.5181 | 15.1017 | | 38.3277 | 0.4226 | 12319 | | | 93.91% | |
| y = 40.0251 - 0.1435 | | | | | | | | | | |

Cells shaded in dark gray were re-analyzed on 12/05/2016 due to high % RSD.

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**TABLE 5 (cont.) INDIVIDUAL SAMPLE ANALYSES**

Study Day 7 (Analyzed on 10/27/2016)

| Sample ID | Sample Wt. (g) | Lysis Reagent Wt. (g) | Dose Level (ppm) | Peak Area | Calc. Conc. (mg/g) | Dose Conc. (ppm) | Average (ppm) | %RSD | % Target | % Target Average |
|---|---|---|---|---|---|---|---|---|---|---|
| CV 1 A-1 | 0.5006 | 5.0892 | 0 | ND | NA | NA | NA | NA | NA | NA |
| CV 1 A-2 | 0.5266 | 5.0722 | | ND | NA | NA | | | NA | |
| CV 1 A-3 | 0.5298 | 5.0778 | | ND | NA | NA | | | NA | |
| CV 2 A-1 | 0.5092 | 5.0349 | 6093 | 58.3544 | 0.6135 | 6066 | 6158 | 1.26% | 99.56% | 101.06% |
| CV 2 A-2 | 0.5008 | 5.0774 | | 57.9503 | 0.6092 | 6177 | | | 101.37% | |
| CV 2 A-3 | 0.5195 | 5.0811 | | 60.5470 | 0.6370 | 6211 | | | 102.26% | |
| CV 3 A-1 | 0.5299 | 10.0718 | 5924 | 27.6551 | 0.2838 | 5395 | 5326 | 1.85% | 92.63% | 91.45% |
| CV 3 A-2 | 0.5067 | 10.0522 | | 25.6958 | 0.2628 | 5213 | | | 89.51% | |
| CV 3 A-3 | 0.503 | 10.0550 | | 26.2448 | 0.2687 | 5371 | | | 92.22% | |
| CV 4 A-1 | 0.5057 | 5.0530 | 12318 | 106.3060 | 1.1505 | 11565 | 10861 | 7.20% | 93.88% | 88.17% |
| CV 4 A-2 | 0.5048 | 5.0435 | | 94.6081 | 1.0028 | 10019 | | | 81.34% | |
| CV 4 A-3 | 0.5101 | 5.0590 | | 104.3082 | 1.1001 | 11000 | | | 89.30% | |
| CV 5 A-1 | 0.5251 | 10.0494 | 11664 | 53.2433 | 0.5586 | 10691 | 10276 | 3.68% | 91.66% | 88.10% |
| CV 5 A-2 | 0.5197 | 10.0508 | | 50.2725 | 0.5267 | 10186 | | | 87.31% | |
| CV 5 A-3 | 0.5029 | 10.0162 | | 47.7505 | 0.4996 | 9951 | | | 85.31% | |
| CV 6 A-1 | 0.503 | 15.0725 | 18362 | 54.2243 | 0.5691 | 17055 | 16298 | 5.25% | 92.88% | 88.76% |
| CV 6 A-2 | 0.5215 | 14.7264 | | 51.9149 | 0.5443 | 15171 | | | 83.71% | |
| CV 6 A-3 | 0.5344 | 15.0972 | | 55.9118 | 0.5830 | 16469 | | | 89.09% | |
| CV 7 A-1 | 0.5114 | 15.0958 | 17567 | 46.0137 | 0.4810 | 14197 | 13655 | 3.48% | 80.82% | 77.73% |
| CV 7 A-2 | 0.5273 | 15.1903 | | 44.2578 | 0.4621 | 13312 | | | 75.78% | |
| CV 7 A-3 | 0.5016 | 15.1680 | | 43.6654 | 0.4450 | 13457 | | | 76.60% | |
| y = 93.1217x + 1.2231 | | | | | | | | | | |

ND - Not Detected. NA - Not applicable.

Cells shaded in gray were re-analyzed on 10/31/2016 due to low signal.

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**TABLE 5 (cont.) INDIVIDUAL SAMPLE ANALYSES**

Study Day 21 (Analyzed on 10/27/2016)

| Sample ID | Sample Wt. (g) | Lysis Reagent Wt. (g) | Dose Level (ppm) | Peak Area | Calc. Conc. (mg/g) | Dose Conc. (ppm) | Average (ppm) | %RSD | % Target | % Target Average |
|---|---|---|---|---|---|---|---|---|---|---|
| CV 8 A-1 | 0.537 | 49.959 | 0 | ND | NA | NA | NA | NA | NA | NA |
| CV 8 A-2 | 0.5007 | 50.770 | | ND | NA | NA | | | NA | |
| CV 8 A-3 | 0.529 | 50.063 | | ND | NA | NA | | | NA | |
| CV 9 A-1 | 0.5016 | 50.933 | 7407 | * | * | * | 6906 | 3.63% | 79.76% | 93.24% |
| CV 9 A-2 | 0.5121 | 50.061 | | 66.9936 | 0.7062 | 6987 | | | 94.33% | |
| CV 9 A-3 | 0.5022 | 50.729 | | 64.1558 | 0.6759 | 6826 | | | 92.16% | |
| CV 10 A-1 | 0.5272 | 50.859 | 5925 | 55.6407 | 0.5841 | 5982 | 5598 | 2.69% | 94.21% | 92.80% |
| CV 10 A-2 | 0.526 | 50.816 | | 52.7617 | 0.5554 | 5529 | | | 89.95% | |
| CV 10 A-3 | 0.5046 | 50.192 | | 51.9989 | 0.5613 | 5664 | | | 94.21% | |
| CV 11 A-1 | 0.5087 | 10.0415 | 14727 | 35.4971 | 0.3828 | 11262 | 11082 | 3.24% | 76.51% | 75.25% |
| CV 11 A-2 | 0.5187 | 10.0322 | | 30.2739 | 0.3389 | 10605 | | | 73.37% | |
| CV 11 A-3 | 0.5015 | 10.0588 | | 31.0287 | 0.3563 | 11156 | | | 75.76% | |
| CV 12 A-1 | 0.5128 | 10.0763 | 12901 | 31.5607 | 0.3496 | 10621 | 10548 | 3.75% | 82.34% | 81.76% |
| CV 12 A-2 | 0.5066 | 10.1009 | | 30.6700 | 0.3396 | 10120 | | | 78.45% | |
| CV 12 A-3 | 0.5043 | 10.0722 | | 32.0438 | 0.3457 | 10900 | | | 84.49% | |
| CV 13 A-1 | 0.5023 | 15.1993 | 21943 | 39.1589 | 0.0221 | 18801 | 17978 | 4.68% | 85.73% | 81.93% |
| CV 13 A-2 | 0.5046 | 15.1344 | | 37.1058 | 0.0000 | 17905 | | | 82.01% | |
| CV 13 A-3 | 0.5093 | 15.1557 | | 34.8286 | 0.3736 | 17329 | | | 78.86% | |
| CV 14 A-1 | 0.515 | 15.2176 | 18281 | 47.3566 | 0.4954 | 14639 | 13991 | 2.97% | 75.92% | 78.27% |
| CV 14 A-2 | 0.5141 | 15.1631 | | 48.8979 | 0.5115 | 15094 | | | 78.35% | |
| CV 14 A-3 | 0.507 | 15.0909 | | 49.0208 | 0.5218 | 15536 | | | 80.58% | |
| | | | | | y = 0.11573 + 1.2237 | | | | | |

ND = Not Detected, NA = Not applicable.

* Excluded due to non-trending result

Cells shaded in gray were re-analyzed on 10/31/2016 due to low signal.

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**TABLE 5 (cont.) INDIVIDUAL SAMPLE ANALYSES**

Study Days 7 and 21 (Analyzed on 10/31/2016)

| Sample ID | Sample Wt. (g) | Lysis Reagent Wt. (g) | Dose Level (ppm) | Peak Area | Calc. Conc. (mg/g) | Dose Conc. (ppm) | Average (ppm) | %RSD | % Target | % Target Average |
|---|---|---|---|---|---|---|---|---|---|---|
| CV 4 A-1 | 0.5027 | 5.0530 | 12318 | 106.6878 | 1.1325 | 11384 | 12189 | 5.76% | 92.41% | 98.96% |
| CV 4 A-2 | 0.5048 | 5.0435 | | 119.3389 | 1.2683 | 12672 | | | 102.87% | |
| CV 4 A-3 | 0.5101 | 5.0590 | | 118.7180 | 1.2617 | 12513 | | | 101.58% | |
| CV 5 A-1 | 0.5251 | 10.0494 | 11664 | 59.1429 | 0.6219 | 11903 | 11408 | 3.90% | 102.05% | 97.81% |
| CV 5 A-2 | 0.5197 | 10.0508 | | 55.5551 | 0.5834 | 11283 | | | 96.73% | |
| CV 5 A-3 | 0.5029 | 10.0162 | | 52.8410 | 0.5543 | 11039 | | | 94.65% | |
| CV 6 A-1 | 0.503 | 15.0735 | 18362 | 63.6259 | 0.6701 | 20080 | 19409 | 4.71% | 109.36% | 105.70% |
| CV 6 A-2 | 0.5215 | 14.7264 | | 61.7805 | 0.6503 | 18363 | | | 100.03% | |
| CV 6 A-3 | 0.5344 | 15.0972 | | 66.4426 | 0.7003 | 19785 | | | 107.75% | |
| CV 7 A-1 | 0.5114 | 15.0958 | 17567 | 57.5589 | 0.6049 | 17857 | 17218 | 3.29% | 97.25% | 93.88% |
| CV 7 A-2 | 0.5273 | 15.1503 | | 55.3460 | 0.5812 | 16742 | | | 91.18% | |
| CV 7 A-3 | 0.5016 | 15.1680 | | 53.9333 | 0.5660 | 17116 | | | 93.21% | |
| CV 11 A-1 | 0.5187 | 10.0415 | 14727 | 63.8008 | 0.6720 | 13039 | 13093 | 4.18% | 88.31% | 88.91% |
| CV 11 A-2 | 0.5187 | 10.0272 | | 62.5295 | 0.6583 | 12726 | | | 86.41% | |
| CV 11 A-3 | 0.5015 | 10.0589 | | 64.1103 | 0.6753 | 13545 | | | 91.97% | |
| CV 12 A-1 | 0.5128 | 10.0767 | 12901 | 63.0154 | 0.6635 | 13038 | 12612 | 3.44% | 101.06% | 97.76% |
| CV 12 A-2 | 0.5066 | 10.1009 | | 58.2956 | 0.6128 | 12171 | | | 94.34% | |
| CV 12 A-3 | 0.5043 | 10.0722 | | 60.0914 | 0.6321 | 12625 | | | 97.86% | |
| CV 13 A-1 | 0.5023 | 15.1893 | 21943 | 67.1985 | 0.7085 | 21423 | 20786 | 3.11% | 97.63% | 94.73% |
| CV 13 A-2 | 0.5046 | 15.1344 | | 65.8189 | 0.6936 | 20904 | | | 94.81% | |
| CV 13 A-3 | 0.5095 | 15.1557 | | 64.2218 | 0.6765 | 20131 | | | 91.74% | |
| CV 14 A-1 | 0.515 | 15.2136 | 19281 | 59.1638 | 0.6222 | 18384 | 18829 | 2.66% | 95.35% | 97.65% |
| CV 14 A-2 | 0.5141 | 15.1631 | | 60.5584 | 0.6350 | 18729 | | | 97.14% | |
| CV 14 A-3 | 0.507 | 15.0939 | | 63.8215 | 0.6507 | 19372 | | | 100.47% | |
| y = 93.1257x + 1.2237 | | | | | | | | | | |

Cells shaded in gray were re-analyzed on 12/05/2016 due to low signal.

IMPOSSIBLE

**TABLE 5 (cont.) INDIVIDUAL SAMPLE ANALYSES**

Study Days 0, 7 and 21 (Analyzed on 12/05/2016)

| Sample ID | Sample Wt. (g) | Lysis Reagent Wt. (g) | Dose Level (ppm) | Peak Area | Calc. Conc. (mg/g) | Dose Conc. (ppm) | Average (ppm) | %RSD | % Target | % Target Average |
|---|---|---|---|---|---|---|---|---|---|---|
| CV 11 A-1 | 0.5292 | 10.0256 | 14727 | 69.4856 | 0.7603 | 14404 | 14292 | 2.61% | 97.81% | 97.05% |
| CV 11 A-2 | 0.5230 | 10.0164 | | 66.2234 | 0.7245 | 13876 | | | 94.22% | |
| CV 11 A-3 | 0.5191 | 10.0179 | | 69.1265 | 0.7564 | 14597 | | | 99.12% | |
| HO 4 A B-1 | 0.5035 | 5.1007 | 4573 | 47.3784 | 0.5180 | 5047 | 4873 | 6.87% | 119.99% | 111.43% |
| HO 4 A B-2 | 0.5161 | 5.1545 | | 42.1655 | 0.4608 | 4602 | | | 105.24% | |
| HO 4 A B-3 | 0.5101 | 5.1601 | | 43.1389 | 0.4715 | 4769 | | | 109.08% | |
| CV 9 A-1 | 0.5014 | 5.1682 | 7407 | 60.8553 | 0.6657 | 6862 | 7421 | 7.05% | 92.64% | 100.19% |
| CV 9 A-2 | 0.5034 | 5.1496 | | 67.5114 | 0.7365 | 7504 | | | 101.31% | |
| CV 9 A-3 | 0.5068 | 5.1549 | | 70.9612 | 0.7769 | 7898 | | | 106.63% | |
| HO 10 A B-1 | 0.5221 | 10.0158 | 8746 | 41.1593 | 0.4498 | 8628 | 8250 | 4.06% | 98.69% | 94.33% |
| HO 10 A B-2 | 0.5057 | 10.0045 | | 36.9704 | 0.4040 | 7992 | | | 91.37% | |
| HO 10 A B-3 | 0.5081 | 9.9898 | | 37.8552 | 0.4136 | 8131 | | | 92.97% | |
| HO 14 A T-1 | 0.5159 | 15.1945 | 13118 | 38.5961 | 0.4217 | 12419 | 12226 | 3.70% | 94.67% | 93.20% |
| HO 14 A T-2 | 0.5051 | 15.1446 | | 38.3451 | 0.4189 | 12561 | | | 95.79% | |
| HO 14 A T-3 | 0.5085 | 15.2688 | | 35.6651 | 0.3895 | 11697 | | | 89.17% | |
| SA 0- 2 A-1 | 0.5212 | 5.1675 | 4373 | 42.5967 | 0.4652 | 4593 | 4508 | 5.08% | 105.03% | 103.08% |
| SA 0- 2 A-2 | 0.5251 | 5.1692 | | 41.9133 | 0.4800 | 4725 | | | 108.05% | |
| SA 0- 2 A-3 | 0.5184 | 5.1511 | | 38.7419 | 0.4233 | 4206 | | | 96.18% | |
| SA 10- 27 A-1 | 0.5325 | 15.2288 | 13118 | 36.7208 | 0.4011 | 11471 | 10559 | 7.49% | 87.45% | 80.49% |
| SA 10- 27 A-2 | 0.5217 | 15.1745 | | 31.8556 | 0.3478 | 10116 | | | 77.11% | |
| SA 10- 27 A-3 | 0.5364 | 15.2121 | | 32.5808 | 0.3557 | 10088 | | | 76.91% | |
| SA 0- 4 A-1 | 0.5233 | 9.9558 | 8746 | 38.0974 | 0.4162 | 7918 | 7951 | 0.57% | 90.54% | 90.91% |
| SA 0- 4 A-2 | 0.5322 | 10.0217 | | 38.9961 | 0.4250 | 8002 | | | 91.50% | |
| SA 0- 4 A-3 | 0.5051 | 10.0204 | | 36.5978 | 0.3998 | 7931 | | | 90.68% | |
| y = 91.2192x - 0.1319 | | | | | | | | | | |

Cells shaded in gray were excluded from analysis due to high %RSD. Original data was used in analysis.

# APPENDIX E: OPHTHALMOLOGY

## PRODUCT IDENTIFICATION

Soy Leghemoglobin Preparation

Kristina R. Vygantas, DVM, Diplomate American College of Veterinary Ophthalmologists
319 Perrineville Rd.
Robbinsville, NJ 08691
609.259.8300 (work)

Exam Date: September 23, 2016

Eurofins Study No: ~~160720-5R~~ 43166 (b) 11/15/16
PSL No. 160720-5R

44 male and 44 female SD rats were examined. The examination was performed under dim light conditions after pharmacologic mydriasis with 1% tropicamide ophthalmic solution. Both eyes of each animal were examined using slit lamp biomicroscopy and indirect ophthalmoscopy. All animals were all normal on ophthalmic exam and thus, suitable for inclusion in this study.

(b) (6)

Kristina R. Vygantas, DVM
Diplomate, American College of Veterinary Ophthalmologists

Kristina R. Vygantas, DVM, Diplomate American College of Veterinary Ophthalmologists
319 Perrineville Rd.
Robbinsville, NJ 08691
609.259.8300 (work)

Exam Date: October 21, 2016

Eurofins Study No: 43166
PSL No. 160720-5R

40 male and 40 female SD rats were examined. The examination was performed under dim light conditions after pharmacologic mydriasis with 1% tropicamide ophthalmic solution. Both eyes of each animal were examined using slit lamp biomicroscopy and indirect ophthalmoscopy. All animals were all normal on ophthalmic exam, thus the test substance was not considered an ocular toxicant.

(b) (6)

Kristina R. Vygantas, DVM
Diplomate, American College of Veterinary Ophthalmologists

# APPENDIX F: INDIVIDUAL ANIMAL IN-LIFE CLINICAL OBSERVATIONS[1]

## PRODUCT IDENTIFICATION

Soy Leghemoglobin Preparation

[1] Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient.
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

Individual Animal Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Day numbers relative to Start Date

| Group | Sex | Animal | Clinical Sign | Site | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | m | 7001 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 7002 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 7003 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 7004 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 7005 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 7006 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 7007 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 7008 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 7009 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 7010 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

Severity Codes: X = Present; S = Slight; M = Moderate; F = Superficial

Group 1 - 0 mg/kg/day Group 2 - 512 mg/kg/day
Group 3 - 1024 mg/kg/day Group 4 - 1536 mg/kg/day

Individual Animal Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Day numbers relative to Start Date

| Group | Sex | Animal | Clinical Sign | Site | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | m | 7001 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | . |
| | | 7002 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | . |
| | | 7003 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | . |
| | | 7004 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | . |
| | | 7005 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | . |
| | | 7006 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | . |
| | | 7007 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | . |
| | | 7008 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | . |
| | | 7009 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | . |
| | | 7010 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | . |

Severity Codes: X = Present; S = Slight; M = Moderate; F = Superficial

Group 1 - 0 mg/kg/day Group 2 - 512 mg/kg/day
Group 3 - 1024 mg/kg/day Group 4 - 1536 mg/kg/day

Individual Animal Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Day numbers relative to Start Date

| Group | Sex | Animal | Clinical Sign | Site | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2 | m | 7021 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 7022 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 7023 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 7024 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 7025 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 7026 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 7027 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 7028 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 7029 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 7030 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

Severity Codes: X = Present; S = Slight; M = Moderate; F = Superficial

Group 1 - 0 mg/kg/day Group 2 - 512 mg/kg/day
Group 3 - 1024 mg/kg/day Group 4 - 1536 mg/kg/day

Individual Animal Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Day numbers relative to Start Date

| Group | Sex | Animal | Clinical Sign | Site | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2 | m | 7021 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | . |
| | | 7022 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | . |
| | | 7023 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | . |
| | | 7024 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | . |
| | | 7025 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | . |
| | | 7026 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | . |
| | | 7027 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | . |
| | | 7028 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | . |
| | | 7029 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | . |
| | | 7030 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | . |

Severity Codes: X = Present; S = Slight; M = Moderate; F = Superficial

Group 1 - 0 mg/kg/day Group 2 - 512 mg/kg/day
Group 3 - 1024 mg/kg/day Group 4 - 1536 mg/kg/day

Individual Animal Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Day numbers relative to Start Date

| Group | Sex | Animal | Clinical Sign | Site | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 3 | m | 7041 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 7042 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 7043 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 7044 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 7045 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 7046 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 7047 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 7048 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 7049 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 7050 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

Severity Codes: X = Present; S = Slight; M = Moderate; F = Superficial

Group 1 - 0 mg/kg/day Group 2 - 512 mg/kg/day
Group 3 - 1024 mg/kg/day Group 4 - 1536 mg/kg/day

Individual Animal Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Day numbers relative to Start Date

| Group | Sex | Animal | Clinical Sign | Site | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 3 | m | 7041 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | . |
| | | 7042 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | . |
| | | 7043 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | . |
| | | 7044 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | . |
| | | 7045 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | . |
| | | 7046 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | . |
| | | 7047 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | . |
| | | 7048 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | . |
| | | 7049 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | . |
| | | 7050 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | . |

Severity Codes: X = Present; S = Slight; M = Moderate; F = Superficial

Group 1 - 0 mg/kg/day Group 2 - 512 mg/kg/day
Group 3 - 1024 mg/kg/day Group 4 - 1536 mg/kg/day

Individual Animal Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Day numbers relative to Start Date

| Group | Sex | Animal | Clinical Sign | Site | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 4 | m | 7061 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | . | X | X | X | X | X | X |
| | | | Staining | Cage Pan | . | . | . | . | . | . | . | . | . | . | . | . | . | X | . | . | . | . | . | . |
| | | 7062 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 7063 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 7064 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 7065 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | . | X | X | X | X | X | X |
| | | | Staining | Cage Pan | . | . | . | . | . | . | . | . | . | . | . | . | . | X | . | . | . | . | . | . |
| | | 7066 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | . | X | X | X | X | X | X |
| | | | Staining | Cage Pan | . | . | . | . | . | . | . | . | . | . | . | . | . | X | . | . | . | . | . | . |
| | | 7067 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | . | X | X | X | X | X | X |
| | | | Staining | Cage Pan | . | . | . | . | . | . | . | . | . | . | . | . | . | X | . | . | . | . | . | . |
| | | 7068 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | . | X | X | X | X | X | X |
| | | | Staining | Cage Pan | . | . | . | . | . | . | . | . | . | . | . | . | . | X | . | . | . | . | . | . |
| | | 7069 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | . | X | X | X | X | X | X |
| | | | Staining | Cage Pan | . | . | . | . | . | . | . | . | . | . | . | . | . | X | . | . | . | . | . | . |
| | | | Eschar | Head | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| | | 7070 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | . | X | X | X | X | X | X |
| | | | Staining | Cage Pan | . | . | . | . | . | . | . | . | . | . | . | . | . | X | . | . | . | . | . | . |

Severity Codes: X = Present; S = Slight; M = Moderate; F = Superficial

Group 1 - 0 mg/kg/day Group 2 - 512 mg/kg/day
Group 3 - 1024 mg/kg/day Group 4 - 1536 mg/kg/day

Individual Animal Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Day numbers relative to Start Date

| Group | Sex | Animal | Clinical Sign | Site | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 4 | m | 7061 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | . |
| | | | Staining | Cage Pan | . | . | . | . | . | . | . | . | . | . | . |
| | | 7062 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | . |
| | | 7063 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | . |
| | | 7064 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | . |
| | | 7065 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | . |
| | | | Staining | Cage Pan | . | . | . | . | . | . | . | . | . | . | . |
| | | 7066 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | . |
| | | | Staining | Cage Pan | . | . | . | . | . | . | . | . | . | . | . |
| | | 7067 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | . |
| | | | Staining | Cage Pan | . | . | . | . | . | . | . | . | . | . | . |
| | | 7068 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | . |
| | | | Staining | Cage Pan | . | . | . | . | . | . | . | . | . | . | . |
| | | 7069 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | . | . | . |
| | | | Staining | Cage Pan | . | . | . | . | . | . | . | . | . | . | . |
| | | | Eschar | Head | . | . | . | . | . | . | . | . | F | F | . |
| | | 7070 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | . |
| | | | Staining | Cage Pan | . | . | . | . | . | . | . | . | . | . | . |

Severity Codes: X = Present; S = Slight; M = Moderate; F = Superficial

Group 1 - 0 mg/kg/day Group 2 - 512 mg/kg/day
Group 3 - 1024 mg/kg/day Group 4 - 1536 mg/kg/day

Individual Animal Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Day numbers relative to Start Date

| Group | Sex | Animal | Clinical Sign | Site | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | f | 7011 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 7012 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 7013 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 7014 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 7015 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 7016 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 7017 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 7018 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 7019 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 7020 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

Severity Codes: X = Present; S = Slight; M = Moderate; F = Superficial

Group 1 - 0 mg/kg/day Group 2 - 512 mg/kg/day
Group 3 - 1024 mg/kg/day Group 4 - 1536 mg/kg/day

Individual Animal Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Day numbers relative to Start Date

| Group | Sex | Animal | Clinical Sign | Site | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | f | 7011 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X |
| | | 7012 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X |
| | | 7013 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X |
| | | 7014 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X |
| | | 7015 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X |
| | | 7016 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X |
| | | 7017 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X |
| | | 7018 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X |
| | | 7019 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X |
| | | 7020 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X |

Severity Codes: X = Present; S = Slight; M = Moderate; F = Superficial

Group 1 - 0 mg/kg/day Group 2 - 512 mg/kg/day
Group 3 - 1024 mg/kg/day Group 4 - 1536 mg/kg/day

Individual Animal Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Day numbers relative to Start Date

| Group | Sex | Animal | Clinical Sign | Site | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2 | f | 7031 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 7032 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 7033 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 7034 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 7035 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | | Alopecia | Left Forelimb | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| | | | Alopecia | Right Forelimb | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| | | 7036 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 7037 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 7038 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 7039 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 7040 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

Severity Codes: X = Present; S = Slight; M = Moderate; F = Superficial

Group 1 - 0 mg/kg/day Group 2 - 512 mg/kg/day
Group 3 - 1024 mg/kg/day Group 4 - 1536 mg/kg/day

Individual Animal Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Day numbers relative to Start Date

| Group | Sex | Animal | Clinical Sign | Site | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2 | f | 7031 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X |
| | | 7032 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X |
| | | 7033 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X |
| | | 7034 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X |
| | | 7035 | No Abnormalities Detected | | X | . | . | . | . | . | . | . | . | . | . |
| | | | Alopecia | Left Forelimb | . | S | S | S | S | S | S | S | M | M | M |
| | | | Alopecia | Right Forelimb | . | S | S | S | S | S | S | S | M | M | M |
| | | 7036 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X |
| | | 7037 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X |
| | | 7038 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X |
| | | 7039 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X |
| | | 7040 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X |

Severity Codes: X = Present; S = Slight; M = Moderate; F = Superficial

Group 1 - 0 mg/kg/day Group 2 - 512 mg/kg/day
Group 3 - 1024 mg/kg/day Group 4 - 1536 mg/kg/day

Individual Animal Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Day numbers relative to Start Date

| Group | Sex | Animal | Clinical Sign | Site | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 3 | f | 7051 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 7052 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 7053 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 7054 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 7055 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 7056 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 7057 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 7058 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 7059 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 7060 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

Severity Codes: X = Present; S = Slight; M = Moderate; F = Superficial

Group 1 - 0 mg/kg/day Group 2 - 512 mg/kg/day
Group 3 - 1024 mg/kg/day Group 4 - 1536 mg/kg/day

Individual Animal Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Day numbers relative to Start Date

| Group | Sex | Animal | Clinical Sign | Site | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 3 | f | 7051 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X |
| | | 7052 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X |
| | | 7053 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X |
| | | 7054 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X |
| | | 7055 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X |
| | | 7056 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X |
| | | 7057 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X |
| | | 7058 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X |
| | | 7059 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X |
| | | 7060 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X |

Severity Codes: X = Present; S = Slight; M = Moderate; F = Superficial

Group 1 - 0 mg/kg/day Group 2 - 512 mg/kg/day
Group 3 - 1024 mg/kg/day Group 4 - 1536 mg/kg/day

Individual Animal Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Day numbers relative to Start Date

| Group | Sex | Animal | Clinical Sign | Site | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 4 | f | 7071 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 7072 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 7073 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 7074 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 7075 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 7076 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 7077 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 7078 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 7079 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | 7080 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

Severity Codes: X = Present; S = Slight; M = Moderate; F = Superficial

Group 1 - 0 mg/kg/day Group 2 - 512 mg/kg/day
Group 3 - 1024 mg/kg/day Group 4 - 1536 mg/kg/day

Individual Animal Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Day numbers relative to Start Date

| Group | Sex | Animal | Clinical Sign | Site | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 4 | f | 7071 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X |
| | | 7072 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X |
| | | 7073 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X |
| | | 7074 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X |
| | | 7075 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X |
| | | 7076 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X |
| | | 7077 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X |
| | | 7078 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X |
| | | 7079 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X |
| | | 7080 | No Abnormalities Detected | | X | X | X | X | X | X | X | X | X | X | X |

Severity Codes: X = Present; S = Slight; M = Moderate; F = Superficial

Group 1 - 0 mg/kg/day Group 2 - 512 mg/kg/day
Group 3 - 1024 mg/kg/day Group 4 - 1536 mg/kg/day

# APPENDIX G: DETAILED CLINICAL OBSERVATIONS ASSESSMENT METHODS SCORING KEY

## PRODUCT IDENTIFICATION

Soy Leghemoglobin Preparation

# APPENDIX G: DETAILED CLINICAL OBSERVATIONS ASSESSMENT METHODS SCORING KEY

| **Removal from Cage and Open Field Observations** | |
|---|---|
| Activity/Arousal | 0. Alternating behaviors - animal goes through normal repertoire of behaviors during observation period. These consist of exploring, sniffing, grooming, rearing, etc.<br>1. Inactive/Alert - animal sits in one place during the observation period but appears to be aware of its surroundings. It may go through its normal repertoire of activities but the majority of the observation period is spent not moving.<br>2. Hypoactive/Not alert - animal sits in one place during the observation period. Animal appears to be unaware of its surroundings or in a stupor.<br>3. Hyperactive/Hyperalert - animal appears excited. Animal may dart and freeze during the observation period or animal may sit in one place and jump at any sound or movement. |
| Biting | 0. None<br>1. Biting cage<br>2. Self-mutilation |
| Circling | 0. Absent<br>1. Present |
| Convulsions | 0. None<br>1. Clonic – alternating periods of contraction and relaxation of muscles<br>2. Tonic – prolonged period of muscle contractions |
| Defecation | 0. None/Normal<br>1. Soft (partially formed)<br>2. Diarrhea (watery feces) |
| Ease of Removal/Handling | 0. Slight/moderate resistance - animal is easy to handle, may squirm or vocalize occasionally.<br>1. No resistance - animal is limp/flaccid when being handled.<br>2. High resistance/aggressive - animal is difficult to handle, and/or squirms continuously, and/or tries to bite handler.<br>3. Aggressive - biting or lunging behavior specifically directed at handler. |
| Emaciation | 0. Absent<br>1. Present (confirmed using body weights) |
| Eyes | 0. Normal<br>1. Exophthalmos - abnormal protrusion of eyeball<br>2. Endophthalmus – sunken eyeball<br>3. Eye damaged – mechanical damage (e.g. orbital bleeding, etc.) |
| Fur/Skin Appearance | 0. Normal<br>1. Unkempt - coat rough or ungroomed, may be slightly stained<br>2. Urine stained/wetness (Ano-genital staining)<br>3. Hair loss |
| Gait | 0. Normal<br>1. Abnormal – limbs exaggerated/splayed, hind limbs and/or forelimbs show exaggerated placement or movement<br>2. Non weight bearing (Limping) |
| Lacrimation | 0. Absent<br>1. Present - lacrimation noticeable.<br>2. Excessive - animal has excessive amount of tearing.<br>Note: Descriptors (i.e. color of ocular discharge will be noted on daily observation sheet). |
| Locomotion | 0. Normal<br>1. Somewhat impaired<br>2. Totally impaired |

## APPENDIX G (cont.): DETAILED CLINICAL OBSERVATIONS ASSESSMENT METHODS SCORING KEY

| | |
|---|---|
| Mucous Membranes | 0. Normal<br>1. Present – mucous noticeable<br>2. Excessive – animal has an excessive amount of mucous present |
| Muscle Tone | 0. Normal - muscles are resilient and firm and the hind legs go through their full range of motion.<br>1. Increased - muscles are rigid, hind limbs will not go through their full range of motion.<br>2. Decreased - muscles are flaccid, hind limbs have little or no resistance to movement |
| Palpebral Closure | 0. Eyes wide open<br>1. Eyes halfway shut<br>2. Eyes completely shut |
| Piloerection | 0. Absent<br>1. Present |
| Posture | 0. Normal (awake) – alert, sitting, standing, or rearing<br>1. Normal (sleeping) – curled up, usually with head down<br>2. Hunched – abnormal posture<br>3. Flattened (prone) – limbs spread out lying flat or on one side |
| Respiratory Pattern | 0. Normal<br>1. Slow<br>2. Rapid<br>3. Rales (Moist or Dry)<br>4. Gasping<br>5. Labored - Dyspnea |
| Salivation | 0. None<br>1. Present - salivation is noticeable around the edge of the mouth<br>2. Excessive - salivation extends to the fur around the jaw |
| Tremors | 0. None<br>1. Slight – localized to one area, or a twitch/spasm of a localized area<br>2. Severe – more than one area or involving whole body<br>3. Fasciculation – wave-like ripples of a muscle or group of muscles |
| Unusual Behaviors | 0. Absent<br>1. Present – Be specific in describing all unusual behaviors on data sheet. |
| Urination | 0. None/Normal<br>1. Excessive |
| Vocalization, removal from cage | 0. Absent<br>1. Present - animal vocalizes unprovoked or continuously vocalizes when being handled. |
| Vocalizations, open field observations | 0. Absent<br>1. Present |
| Writhing | 0. Absent<br>1. Present |
| **Manipulative Tests** | |
| Pupillary reflex | 0. Normal<br>1. Slow or absent- pupil reaction is slow or absent. |

# APPENDIX H: INDIVIDUAL ANIMAL DETAILED CLINICAL OBSERVATIONS[1]

## PRODUCT IDENTIFICATION

Soy Leghemoglobin Preparation

[1] Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient.
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male  Day(s) Relative to Start Date

| 0 mg/kg/day Group 1 | DetClinObs (Removal from Cage) | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Handling Reactivity | Handling Reactivity | Handling Reactivity | Handling Reactivity | Handling Reactivity | Vocalization (RC) | Vocalization (RC) | Voculization (RC) | Vocalization (RC) | Vocalization (RC) | Palpebral Closure | Palpebral Closure | Palpebral Closure | Palpebral Closure |
| | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 |
| 7001 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7002 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7003 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7004 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7005 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7006 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7007 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7008 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7009 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7010 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |



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U.S. Patent No. 11,013,250

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

| 0 mg/kg/day Group 1 | DetClinObs (Removal from Cage) | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Palpebral Closure | Lacrimation | Lacrimation | Lacrimation | Lacrimation | Lacrimation | Eye | Eye | Eye | Eye | Eye | Mucous Membranes | Mucous Membranes | Mucous Membranes |
| | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 |
| 7001 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7002 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7003 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7004 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7005 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7006 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7007 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7008 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7009 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7010 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |



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Case No.: IPR2023-00208
U.S. Patent No. 11,013,250

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male  Day(s) Relative to Start Date

| 0 mg/kg/day Group 1 | DetClinObs (Removal from Cage) | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mucous Membranes | Mucous Membranes | Salivation | Salivation | Salivation | Salivation | Salivation | Emaciation | Emaciation | Emaciation | Emaciation | Emaciation | Piloerection | Piloerection |
| | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 |
| 7001 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7002 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7003 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7004 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7005 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7006 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7007 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7008 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7009 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7010 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |



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Case No.: IPR2023-00208
U.S. Patent No. 11,013,250

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male  Day(s) Relative to Start Date

| 0 mg/kg/day Group 1 | DetClinObs (Removal from Cage) | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Piloerection | Piloerection | Piloerection | Fur/Skin | Fur/Skin | Fur/Skin | Fur/Skin | Fur/Skin | Muscle Tone | Muscle Tone | Muscle Tone | Muscle Tone | Muscle Tone | Respiratory Pattern |
| | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 |
| 7001 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7002 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7003 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7004 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7005 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7006 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7007 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7008 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7009 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7010 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |



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Case No.: IPR2023-00208
U.S. Patent No. 11,013,250

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male  Day(s) Relative to Start Date

| 0 mg/kg/day Group 1 | DetClinObs (Removal from Cage) | | | | | | | | | DetClinObs (Open Field Obs) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Respiratory Pattern | Respiratory Pattern | Respiratory Pattern | Respiratory Pattern | Pupillary Reflex | Pupillary Reflex | Pupillary Reflex | Pupillary Reflex | Pupillary Reflex | Activity/ Arousal | Activity/ Arousal | Activity/ Arousal | Activity/ Arousal | Activity/ Arousal |
| | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 |
| 7001 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7002 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7003 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7004 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7005 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7006 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7007 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7008 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7009 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7010 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |



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Case No.: IPR2023-00208
U.S. Patent No. 11,013,250

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male  Day(s) Relative to Start Date

| 0 mg/kg/day Group 1 | DetClinObs (Open Field Obs) | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Convulsions | Convulsions | Convulsions | Convulsions | Convulsions | Tremors | Tremors | Tremors | Tremors | Tremors | Posture | Posture | Posture | Posture |
| | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 |
| 7001 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7002 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7003 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7004 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7005 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7006 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7007 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7008 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7009 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7010 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |



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Case No.: IPR2023-00208
U.S. Patent No. 11,013,250

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male  Day(s) Relative to Start Date

| 0 mg/kg/day Group 1 | DetClinObs (Open Field Obs) | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Posture | Gait | Gait | Gait | Gait | Gait | Locomotion | Locomotion | Locomotion | Locomotion | Locomotion | Defecation | Defecation | Defecation |
| | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 |
| 7001 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7002 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7003 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7004 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7005 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7006 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7007 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7008 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7009 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7010 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |



Case No.: IPR2023-00208
U.S. Patent No. 11,013,250

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male  Day(s) Relative to Start Date

| 0 mg/kg/day Group 1 | DetClinObs (Open Field Obs) | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Defecation | Defecation | Urination | Urination | Urination | Urination | Urination | Unusual Behaviors | Unusual Behaviors | Unusual Behaviors | Unusual Behaviors | Unusual Behaviors | Vocalization (OF) | Vocalization (OF) |
| | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 |
| 7001 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7002 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7003 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7004 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7005 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7006 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7007 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7008 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7009 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7010 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |



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Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male  Day(s) Relative to Start Date

| 0 mg/kg/day Group 1 | DetClinObs (Open Field Obs) | | |
|---|---|---|---|
| | Vocalization (OF) | Vocalization (OF) | Vocalization (OF) |
| | 14 | 21 | 28 |
| 7001 | 0 | 0 | 0 |
| 7002 | 0 | 0 | 0 |
| 7003 | 0 | 0 | 0 |
| 7004 | 0 | 0 | 0 |
| 7005 | 0 | 0 | 0 |
| 7006 | 0 | 0 | 0 |
| 7007 | 0 | 0 | 0 |
| 7008 | 0 | 0 | 0 |
| 7009 | 0 | 0 | 0 |
| 7010 | 0 | 0 | 0 |



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Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

| 512 mg/kg/day Group 2 | DetClinObs (Removal from Cage) | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Handling Reactivity | Handling Reactivity | Handling Reactivity | Handling Reactivity | Handling Reactivity | Vocalization (RC) | Vocalization (RC) | Vocalization (RC) | Vocalization (RC) | Vocalization (RC) | Palpebral Closure | Palpebral Closure | Palpebral Closure | Palpebral Closure |
| | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 |
| 7021 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7022 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7023 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7024 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7025 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7026 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7027 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7028 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7029 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7030 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male  Day(s) Relative to Start Date

| 512 mg/kg/day Group 2 | DetClinObs (Removal from Cage) | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Palpebral Closure | Lacrimation | Lacrimation | Lacrimation | Lacrimation | Lacrimation | Eye | Eye | Eye | Eye | Eye | Mucous Membranes | Mucous Membranes | Mucous Membranes |
| | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 |
| 7021 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7022 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7023 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7024 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7025 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7026 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7027 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7028 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7029 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7030 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |



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U.S. Patent No. 11,013,250

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male  Day(s) Relative to Start Date

| 512 mg/kg/day Group 2 | DetClinObs (Removal from Cage) | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mucous Membranes | Mucous Membranes | Salivation | Salivation | Salivation | Salivation | Salivation | Emaciation | Emaciation | Emaciation | Emaciation | Emaciation | Piloerection | Piloerection |
| | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 |
| 7021 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7022 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7023 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7024 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7025 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7026 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7027 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7028 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7029 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7030 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |



Case No.: IPR2023-00208
U.S. Patent No. 11,013,250

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

| 512 mg/kg/day Group 2 | DetClinObs (Removal from Cage) | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Piloerection | Piloerection | Piloerection | Fur/Skin | Fur/Skin | Fur/Skin | Fur/Skin | Fur/Skin | Muscle Tone | Muscle Tone | Muscle Tone | Muscle Tone | Muscle Tone | Respiratory Pattern |
| | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 |
| 7021 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7022 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7023 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7024 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7025 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7026 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7027 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7028 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7029 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7030 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |



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Case No.: IPR2023-00208
U.S. Patent No. 11,013,250

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

| 512 mg/kg/day Group 2 | DetClinObs (Removal from Cage) | | | | | | | | | DetClinObs (Open Field Obs) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Respiratory Pattern | Respiratory Pattern | Respiratory Pattern | Respiratory Pattern | Pupillary Reflex | Pupillary Reflex | Pupillary Reflex | Pupillary Reflex | Pupillary Reflex | Activity/ Arousal | Activity/ Arousal | Activity/ Arousal | Activity/ Arousal | Activity/ Arousal |
| | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 |
| 7021 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7022 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7023 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7024 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7025 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7026 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7027 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7028 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7029 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7030 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |



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Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

| 512 mg/kg/day Group 2 | DetClinObs (Open Field Obs) | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Convulsions | Convulsions | Convulsions | Convulsions | Convulsions | Tremors | Tremors | Tremors | Tremors | Tremors | Posture | Posture | Posture | Posture |
| | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 |
| 7021 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7022 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7023 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7024 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7025 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7026 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7027 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7028 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7029 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7030 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |



Case No.: IPR2023-00208
U.S. Patent No. 11,013,250

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male  Day(s) Relative to Start Date

| 512 mg/kg/day Group 2 | DetClinObs (Open Field Obs) | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Posture | Gait | Gait | Gait | Gait | Gait | Locomotion | Locomotion | Locomotion | Locomotion | Locomotion | Defecation | Defecation | Defecation |
| | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 |
| 7021 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7022 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7023 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7024 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7025 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7026 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7027 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7028 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7029 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7030 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |



Case No.: IPR2023-00208
U.S. Patent No. 11,013,250

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male  Day(s) Relative to Start Date

| 512 mg/kg/day Group 2 | DetClinObs (Open Field Obs) | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Defecation | Defecation | Urination | Urination | Urination | Urination | Urination | Unusual Behaviors | Unusual Behaviors | Unusual Behaviors | Unusual Behaviors | Unusual Behaviors | Vocalization (OF) | Vocalization (OF) |
| | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 |
| 7021 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7022 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7023 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7024 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7025 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7026 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7027 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7028 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7029 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7030 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |



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Case No.: IPR2023-00208
U.S. Patent No. 11,013,250

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

| 512 mg/kg/day Group 2 | DetClinObs (Open Field Obs) | | |
|---|---|---|---|
| | Vocalization (OF) | Vocalization (OF) | Vocalization (OF) |
| | 14 | 21 | 28 |
| 7021 | 0 | 0 | 0 |
| 7022 | 0 | 0 | 0 |
| 7023 | 0 | 0 | 0 |
| 7024 | 0 | 0 | 0 |
| 7025 | 0 | 0 | 0 |
| 7026 | 0 | 0 | 0 |
| 7027 | 0 | 0 | 0 |
| 7028 | 0 | 0 | 0 |
| 7029 | 0 | 0 | 0 |
| 7030 | 0 | 0 | 0 |



Case No.: IPR2023-00208
U.S. Patent No. 11,013,250

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male  Day(s) Relative to Start Date

| 1024 mg/kg/day Group 3 | DetClinObs (Removal from Cage) | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Handling Reactivity | Handling Reactivity | Handling Reactivity | Handling Reactivity | Handling Reactivity | Vocalization (RC) | Vocalization (RC) | Vocalization (RC) | Vocalization (RC) | Vocalization (RC) | Palpebral Closure | Palpebral Closure | Palpebral Closure | Palpebral Closure |
| | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 |
| 7041 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7042 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7043 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7044 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7045 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7046 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7047 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7048 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7049 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7050 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |



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Case No.: IPR2023-00208
U.S. Patent No. 11,013,250

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male  Day(s) Relative to Start Date

| 1024 mg/kg/day Group 3 | DetClinObs (Removal from Cage) | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Palpebral Closure | Lacrimation | Lacrimation | Lacrimation | Lacrimation | Lacrimation | Eye | Eye | Eye | Eye | Eye | Mucous Membranes | Mucous Membranes | Mucous Membranes |
| | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 |
| 7041 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7042 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7043 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7044 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7045 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7046 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7047 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7048 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7049 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7050 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |



Case No.: IPR2023-00208
U.S. Patent No. 11,013,250

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male  Day(s) Relative to Start Date

| 1024 mg/kg/day Group 3 | DetClinObs (Removal from Cage) | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mucous Membranes | Mucous Membranes | Salivation | Salivation | Salivation | Salivation | Salivation | Emaciation | Emaciation | Emaciation | Emaciation | Emaciation | Piloerection | Piloerection |
| | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 |
| 7041 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7042 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7043 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7044 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7045 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7046 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7047 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7048 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7049 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7050 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |



Case No.: IPR2023-00208
U.S. Patent No. 11,013,250

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male  Day(s) Relative to Start Date

| 1024 mg/kg/day Group 3 | DetClinObs (Removal from Cage) | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Piloerection | Piloerection | Piloerection | Fur/Skin | Fur/Skin | Fur/Skin | Fur/Skin | Fur/Skin | Muscle Tone | Muscle Tone | Muscle Tone | Muscle Tone | Muscle Tone | Respiratory Pattern |
| | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 |
| 7041 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7042 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7043 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7044 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7045 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7046 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7047 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7048 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7049 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7050 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

| 1024 mg/kg/day Group 3 | DetClinObs (Removal from Cage) | | | | | | | | | DetClinObs (Open Field Obs) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Respiratory Pattern | Respiratory Pattern | Respiratory Pattern | Respiratory Pattern | Pupillary Reflex | Pupillary Reflex | Pupillary Reflex | Pupillary Reflex | Pupillary Reflex | Activity/ Arousal | Activity/ Arousal | Activity/ Arousal | Activity/ Arousal | Activity/ Arousal |
| | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 |
| 7041 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7042 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7043 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7044 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7045 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7046 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7047 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7048 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7049 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7050 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

| 1024 mg/kg/day Group 3 | DetClinObs (Open Field Obs) | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Convulsions | Convulsions | Convulsions | Convulsions | Convulsions | Tremors | Tremors | Tremors | Tremors | Tremors | Posture | Posture | Posture | Posture |
| | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 |
| 7041 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7042 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7043 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7044 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7045 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7046 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7047 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7048 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7049 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7050 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male  Day(s) Relative to Start Date

| 1024 mg/kg/day Group 3 | DetClinObs (Open Field Obs) | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Posture | Gait | Gait | Gait | Gait | Gait | Locomotion | Locomotion | Locomotion | Locomotion | Locomotion | Defecation | Defecation | Defecation |
| | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 |
| 7041 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7042 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7043 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7044 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7045 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7046 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7047 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7048 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7049 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7050 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |



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Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

| 1024 mg/kg/day Group 3 | DetClinObs (Open Field Obs) | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Defecation | Defecation | Urination | Urination | Urination | Urination | Urination | Unusual Behaviors | Unusual Behaviors | Unusual Behaviors | Unusual Behaviors | Unusual Behaviors | Vocalization (OF) | Vocalization (OF) |
| | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 |
| 7041 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7042 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7043 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7044 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7045 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7046 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7047 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7048 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7049 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7050 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |



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Case No.: IPR2023-00208
U.S. Patent No. 11,013,250

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

| 1024 mg/kg/day Group 3 | DetClinObs (Open Field Obs) | | |
|---|---|---|---|
| | Vocalization (OF) | Vocalization (OF) | Vocalization (OF) |
| | 14 | 21 | 28 |
| 7041 | 0 | 0 | 0 |
| 7042 | 0 | 0 | 0 |
| 7043 | 0 | 0 | 0 |
| 7044 | 0 | 0 | 0 |
| 7045 | 0 | 0 | 0 |
| 7046 | 0 | 0 | 0 |
| 7047 | 0 | 0 | 0 |
| 7048 | 0 | 0 | 0 |
| 7049 | 0 | 0 | 0 |
| 7050 | 0 | 0 | 0 |



Case No.: IPR2023-00208
U.S. Patent No. 11,013,250

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male  Day(s) Relative to Start Date

| 1536 mg/kg/day Group 4 | DetClinObs (Removal from Cage) | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Handling Reactivity | Handling Reactivity | Handling Reactivity | Handling Reactivity | Handling Reactivity | Vocalization (RC) | Vocalization (RC) | Vocalization (RC) | Vocalization (RC) | Vocalization (RC) | Palpebral Closure | Palpebral Closure | Palpebral Closure | Palpebral Closure |
| | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 |
| 7061 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7062 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7063 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7064 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7065 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7066 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7067 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7068 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7069 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7070 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |



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Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male  Day(s) Relative to Start Date

| 1536 mg/kg/day Group 4 | DetClinObs (Removal from Cage) | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Palpebral Closure | Lacrimation | Lacrimation | Lacrimation | Lacrimation | Lacrimation | Eye | Eye | Eye | Eye | Eye | Mucous Membranes | Mucous Membranes | Mucous Membranes |
| | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 |
| 7061 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7062 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7063 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7064 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7065 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7066 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7067 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7068 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7069 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7070 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

| 1536 mg/kg/day Group 4 | DetClinObs (Removal from Cage) | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mucous Membranes | Mucous Membranes | Salivation | Salivation | Salivation | Salivation | Salivation | Emaciation | Emaciation | Emaciation | Emaciation | Emaciation | Piloerection | Piloerection |
| | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 |
| 7061 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7062 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7063 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7064 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7065 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7066 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7067 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7068 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7069 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7070 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |



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Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

| 1536 mg/kg/day Group 4 | DetClinObs (Removal from Cage) | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Piloerection | Piloerection | Piloerection | Fur/Skin | Fur/Skin | Fur/Skin | Fur/Skin | Fur/Skin | Muscle Tone | Muscle Tone | Muscle Tone | Muscle Tone | Muscle Tone | Respiratory Pattern |
| | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 |
| 7061 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7062 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7063 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7064 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7065 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7066 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7067 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7068 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7069 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7070 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |



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Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male  Day(s) Relative to Start Date

| 1536 mg/kg/day Group 4 | DetClinObs (Removal from Cage) | | | | | | | | | DetClinObs (Open Field Obs) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Respiratory Pattern | Respiratory Pattern | Respiratory Pattern | Respiratory Pattern | Pupillary Reflex | Pupillary Reflex | Pupillary Reflex | Pupillary Reflex | Pupillary Reflex | Activity/ Arousal | Activity/ Arousal | Activity/ Arousal | Activity/ Arousal | Activity/ Arousal |
| | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 |
| 7061 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7062 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7063 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7064 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7065 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7066 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7067 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7068 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7069 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7070 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |



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Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male  Day(s) Relative to Start Date

| 1536 mg/kg/day Group 4 | DetClinObs (Open Field Obs) | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Convulsions | Convulsions | Convulsions | Convulsions | Convulsions | Tremors | Tremors | Tremors | Tremors | Tremors | Posture | Posture | Posture | Posture |
| | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 |
| 7061 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7062 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7063 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7064 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7065 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7066 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7067 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7068 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7069 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7070 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |



Case No.: IPR2023-00208
U.S. Patent No. 11,013,250

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male  Day(s) Relative to Start Date

| 1536 mg/kg/day Group 4 | DetClinObs (Open Field Obs) | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Posture | Gait | Gait | Gait | Gait | Gait | Locomotion | Locomotion | Locomotion | Locomotion | Locomotion | Defecation | Defecation | Defecation |
| | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 |
| 7061 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7062 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7063 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7064 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7065 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7066 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7067 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7068 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7069 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7070 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |



Case No.: IPR2023-00208
U.S. Patent No. 11,013,250

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male  Day(s) Relative to Start Date

| 1536 mg/kg/day Group 4 | DetClinObs (Open Field Obs) | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Defecation | Defecation | Urination | Urination | Urination | Urination | Urination | Unusual Behaviors | Unusual Behaviors | Unusual Behaviors | Unusual Behaviors | Unusual Behaviors | Vocalization (OF) | Vocalization (OF) |
| | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 |
| 7061 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7062 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7063 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7064 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7065 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7066 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7067 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7068 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7069 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7070 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |



Case No.: IPR2023-00208
U.S. Patent No. 11,013,250

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

| 1536 mg/kg/day Group 4 | DetClinObs (Open Field Obs) | | |
|---|---|---|---|
| | Vocalization (OF) | Vocalization (OF) | Vocalization (OF) |
| | 14 | 21 | 28 |
| 7061 | 0 | 0 | 0 |
| 7062 | 0 | 0 | 0 |
| 7063 | 0 | 0 | 0 |
| 7064 | 0 | 0 | 0 |
| 7065 | 0 | 0 | 0 |
| 7066 | 0 | 0 | 0 |
| 7067 | 0 | 0 | 0 |
| 7068 | 0 | 0 | 0 |
| 7069 | 0 | 0 | 0 |
| 7070 | 0 | 0 | 0 |



Case No.: IPR2023-00208
U.S. Patent No. 11,013,250

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

| 0 mg/kg/day Group 1 | DetClinObs (Removal from Cage) | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Handling Reactivity | Handling Reactivity | Handling Reactivity | Handling Reactivity | Handling Reactivity | Vocalization (RC) | Vocalization (RC) | Vocalization (RC) | Vocalization (RC) | Vocalization (RC) | Palpebral Closure | Palpebral Closure | Palpebral Closure | Palpebral Closure |
| | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 |
| 7011 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7012 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7013 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7014 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7015 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7016 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7017 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7018 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7019 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7020 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

| 0 mg/kg/day Group 1 | DetClinObs (Removal from Cage) | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Palpebral Closure | Lacrimation | Lacrimation | Lacrimation | Lacrimation | Lacrimation | Eye | Eye | Eye | Eye | Eye | Mucous Membranes | Mucous Membranes | Mucous Membranes |
| | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 |
| 7011 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7012 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7013 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7014 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7015 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7016 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7017 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7018 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7019 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7020 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |



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Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female  Day(s) Relative to Start Date

| 0 mg/kg/day Group 1 | DetClinObs (Removal from Cage) | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mucous Membranes | Mucous Membranes | Salivation | Salivation | Salivation | Salivation | Salivation | Emaciation | Emaciation | Emaciation | Emaciation | Emaciation | Piloerection | Piloerection |
| | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 |
| 7011 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7012 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7013 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7014 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7015 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7016 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7017 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7018 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7019 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7020 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |



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Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female  Day(s) Relative to Start Date

| 0 mg/kg/day Group 1 | DetClinObs (Removal from Cage) | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Piloerection | Piloerection | Piloerection | Fur/Skin | Fur/Skin | Fur/Skin | Fur/Skin | Fur/Skin | Muscle Tone | Muscle Tone | Muscle Tone | Muscle Tone | Muscle Tone | Respiratory Pattern |
| | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 |
| 7011 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7012 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7013 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7014 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7015 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7016 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7017 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7018 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7019 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7020 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |



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Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

| 0 mg/kg/day Group 1 | DetClinObs (Removal from Cage) | | | | | | | | | DetClinObs (Open Field Obs) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Respiratory Pattern | Respiratory Pattern | Respiratory Pattern | Respiratory Pattern | Pupillary Reflex | Pupillary Reflex | Pupillary Reflex | Pupillary Reflex | Pupillary Reflex | Activity/ Arousal | Activity/ Arousal | Activity/ Arousal | Activity/ Arousal | Activity/ Arousal |
| | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 |
| 7011 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7012 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7013 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7014 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7015 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7016 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7017 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7018 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7019 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7020 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female  Day(s) Relative to Start Date

| 0 mg/kg/day Group 1 | DetClinObs (Open Field Obs) | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Convulsions | Convulsions | Convulsions | Convulsions | Convulsions | Tremors | Tremors | Tremors | Tremors | Tremors | Posture | Posture | Posture | Posture |
| | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 |
| 7011 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7012 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7013 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7014 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7015 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7016 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7017 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7018 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7019 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7020 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |



Case No.: IPR2023-00208
U.S. Patent No. 11,013,250

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female  Day(s) Relative to Start Date

| 0 mg/kg/day Group 1 | DetClinObs (Open Field Obs) | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Posture | Gait | Gait | Gait | Gait | Gait | Locomotion | Locomotion | Locomotion | Locomotion | Locomotion | Defecation | Defecation | Defecation |
| | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 |
| 7011 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7012 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7013 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7014 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7015 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7016 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7017 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7018 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7019 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7020 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |



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Case No.: IPR2023-00208
U.S. Patent No. 11,013,250

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female  Day(s) Relative to Start Date

| 0 mg/kg/day Group 1 | DetClinObs (Open Field Obs) | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Defecation | Defecation | Urination | Urination | Urination | Urination | Urination | Unusual Behaviors | Unusual Behaviors | Unusual Behaviors | Unusual Behaviors | Unusual Behaviors | Vocalization (OF) | Vocalization (OF) |
| | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 |
| 7011 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7012 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7013 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7014 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7015 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7016 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7017 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7018 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7019 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7020 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |



Case No.: IPR2023-00208
U.S. Patent No. 11,013,250

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female  Day(s) Relative to Start Date

| 0 mg/kg/day Group 1 | DetClinObs (Open Field Obs) | | |
|---|---|---|---|
| | Vocalization (OF) | Vocalization (OF) | Vocalization (OF) |
| | 14 | 21 | 28 |
| 7011 | 0 | 0 | 0 |
| 7012 | 0 | 0 | 0 |
| 7013 | 0 | 0 | 0 |
| 7014 | 0 | 0 | 0 |
| 7015 | 0 | 0 | 0 |
| 7016 | 0 | 0 | 0 |
| 7017 | 0 | 0 | 0 |
| 7018 | 0 | 0 | 0 |
| 7019 | 0 | 0 | 0 |
| 7020 | 0 | 0 | 0 |



Case No.: IPR2023-00208
U.S. Patent No. 11,013,250

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

| 512 mg/kg/day Group 2 | DetClinObs (Removal from Cage) | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Handling Reactivity | Handling Reactivity | Handling Reactivity | Handling Reactivity | Handling Reactivity | Vocalization (RC) | Vocalization (RC) | Vocalization (RC) | Vocalization (RC) | Vocalization (RC) | Palpebral Closure | Palpebral Closure | Palpebral Closure | Palpebral Closure |
| | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 |
| 7031 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7032 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7033 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7034 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7035 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7036 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7037 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7038 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7039 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7040 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |



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Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female  Day(s) Relative to Start Date

| 512 mg/kg/day Group 2 | DetClinObs (Removal from Cage) | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Palpebral Closure | Lacrimation | Lacrimation | Lacrimation | Lacrimation | Lacrimation | Eye | Eye | Eye | Eye | Eye | Mucous Membranes | Mucous Membranes | Mucous Membranes |
| | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 |
| 7031 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7032 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7033 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7034 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7035 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7036 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7037 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7038 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7039 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7040 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |



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Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female  Day(s) Relative to Start Date

| 512 mg/kg/day Group 2 | DetClinObs (Removal from Cage) | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mucous Membranes | Mucous Membranes | Salivation | Salivation | Salivation | Salivation | Salivation | Emaciation | Emaciation | Emaciation | Emaciation | Emaciation | Piloerection | Piloerection |
| | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 |
| 7031 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7032 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7033 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7034 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7035 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7036 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7037 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7038 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7039 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7040 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |



Case No.: IPR2023-00208
U.S. Patent No. 11,013,250

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

| 512 mg/kg/day Group 2 | DetClinObs (Removal from Cage) | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Piloerection | Piloerection | Piloerection | Fur/Skin | Fur/Skin | Fur/Skin | Fur/Skin | Fur/Skin | Muscle Tone | Muscle Tone | Muscle Tone | Muscle Tone | Muscle Tone | Respiratory Pattern |
| | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 |
| 7031 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7032 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7033 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7034 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7035 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7036 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7037 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7038 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7039 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7040 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

| 512 mg/kg/day Group 2 | DetClinObs (Removal from Cage) | | | | | | | | | DetClinObs (Open Field Obs) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Respiratory Pattern | Respiratory Pattern | Respiratory Pattern | Respiratory Pattern | Pupillary Reflex | Pupillary Reflex | Pupillary Reflex | Pupillary Reflex | Pupillary Reflex | Activity/ Arousal | Activity/ Arousal | Activity/ Arousal | Activity/ Arousal | Activity/ Arousal |
| | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 |
| 7031 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7032 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7033 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7034 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7035 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7036 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7037 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7038 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7039 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7040 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female  Day(s) Relative to Start Date

| 512 mg/kg/day Group 2 | DetClinObs (Open Field Obs) | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Convulsions | Convulsions | Convulsions | Convulsions | Convulsions | Tremors | Tremors | Tremors | Tremors | Tremors | Posture | Posture | Posture | Posture |
| | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 |
| 7031 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7032 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7033 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7034 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7035 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7036 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7037 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7038 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7039 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7040 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |



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U.S. Patent No. 11,013,250

Individual Animal Detailed Clinical Observations

PSL Study Number 43168
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

| 512 mg/kg/day Group 2 | DetClinObs (Open Field Obs) | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Posture | Gait | Gait | Gait | Gait | Gait | Locomotion | Locomotion | Locomotion | Locomotion | Locomotion | Defecation | Defecation | Defecation |
| | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 |
| 7031 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7032 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7033 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7034 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7035 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7036 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7037 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7038 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7039 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7040 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female  Day(s) Relative to Start Date

| 512 mg/kg/day Group 2 | DetClinObs (Open Field Obs) | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Defecation | Defecation | Urination | Urination | Urination | Urination | Urination | Unusual Behaviors | Unusual Behaviors | Unusual Behaviors | Unusual Behaviors | Unusual Behaviors | Vocalization (OF) | Vocalization (OF) |
| | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 |
| 7031 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7032 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7033 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7034 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7035 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7036 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7037 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7038 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7039 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7040 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |



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Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female  Day(s) Relative to Start Date

| 512 mg/kg/day Group 2 | DetClinObs (Open Field Obs) | | |
|---|---|---|---|
| | Vocalization (OF) | Vocalization (OF) | Vocalization (OF) |
| | 14 | 21 | 28 |
| 7031 | 0 | 0 | 0 |
| 7032 | 0 | 0 | 0 |
| 7033 | 0 | 0 | 0 |
| 7034 | 0 | 0 | 0 |
| 7035 | 0 | 0 | 0 |
| 7036 | 0 | 0 | 0 |
| 7037 | 0 | 0 | 0 |
| 7038 | 0 | 0 | 0 |
| 7039 | 0 | 0 | 0 |
| 7040 | 0 | 0 | 0 |



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Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female  Day(s) Relative to Start Date

| 1024 mg/kg/day Group 3 | DetClinObs (Removal from Cage) | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Handling Reactivity | Handling Reactivity | Handling Reactivity | Handling Reactivity | Handling Reactivity | Vocalization (RC) | Vocalization (RC) | Vocalization (RC) | Vocalization (RC) | Vocalization (RC) | Palpebral Closure | Palpebral Closure | Palpebral Closure | Palpebral Closure |
| | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 |
| 7051 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7052 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7053 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7054 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7055 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7056 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7057 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7058 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7059 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7060 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |



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Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

| 1024 mg/kg/day Group 3 | DetClinObs (Removal from Cage) | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Palpebral Closure | Lacrimation | Lacrimation | Lacrimation | Lacrimation | Lacrimation | Eye | Eye | Eye | Eye | Eye | Mucous Membranes | Mucous Membranes | Mucous Membranes |
| | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 |
| 7051 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7052 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7053 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7054 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7055 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7056 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7057 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7058 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7059 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7060 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |



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Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

| 1024 mg/kg/day Group 3 | DetClinObs (Removal from Cage) | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mucous Membranes | Mucous Membranes | Salivation | Salivation | Salivation | Salivation | Salivation | Emaciation | Emaciation | Emaciation | Emaciation | Emaciation | Piloerection | Piloerection |
| | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 |
| 7051 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7052 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7053 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7054 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7055 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7056 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7057 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7058 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7059 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7060 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female  Day(s) Relative to Start Date

| 1024 mg/kg/day Group 3 | DetClinObs (Removal from Cage) | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Piloerection | Piloerection | Piloerection | Fur/Skin | Fur/Skin | Fur/Skin | Fur/Skin | Fur/Skin | Muscle Tone | Muscle Tone | Muscle Tone | Muscle Tone | Muscle Tone | Respiratory Pattern |
| | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 |
| 7051 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7052 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7053 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7054 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7055 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7056 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7057 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7058 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7059 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7060 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |



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Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

| 1024 mg/kg/day Group 3 | DetClinObs (Removal from Cage) | | | | | | | | | DetClinObs (Open Field Obs) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Respiratory Pattern | Respiratory Pattern | Respiratory Pattern | Respiratory Pattern | Pupillary Reflex | Pupillary Reflex | Pupillary Reflex | Pupillary Reflex | Pupillary Reflex | Activity/ Arousal | Activity/ Arousal | Activity/ Arousal | Activity/ Arousal | Activity/ Arousal |
| | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 |
| 7051 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7052 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7053 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7054 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7055 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7056 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7057 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7058 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7059 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7060 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |



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Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female  Day(s) Relative to Start Date

| 1024 mg/kg/day Group 3 | DetClinObs (Open Field Obs) | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Convulsions | Convulsions | Convulsions | Convulsions | Convulsions | Tremors | Tremors | Tremors | Tremors | Tremors | Posture | Posture | Posture | Posture |
| | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 |
| 7051 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7052 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7053 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7054 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7055 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7056 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7057 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7058 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7059 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7060 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |



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Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female  Day(s) Relative to Start Date

| 1024 mg/kg/day Group 3 | DetClinObs (Open Field Obs) | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Posture | Gait | Gait | Gait | Gait | Gait | Locomotion | Locomotion | Locomotion | Locomotion | Locomotion | Defecation | Defecation | Defecation |
| | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 |
| 7051 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7052 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7053 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7054 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7055 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7056 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7057 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7058 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7059 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7060 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |



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Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

| 1024 mg/kg/day Group 3 | DetClinObs (Open Field Obs) | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Defecation | Defecation | Urination | Urination | Urination | Urination | Urination | Unusual Behaviors | Unusual Behaviors | Unusual Behaviors | Unusual Behaviors | Unusual Behaviors | Vocalization (OF) | Vocalization (OF) |
| | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 |
| 7051 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7052 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7053 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7054 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7055 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7056 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7057 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7058 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7059 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7060 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

| 1024 mg/kg/day Group 3 | DetClinObs (Open Field Obs) | | |
|---|---|---|---|
| | Vocalization (OF) | Vocalization (OF) | Vocalization (OF) |
| | 14 | 21 | 28 |
| 7051 | 0 | 0 | 0 |
| 7052 | 0 | 0 | 0 |
| 7053 | 0 | 0 | 0 |
| 7054 | 0 | 0 | 0 |
| 7055 | 0 | 0 | 0 |
| 7056 | 0 | 0 | 0 |
| 7057 | 0 | 0 | 0 |
| 7058 | 0 | 0 | 0 |
| 7059 | 0 | 0 | 0 |
| 7060 | 0 | 0 | 0 |



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Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female  Day(s) Relative to Start Date

| 1536 mg/kg/day Group 4 | DetClinObs (Removal from Cage) | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Handling Reactivity | Handling Reactivity | Handling Reactivity | Handling Reactivity | Handling Reactivity | Vocalization (RC) | Vocalization (RC) | Vocalization (RC) | Vocalization (RC) | Vocalization (RC) | Palpebral Closure | Palpebral Closure | Palpebral Closure | Palpebral Closure |
| | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 |
| 7071 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7072 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7073 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7074 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7075 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7076 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7077 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7078 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7079 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7080 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |



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Case No.: IPR2023-00208
U.S. Patent No. 11,013,250

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female  Day(s) Relative to Start Date

| 1536 mg/kg/day Group 4 | DetClinObs (Removal from Cage) | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Palpebral Closure | Lacrimation | Lacrimation | Lacrimation | Lacrimation | Lacrimation | Eye | Eye | Eye | Eye | Eye | Mucous Membranes | Mucous Membranes | Mucous Membranes |
| | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 |
| 7071 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7072 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7073 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7074 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7075 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7076 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7077 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7078 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7079 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7080 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |



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Case No.: IPR2023-00208
U.S. Patent No. 11,013,250

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female  Day(s) Relative to Start Date

| 1536 mg/kg/day Group 4 | DetClinObs (Removal from Cage) | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mucous Membranes | Mucous Membranes | Salivation | Salivation | Salivation | Salivation | Salivation | Emaciation | Emaciation | Emaciation | Emaciation | Emaciation | Piloerection | Piloerection |
| | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 |
| 7071 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7072 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7073 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7074 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7075 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7076 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7077 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7078 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7079 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7080 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |



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Case No.: IPR2023-00208
U.S. Patent No. 11,013,250

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

| 1536 mg/kg/day Group 4 | DetClinObs (Removal from Cage) | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Piloerection | Piloerection | Piloerection | Fur/Skin | Fur/Skin | Fur/Skin | Fur/Skin | Fur/Skin | Muscle Tone | Muscle Tone | Muscle Tone | Muscle Tone | Muscle Tone | Respiratory Pattern |
| | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 |
| 7071 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7072 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7073 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7074 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7075 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7076 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7077 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7078 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7079 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7080 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

| 1536 mg/kg/day Group 4 | DetClinObs (Removal from Cage) | | | | | | | | | DetClinObs (Open Field Obs) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Respiratory Pattern | Respiratory Pattern | Respiratory Pattern | Respiratory Pattern | Pupillary Reflex | Pupillary Reflex | Pupillary Reflex | Pupillary Reflex | Pupillary Reflex | Activity/ Arousal | Activity/ Arousal | Activity/ Arousal | Activity/ Arousal | Activity/ Arousal |
| | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 |
| 7071 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7072 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7073 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7074 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7075 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7076 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7077 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7078 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7079 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7080 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |



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Case No.: IPR2023-00208
U.S. Patent No. 11,013,250

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female  Day(s) Relative to Start Date

| 1536 mg/kg/day Group 4 | DetClinObs (Open Field Obs) | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Convulsions | Convulsions | Convulsions | Convulsions | Convulsions | Tremors | Tremors | Tremors | Tremors | Tremors | Posture | Posture | Posture | Posture |
| | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 |
| 7071 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7072 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7073 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7074 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7075 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7076 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7077 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7078 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7079 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7080 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |



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Case No.: IPR2023-00208
U.S. Patent No. 11,013,250

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female  Day(s) Relative to Start Date

| 1536 mg/kg/day Group 4 | DetClinObs (Open Field Obs) | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Posture | Gait | Gait | Gait | Gait | Gait | Locomotion | Locomotion | Locomotion | Locomotion | Locomotion | Defecation | Defecation | Defecation |
| | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 |
| 7071 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7072 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7073 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7074 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7075 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7076 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7077 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7078 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7079 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7080 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |



Case No.: IPR2023-00208
U.S. Patent No. 11,013,250

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

| 1536 mg/kg/day Group 4 | DetClinObs (Open Field Obs) | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Defecation | Defecation | Urination | Urination | Urination | Urination | Urination | Unusual Behaviors | Unusual Behaviors | Unusual Behaviors | Unusual Behaviors | Unusual Behaviors | Vocalization (OF) | Vocalization (OF) |
| | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 |
| 7071 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7072 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7073 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7074 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7075 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7076 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7077 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7078 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7079 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7080 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

Individual Animal Detailed Clinical Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female  Day(s) Relative to Start Date

| 1536 mg/kg/day Group 4 | DetClinObs (Open Field Obs) | | |
|---|---|---|---|
| | Vocalization (OF) | Vocalization (OF) | Vocalization (OF) |
| | 14 | 21 | 28 |
| 7071 | 0 | 0 | 0 |
| 7072 | 0 | 0 | 0 |
| 7073 | 0 | 0 | 0 |
| 7074 | 0 | 0 | 0 |
| 7075 | 0 | 0 | 0 |
| 7076 | 0 | 0 | 0 |
| 7077 | 0 | 0 | 0 |
| 7078 | 0 | 0 | 0 |
| 7079 | 0 | 0 | 0 |
| 7080 | 0 | 0 | 0 |



Case No.: IPR2023-00208
U.S. Patent No. 11,013,250

# APPENDIX I: INDIVIDUAL ANIMAL BODY WEIGHTS[1]

## PRODUCT IDENTIFICATION

Soy Leghemoglobin Preparation

[1] Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient.
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

Individual Animal Body Weights

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Bodyweight (g)

| 0 mg/kg/day Group 1 | Day(s) Relative to Start Date | | | | |
|---|---|---|---|---|---|
| | 0 | 7 | 14 | 21 | 28 |
| 7001 | 240 | 297 | 345 | 396 | 429 |
| 7002 | 232 | 273 | 327 | 362 | 382 |
| 7003 | 238 | 288 | 334 | 379 | 401 |
| 7004 | 234 | 271 | 310 | 343 | 360 |
| 7005 | 228 | 267 | 305 | 340 | 357 |
| 7006 | 247 | 303 | 347 | 404 | 434 |
| 7007 | 242 | 308 | 358 | 400 | 430 |
| 7008 | 230 | 283 | 328 | 361 | 379 |
| 7009 | 241 | 297 | 342 | 381 | 400 |
| 7010 | 232 | 290 | 327 | 366 | 375 |
| Mean | 236.4 | 287.7 | 332.3 | 373.2 | 394.7 |
| SD | 6.1 | 14.0 | 16.5 | 22.7 | 28.8 |
| N | 10 | 10 | 10 | 10 | 10 |

Individual Animal Body Weights

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Bodyweight (g)

| 512 mg/kg/day Group 2 | Day(s) Relative to Start Date | | | | |
|---|---|---|---|---|---|
| | 0 | 7 | 14 | 21 | 28 |
| 7021 | 232 | 284 | 324 | 363 | 390 |
| 7022 | 236 | 295 | 346 | 383 | 403 |
| 7023 | 243 | 299 | 353 | 392 | 415 |
| 7024 | 246 | 298 | 346 | 383 | 400 |
| 7025 | 237 | 291 | 331 | 369 | 387 |
| 7026 | 232 | 288 | 345 | 381 | 403 |
| 7027 | 240 | 291 | 330 | 374 | 398 |
| 7028 | 228 | 273 | 309 | 341 | 355 |
| 7029 | 241 | 306 | 370 | 421 | 458 |
| 7030 | 229 | 271 | 316 | 359 | 380 |
| Mean | 236.4 | 289.6 | 337.0 | 376.6 | 398.9 |
| SD | 6.1 | 11.1 | 18.4 | 21.4 | 26.4 |
| N | 10 | 10 | 10 | 10 | 10 |

Individual Animal Body Weights

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Bodyweight (g)

| 1024 mg/kg/day Group 3 | Day(s) Relative to Start Date | | | | |
|---|---|---|---|---|---|
| | 0 | 7 | 14 | 21 | 28 |
| 7041 | 238 | 281 | 333 | 377 | 402 |
| 7042 | 250 | 306 | 367 | 419 | 448 |
| 7043 | 232 | 282 | 322 | 366 | 382 |
| 7044 | 231 | 295 | 353 | 401 | 434 |
| 7045 | 233 | 288 | 337 | 378 | 401 |
| 7046 | 244 | 308 | 371 | 415 | 448 |
| 7047 | 239 | 304 | 360 | 406 | 433 |
| 7048 | 241 | 303 | 360 | 411 | 445 |
| 7049 | 232 | 270 | 309 | 337 | 364 |
| 7050 | 227 | 272 | 304 | 335 | 345 |
| Mean | 236.7 | 290.9 | 341.6 | 384.5 | 410.2 |
| SD | 7.0 | 14.3 | 24.2 | 31.1 | 37.2 |
| N | 10 | 10 | 10 | 10 | 10 |

Individual Animal Body Weights

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Bodyweight (g)

| 1536 mg/kg/day Group 4 | Day(s) Relative to Start Date | | | | |
|---|---|---|---|---|---|
| | 0 | 7 | 14 | 21 | 28 |
| 7061 | 241 | 295 | 342 | 380 | 404 |
| 7062 | 234 | 288 | 335 | 374 | 403 |
| 7063 | 233 | 270 | 305 | 345 | 369 |
| 7064 | 240 | 304 | 363 | 418 | 446 |
| 7065 | 246 | 308 | 362 | 404 | 432 |
| 7066 | 239 | 299 | 351 | 396 | 421 |
| 7067 | 244 | 306 | 355 | 394 | 420 |
| 7068 | 226 | 281 | 326 | 362 | 385 |
| 7069 | 229 | 293 | 326 | 360 | 379 |
| 7070 | 231 | 284 | 330 | 366 | 396 |
| Mean | 236.3 | 292.8 | 339.5 | 379.9 | 405.5 |
| SD | 6.7 | 12.2 | 18.6 | 22.7 | 24.4 |
| N | 10 | 10 | 10 | 10 | 10 |



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U.S. Patent No. 11,013,250

Individual Animal Body Weights

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Bodyweight (g)

| 0 mg/kg/day Group 1 | Day(s) Relative to Start Date | | | | |
|---|---|---|---|---|---|
| | 0 | 7 | 14 | 21 | 28 |
| 7011 | 165 | 178 | 188 | 204 | 208 |
| 7012 | 163 | 188 | 204 | 223 | 228 |
| 7013 | 197 | 210 | 261 | 282 | 288 |
| 7014 | 187 | 222 | 220 [1] | 249 | 253 |
| 7015 | 181 | 205 | 217 | 243 | 252 |
| 7016 | 169 | 195 | 212 | 225 | 250 |
| 7017 | 156 | 176 | 192 | 209 | 223 |
| 7018 | 175 | 201 | 224 | 255 | 262 |
| 7019 | 180 | 212 | 239 | 244 | 264 |
| 7020 | 168 | 196 | 231 | 258 | 270 |
| Mean | 174.1 | 198.3 | 218.8 | 239.2 | 249.8 |
| SD | 12.3 | 14.8 | 21.9 | 24.0 | 24.0 |
| N | 10 | 10 | 10 | 10 | 10 |

1 [RC:Reweighed, food and water OK]

Individual Animal Body Weights

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Bodyweight (g)

| 512 mg/kg/day Group 2 | Day(s) Relative to Start Date | | | | |
|---|---|---|---|---|---|
| | 0 | 7 | 14 | 21 | 28 |
| 7031 | 192 | 217 | 239 | 246 | 257 |
| 7032 | 175 | 195 | 208 | 224 | 237 |
| 7033 | 173 | 200 | 210 | 228[1] | 238 |
| 7034 | 162 | 183 | 198 | 208 | 219 |
| 7035 | 168 | 194 | 218 | 229 | 244 |
| 7036 | 168 | 202 | 218 | 233 | 249 |
| 7037 | 153 | 169 | 182 | 187 | 196 |
| 7038 | 193 | 220 | 236 | 250 | 265 |
| 7039 | 183 | 215 | 241 | 240 [2] | 260 |
| 7040 | 177 | 215 | 235 | 246 | 275 |
| Mean | 174.4 | 201.0 | 218.5 | 229.1 | 244.0 |
| SD | 12.6 | 16.5 | 19.6 | 19.4 | 23.3 |
| N | 10 | 10 | 10 | 10 | 10 |

1 [. RC:Reweighed, food and water OK]

2 [RC:Reweighed, food and water OK]

Individual Animal Body Weights

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Bodyweight (g)

| 1024 mg/kg/day Group 3 | Day(s) Relative to Start Date | | | | |
|---|---|---|---|---|---|
| | 0 | 7 | 14 | 21 | 28 |
| 7051 | 162 | 189 | 202 | 210 | 229 |
| 7052 | 162 | 192 | 216 | 224 | 238 |
| 7053 | 182 | 210 | 231 | 249 | 267 |
| 7054 | 189 | 216 | 239 | 255 | 267 |
| 7055 | 198 | 224 | 236 | 268 | 277 |
| 7056 | 176 | 214 | 239 | 257 | 266 |
| 7057 | 166 | 185 | 204 | 221 | 237 |
| 7058 | 169 | 198 | 215 | 228 | 237 |
| 7059 | 180 | 214 | 238 | 251 | 270 |
| 7060 | 172 | 198 | 217 | 225 | 244 |
| Mean | 175.6 | 204.0 | 223.7 | 238.8 | 253.2 |
| SD | 11.8 | 13.3 | 14.6 | 19.4 | 17.7 |
| N | 10 | 10 | 10 | 10 | 10 |

Individual Animal Body Weights

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Bodyweight (g)

| 1536 mg/kg/day Group 4 | Day(s) Relative to Start Date | | | | |
|---|---|---|---|---|---|
| | 0 | 7 | 14 | 21 | 28 |
| 7071 | 171 | 198 | 212 | 240 | 248 |
| 7072 | 168 | 196 | 218 | 229 | 246 |
| 7073 | 181 | 208 | 232 | 244 | 263 |
| 7074 | 179 | 195 | 215 | 229 | 234 |
| 7075 | 177 | 201 | 218 | 229 | 241 |
| 7076 | 163 | 190 | 219 | 242 | 245 |
| 7077 | 187 | 215 | 241 | 260 | 271 |
| 7078 | 162 | 191 | 213 | 224 | 237 |
| 7079 | 196 | 215 | 246 | 258 | 262 |
| 7080 | 159 | 184 | 199 | 225 | 240 |
| Mean | 174.3 | 199.3 | 221.3 | 238.0 | 248.7 |
| SD | 11.9 | 10.5 | 14.3 | 13.1 | 12.4 |
| N | 10 | 10 | 10 | 10 | 10 |



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U.S. Patent No. 11,013,250

# APPENDIX J: INDIVIDUAL ANIMAL MEAN DAILY BODY WEIGHT GAIN[1]

## PRODUCT IDENTIFICATION

Soy Leghemoglobin Preparation

[1] Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient.
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

Individual Animal Mean Daily Body Weight Gain

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Mean Daily Body Weight Gain (g/day)

| 0 mg/kg/day Group 1 | Day(s) Relative to Start Date | | | | |
|---|---|---|---|---|---|
| | 0 → 7 | 7 → 14 | 14 → 21 | 21 → 28 | 0 → 28 |
| 7001 | 8.1 | 6.9 | 7.3 | 4.7 | 6.8 |
| 7002 | 5.9 | 7.7 | 5.0 | 2.9 | 5.4 |
| 7003 | 7.1 | 6.6 | 6.4 | 3.1 | 5.8 |
| 7004 | 5.3 | 5.6 | 4.7 | 2.4 | 4.5 |
| 7005 | 5.6 | 5.4 | 5.0 | 2.4 | 4.6 |
| 7006 | 8.0 | 6.3 | 8.1 | 4.3 | 6.7 |
| 7007 | 9.4 | 7.1 | 6.0 | 4.3 | 6.7 |
| 7008 | 7.6 | 6.4 | 4.7 | 2.6 | 5.3 |
| 7009 | 8.0 | 6.4 | 5.6 | 2.7 | 5.7 |
| 7010 | 8.3 | 5.3 | 5.6 | 1.3 | 5.1 |
| Mean | 7.33 | 6.37 | 5.84 | 3.07 | 5.65 |
| SD | 1.35 | 0.77 | 1.15 | 1.06 | 0.84 |
| N | 10 | 10 | 10 | 10 | 10 |



Case No.: IPR2023-00208
U.S. Patent No. 11,013,250

Individual Animal Mean Daily Body Weight Gain

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Mean Daily Body Weight Gain (g/day)

| 512 mg/kg/day Group 2 | Day(s) Relative to Start Date | | | | |
|---|---|---|---|---|---|
| | 0 → 7 | 7 → 14 | 14 → 21 | 21 → 28 | 0 → 28 |
| 7021 | 7.4 | 5.7 | 5.6 | 3.9 | 5.6 |
| 7022 | 8.4 | 7.3 | 5.3 | 2.9 | 6.0 |
| 7023 | 8.0 | 7.7 | 5.6 | 3.3 | 6.1 |
| 7024 | 7.4 | 6.9 | 5.3 | 2.4 | 5.5 |
| 7025 | 7.7 | 5.7 | 5.4 | 2.6 | 5.4 |
| 7026 | 8.0 | 8.1 | 5.1 | 3.1 | 6.1 |
| 7027 | 7.3 | 5.6 | 6.3 | 3.4 | 5.6 |
| 7028 | 6.4 | 5.1 | 4.6 | 2.0 | 4.5 |
| 7029 | 9.3 | 9.1 | 7.3 | 5.3 | 7.8 |
| 7030 | 6.0 | 6.4 | 6.1 | 3.0 | 5.4 |
| Mean | 7.60 | 6.77 | 5.66 | 3.19 | 5.80 |
| SD | 0.94 | 1.30 | 0.75 | 0.91 | 0.83 |
| N | 10 | 10 | 10 | 10 | 10 |

Individual Animal Mean Daily Body Weight Gain

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Mean Daily Body Weight Gain (g/day)

| 1024 mg/kg/day Group 3 | Day(s) Relative to Start Date | | | | |
|---|---|---|---|---|---|
| | 0 → 7 | 7 → 14 | 14 → 21 | 21 → 28 | 0 → 28 |
| 7041 | 6.1 | 7.4 | 6.3 | 3.6 | 5.9 |
| 7042 | 8.0 | 8.7 | 7.4 | 4.1 | 7.1 |
| 7043 | 7.1 | 5.7 | 6.3 | 2.3 | 5.4 |
| 7044 | 9.1 | 8.3 | 6.9 | 4.7 | 7.3 |
| 7045 | 7.9 | 7.0 | 5.9 | 3.3 | 6.0 |
| 7046 | 9.1 | 9.0 | 6.3 | 4.7 | 7.3 |
| 7047 | 9.3 | 8.0 | 6.6 | 3.9 | 6.9 |
| 7048 | 8.9 | 8.1 | 7.3 | 4.9 | 7.3 |
| 7049 | 5.4 | 5.6 | 4.0 | 3.9 | 4.7 |
| 7050 | 6.4 | 4.6 | 4.4 | 1.4 | 4.2 |
| Mean | 7.74 | 7.24 | 6.13 | 3.67 | 6.20 |
| SD | 1.40 | 1.49 | 1.12 | 1.10 | 1.14 |
| N | 10 | 10 | 10 | 10 | 10 |



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Case No.: IPR2023-00208
U.S. Patent No. 11,013,250

Individual Animal Mean Daily Body Weight Gain

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male  Mean Daily Body Weight Gain (g/day)

| 1536 mg/kg/day Group 4 | Day(s) Relative to Start Date | | | | |
|---|---|---|---|---|---|
| | 0 → 7 | 7 → 14 | 14 → 21 | 21 → 28 | 0 → 28 |
| 7061 | 7.7 | 6.7 | 5.4 | 3.4 | 5.8 |
| 7062 | 7.7 | 6.7 | 5.6 | 4.1 | 6.0 |
| 7063 | 5.3 | 5.0 | 5.7 | 3.4 | 4.9 |
| 7064 | 9.1 | 8.4 | 7.9 | 4.0 | 7.4 |
| 7065 | 8.9 | 7.7 | 6.0 | 4.0 | 6.6 |
| 7066 | 8.6 | 7.4 | 6.4 | 3.6 | 6.5 |
| 7067 | 8.9 | 7.0 | 5.6 | 3.7 | 6.3 |
| 7068 | 7.9 | 6.4 | 5.1 | 3.3 | 5.7 |
| 7069 | 9.1 | 4.7 | 4.9 | 2.7 | 5.4 |
| 7070 | 7.6 | 6.6 | 5.1 | 4.3 | 5.9 |
| Mean | 8.07 | 6.67 | 5.77 | 3.66 | 6.04 |
| SD | 1.16 | 1.13 | 0.86 | 0.47 | 0.70 |
| N | 10 | 10 | 10 | 10 | 10 |



Motif Exhibit 1064, Page 336 of 526

Case No.: IPR2023-00208
U.S. Patent No. 11,013,250

Individual Animal Mean Daily Body Weight Gain

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Mean Daily Body Weight Gain (g/day)

| 0 mg/kg/day Group 1 | Day(s) Relative to Start Date | | | | |
|---|---|---|---|---|---|
| | 0 → 7 | 7 → 14 | 14 → 21 | 21 → 28 | 0 → 28 |
| 7011 | 1.9 | 1.4 | 2.3 | 0.6 | 1.5 |
| 7012 | 3.6 | 2.3 | 2.7 | 0.7 | 2.3 |
| 7013 | 1.9 | 7.3 | 3.0 | 0.9 | 3.3 |
| 7014 | 5.0 | -0.3 | 4.1 | 0.6 | 2.4 |
| 7015 | 3.4 | 1.7 | 3.7 | 1.3 | 2.5 |
| 7016 | 3.7 | 2.4 | 1.9 | 3.6 | 2.9 |
| 7017 | 2.9 | 2.3 | 2.4 | 2.0 | 2.4 |
| 7018 | 3.7 | 3.3 | 4.4 | 1.0 | 3.1 |
| 7019 | 4.6 | 3.9 | 0.7 | 2.9 | 3.0 |
| 7020 | 4.0 | 5.0 | 3.9 | 1.7 | 3.6 |
| Mean | 3.46 | 2.93 | 2.91 | 1.51 | 2.70 |
| SD | 1.03 | 2.09 | 1.15 | 1.03 | 0.60 |
| N | 10 | 10 | 10 | 10 | 10 |

Individual Animal Mean Daily Body Weight Gain

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Mean Daily Body Weight Gain (g/day)

| 512 mg/kg/day Group 2 | Day(s) Relative to Start Date | | | | |
|---|---|---|---|---|---|
| | 0 → 7 | 7 → 14 | 14 → 21 | 21 → 28 | 0 → 28 |
| 7031 | 3.6 | 3.1 | 1.0 | 1.6 | 2.3 |
| 7032 | 2.9 | 1.9 | 2.3 | 1.9 | 2.2 |
| 7033 | 3.9 | 1.4 | 2.6 | 1.4 | 2.3 |
| 7034 | 3.0 | 2.1 | 1.4 | 1.6 | 2.0 |
| 7035 | 3.7 | 3.4 | 1.6 | 2.1 | 2.7 |
| 7036 | 4.9 | 2.3 | 2.1 | 2.3 | 2.9 |
| 7037 | 2.3 | 1.9 | 0.7 | 1.3 | 1.5 |
| 7038 | 3.9 | 2.3 | 2.0 | 2.1 | 2.6 |
| 7039 | 4.6 | 3.7 | -0.1 | 2.9 | 2.8 |
| 7040 | 5.4 | 2.9 | 1.6 | 4.1 | 3.5 |
| Mean | 3.80 | 2.50 | 1.51 | 2.13 | 2.49 |
| SD | 0.96 | 0.75 | 0.82 | 0.85 | 0.53 |
| N | 10 | 10 | 10 | 10 | 10 |

Individual Animal Mean Daily Body Weight Gain

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female  Mean Daily Body Weight Gain (g/day)

| 1024 mg/kg/day Group 3 | Day(s) Relative to Start Date | | | | |
|---|---|---|---|---|---|
| | 0 → 7 | 7 → 14 | 14 → 21 | 21 → 28 | 0 → 28 |
| 7051 | 3.9 | 1.9 | 1.1 | 2.7 | 2.4 |
| 7052 | 4.3 | 3.4 | 1.1 | 2.0 | 2.7 |
| 7053 | 4.0 | 3.0 | 2.6 | 2.6 | 3.0 |
| 7054 | 3.9 | 3.3 | 2.3 | 1.7 | 2.8 |
| 7055 | 3.7 | 1.7 | 4.6 | 1.3 | 2.8 |
| 7056 | 5.4 | 3.6 | 2.6 | 1.3 | 3.2 |
| 7057 | 2.7 | 2.7 | 2.4 | 2.3 | 2.5 |
| 7058 | 4.1 | 2.4 | 1.9 | 1.3 | 2.4 |
| 7059 | 4.9 | 3.4 | 1.9 | 2.7 | 3.2 |
| 7060 | 3.7 | 2.7 | 1.1 | 2.7 | 2.6 |
| Mean | 4.06 | 2.81 | 2.16 | 2.06 | 2.77 |
| SD | 0.72 | 0.66 | 1.03 | 0.63 | 0.30 |
| N | 10 | 10 | 10 | 10 | 10 |

Individual Animal Mean Daily Body Weight Gain

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female  Mean Daily Body Weight Gain (g/day)

| 1536 mg/kg/day Group 4 | Day(s) Relative to Start Date | | | | |
|---|---|---|---|---|---|
| | 0 → 7 | 7 → 14 | 14 → 21 | 21 → 28 | 0 → 28 |
| 7071 | 3.9 | 2.0 | 4.0 | 1.1 | 2.8 |
| 7072 | 4.0 | 3.1 | 1.6 | 2.4 | 2.8 |
| 7073 | 3.9 | 3.4 | 1.7 | 2.7 | 2.9 |
| 7074 | 2.3 | 2.9 | 2.0 | 0.7 | 2.0 |
| 7075 | 3.4 | 2.4 | 1.6 | 1.7 | 2.3 |
| 7076 | 3.9 | 4.1 | 3.3 | 0.4 | 2.9 |
| 7077 | 4.0 | 3.7 | 2.7 | 1.6 | 3.0 |
| 7078 | 4.1 | 3.1 | 1.6 | 1.9 | 2.7 |
| 7079 | 2.7 | 4.4 | 1.7 | 0.6 | 2.4 |
| 7080 | 3.6 | 2.1 | 3.7 | 2.1 | 2.9 |
| Mean | 3.57 | 3.14 | 2.39 | 1.53 | 2.66 |
| SD | 0.61 | 0.81 | 0.96 | 0.79 | 0.34 |
| N | 10 | 10 | 10 | 10 | 10 |

# APPENDIX K: INDIVIDUAL ANIMAL MEAN DAILY FOOD CONSUMPTION[1]

## PRODUCT IDENTIFICATION

Soy Leghemoglobin Preparation

[1] Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient.
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

Individual Animal Mean Daily Food Consumption

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Mean Daily Food Consumption (g/day)

| 0 mg/kg/day Group 1 | Day(s) Relative to Start Date | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 3 → 7 | 7 → 10 | 10 → 14 | 14 → 17 | 17 → 21 | 21 → 24 | 24 → 28 | 3 → 28 |
| 7001 | 28.0 | 27.3 | 27.0 | 27.3 | 27.9 | 22.3 | 29.3 | 27.2 |
| 7002 | 28.0 | 27.3 | 27.0 | 27.3 | 27.9 | 22.3 | 29.3 | 27.2 |
| 7003 | 27.0 | 24.5 | 26.3 | 24.8 | 25.1 | 20.8 | 26.5 | 25.2 |
| 7004 | 27.0 | 24.5 | 26.3 | 24.8 | 25.1 | 20.8 | 26.5 | 25.2 |
| 7005 | 28.1 | 25.2 | 24.6 | 25.3 | 25.9 | 21.8 | 27.6 | 25.7 |
| 7006 | 28.1 | 25.2 | 24.6 | 25.3 | 25.9 | 21.8 | 27.6 | 25.7 |
| 7007 | 29.9 | 27.7 | 28.0 | 26.0 | 26.8 | 22.8 | 28.3 | 27.2 |
| 7008 | 29.9 | 27.7 | 28.0 | 26.0 | 26.8 | 22.8 | 28.3 | 27.2 |
| 7009 | 27.1 | 26.8 | 26.9 | 26.0 | 26.3 | 21.2 | 26.9 | 26.0 |
| 7010 | 27.1 | 26.8 | 26.9 | 26.0 | 26.3 | 21.2 | 26.9 | 26.0 |
| Mean | 28.03 | 26.30 | 26.55 | 25.90 | 26.38 | 21.80 | 27.70 | 26.26 |
| SD | 1.08 | 1.31 | 1.17 | 0.89 | 0.97 | 0.77 | 1.04 | 0.86 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

Individual Animal Mean Daily Food Consumption

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Mean Daily Food Consumption (g/day)

| 512 mg/kg/day Group 2 | Day(s) Relative to Start Date | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 3 → 7 | 7 → 10 | 10 → 14 | 14 → 17 | 17 → 21 | 21 → 24 | 24 → 28 | 3 → 28 |
| 7021 | 28.8 | 26.2 | 26.9 | 25.2 | 25.9 | 21.5 | 27.6 | 26.2 |
| 7022 | 28.8 | 26.2 | 26.9 | 25.2 | 25.9 | 21.5 | 27.6 | 26.2 |
| 7023 | 29.4 | 27.5 | 27.6 | 25.0 | 26.4 | 21.5 | 27.5 | 26.6 |
| 7024 | 29.4 | 27.5 | 27.6 | 25.0 | 26.4 | 21.5 | 27.5 | 26.6 |
| 7025 | 28.8 | 27.8 | 27.4 | 24.0 | 26.5 | 21.8 | 29.3 | 26.7 |
| 7026 | 28.8 | 27.8 | 27.4 | 24.0 | 26.5 | 21.8 | 29.3 | 26.7 |
| 7027 | 28.1 | 26.2 | 25.9 | 24.3 | 25.9 | 21.5 | 28.8 | 26.0 |
| 7028 | 28.1 | 26.2 | 25.9 | 24.3 | 25.9 | 21.5 | 28.8 | 26.0 |
| 7029 | 28.0 | 27.8 | 28.5 | 28.8 | 27.9 | 24.0 | 30.6 | 28.1 |
| 7030 | 28.0 | 27.8 | 28.5 | 28.8 | 27.9 | 24.0 | 30.6 | 28.1 |
| Mean | 28.60 | 27.10 | 27.25 | 25.47 | 26.50 | 22.07 | 28.75 | 26.73 |
| SD | 0.52 | 0.81 | 0.91 | 1.83 | 0.77 | 1.03 | 1.21 | 0.76 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

Individual Animal Mean Daily Food Consumption

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Mean Daily Food Consumption (g/day)

| 1024 mg/kg/day Group 3 | Day(s) Relative to Start Date | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 3 → 7 | 7 → 10 | 10 → 14 | 14 → 17 | 17 → 21 | 21 → 24 | 24 → 28 | 3 → 28 |
| 7041 | 28.3 | 29.0 | 29.5 | 29.5 | 29.3 | 23.0 | 30.6 | 28.6 |
| 7042 | 28.3 | 29.0 | 29.5 | 29.5 | 29.3 | 23.0 | 30.6 | 28.6 |
| 7043 | 29.8 | 27.8 | 27.6 | 27.8 | 27.1 | 22.0 | 28.4 | 27.4 |
| 7044 | 29.8 | 27.8 | 27.6 | 27.8 | 27.1 | 22.0 | 28.4 | 27.4 |
| 7045 | 30.0 | 29.0 | 29.8 | 25.2 | 27.5 | 24.3 | 30.3 | 28.2 |
| 7046 | 30.0 | 29.0 | 29.8 | 25.2 | 27.5 | 24.3 | 30.3 | 28.2 |
| 7047 | 28.6 | 29.0 | 28.6 | 27.2 | 28.6 | 22.3 | 30.5 | 28.0 |
| 7048 | 28.6 | 29.0 | 28.6 | 27.2 | 28.6 | 22.3 | 30.5 | 28.0 |
| 7049 | 24.5 | 24.2 | 23.9 | 22.0 | 23.0 | 19.7 | 25.9 | 23.5 |
| 7050 | 24.5 | 24.2 | 23.9 | 22.0 | 23.0 | 19.7 | 25.9 | 23.5 |
| Mean | 28.23 | 27.80 | 27.88 | 26.33 | 27.10 | 22.27 | 29.13 | 27.14 |
| SD | 2.08 | 1.97 | 2.25 | 2.71 | 2.31 | 1.61 | 1.92 | 1.98 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

Individual Animal Mean Daily Food Consumption

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex Male Mean Daily Food Consumption (g/day)

| 1536 mg/kg/day Group 4 | Day(s) Relative to Start Date | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 3 → 7 | 7 → 10 | 10 → 14 | 14 → 17 | 17 → 21 | 21 → 24 | 24 → 28 | 3 → 28 |
| 7061 | 27.8 | 27.7 | 26.8 | 26.2 | 25.6 | 21.3 | 28.1 | 26.3 |
| 7062 | 27.8 | 27.7 | 26.8 | 26.2 | 25.6 | 21.3 | 28.1 | 26.3 |
| 7063 | 28.5 | 27.7 | 26.4 | 25.3 | 27.5 | 23.2 | 27.5 | 26.7 |
| 7064 | 28.5 | 27.7 | 26.4 | 25.3 | 27.5 | 23.2 | 27.5 | 26.7 |
| 7065 | 29.4 | 27.7 | 28.6 | 26.7 | 27.9 | 22.8 | 30.1 | 27.8 |
| 7066 | 29.4 | 27.7 | 28.6 | 26.7 | 27.9 | 22.8 | 30.1 | 27.8 |
| 7067 | 30.1 | 29.3 | 28.6 | 27.3 | 27.3 | 22.7 | 30.8 | 28.2 |
| 7068 | 30.1 | 29.3 | 28.6 | 27.3 | 27.3 | 22.7 | 30.8 | 28.2 |
| 7069 | 27.4 | 27.2 | 26.9 | 25.3 | 26.4 | 22.3 | 29.4 | 26.6 |
| 7070 | 27.4 | 27.2 | 26.9 | 25.3 | 26.4 | 22.3 | 29.4 | 26.6 |
| Mean | 28.63 | 27.90 | 27.45 | 26.17 | 26.93 | 22.47 | 29.18 | 27.13 |
| SD | 1.07 | 0.78 | 1.03 | 0.82 | 0.86 | 0.66 | 1.28 | 0.78 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

Individual Animal Mean Daily Food Consumption

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Mean Daily Food Consumption (g/day)

| 0 mg/kg/day Group 1 | Day(s) Relative to Start Date | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 3 → 7 | 7 → 10 | 10 → 14 | 14 → 17 | 17 → 21 | 21 → 24 | 24 → 28 | 3 → 28 |
| 7011 | 19.9 | 17.3 | 17.8 | 18.0 | 17.4 | 14.8 | 18.4 | 17.8 |
| 7012 | 19.9 | 17.3 | 17.8 | 18.0 | 17.4 | 14.8 | 18.4 | 17.8 |
| 7013 | 22.4 | 23.2 | 21.6 | 21.7 | 22.3 | 16.2 | 21.3 | 21.3 |
| 7014 | 22.4 | 23.2 | 21.6 | 21.7 | 22.3 | 16.2 | 21.3 | 21.3 |
| 7015 | 22.1 | 18.3 | 19.0 | 18.7 | 19.6 | 16.5 | 21.3 | 19.5 |
| 7016 | 22.1 | 18.3 | 19.0 | 18.7 | 19.6 | 16.5 | 21.3 | 19.5 |
| 7017 | 21.9 | 17.8 | 18.4 | 18.7 | 19.3 | 15.3 | 20.4 | 19.0 |
| 7018 | 21.9 | 17.8 | 18.4 | 18.7 | 19.3 | 15.3 | 20.4 | 19.0 |
| 7019 | 19.6 | 20.0 | 21.0 | 19.3 | 20.9 | 16.7 | 22.3 | 20.1 |
| 7020 | 19.6 | 20.0 | 21.0 | 19.3 | 20.9 | 16.7 | 22.3 | 20.1 |
| Mean | 21.18 | 19.33 | 19.55 | 19.27 | 19.88 | 15.90 | 20.70 | 19.55 |
| SD | 1.24 | 2.23 | 1.59 | 1.34 | 1.72 | 0.74 | 1.38 | 1.24 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

Individual Animal Mean Daily Food Consumption

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Mean Daily Food Consumption (g/day)

| 512 mg/kg/day Group 2 | Day(s) Relative to Start Date | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 3 → 7 | 7 → 10 | 10 → 14 | 14 → 17 | 17 → 21 | 21 → 24 | 24 → 28 | 3 → 28 |
| 7031 | 22.1 | 19.0 | 23.8 | 20.5 | 19.9 | 16.2 | 23.5 | 21.0 |
| 7032 | 22.1 | 19.0 | 23.8 | 20.5 | 19.9 | 16.2 | 23.5 | 21.0 |
| 7033 | 20.3 | 18.2 | 18.3 | 20.0 | 19.0 | 15.3 | 20.9 | 19.0 |
| 7034 | 20.3 | 18.2 | 18.3 | 20.0 | 19.0 | 15.3 | 20.9 | 19.0 |
| 7035 | 20.3 | 18.3 | 18.9 | 18.7 | 19.0 | 16.0 | 20.1 | 18.9 |
| 7036 | 20.3 | 18.3 | 18.9 | 18.7 | 19.0 | 16.0 | 20.1 | 18.9 |
| 7037 | 22.9 | 17.7 | 20.6 | 18.8 | 22.0 | 16.3 | 19.9 | 20.0 |
| 7038 | 22.9 | 17.7 | 20.6 | 18.8 | 22.0 | 16.3 | 19.9 | 20.0 |
| 7039 | 20.6 | 19.0 | 20.8 | 19.0 | 20.5 | 17.3 | 22.3 | 20.1 |
| 7040 | 20.6 | 19.0 | 20.8 | 19.0 | 20.5 | 17.3 | 22.3 | 20.1 |
| Mean | 21.23 | 18.43 | 20.45 | 19.40 | 20.08 | 16.23 | 21.33 | 19.78 |
| SD | 1.13 | 0.54 | 2.02 | 0.76 | 1.18 | 0.68 | 1.44 | 0.82 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

Individual Animal Mean Daily Food Consumption

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Mean Daily Food Consumption (g/day)

| 1024 mg/kg/day Group 3 | Day(s) Relative to Start Date | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 3 → 7 | 7 → 10 | 10 → 14 | 14 → 17 | 17 → 21 | 21 → 24 | 24 → 28 | 3 → 28 |
| 7051 | 20.9 | 17.5 | 18.4 | 17.7 | 17.3 | 15.8 | 20.5 | 18.4 |
| 7052 | 20.9 | 17.5 | 18.4 | 17.7 | 17.3 | 15.8 | 20.5 | 18.4 |
| 7053 | 22.0 | 19.7 | 20.6 | 19.5 | 20.8 | 15.5 | 22.3 | 20.3 |
| 7054 | 22.0 | 19.7 | 20.6 | 19.5 | 20.8 | 15.5 | 22.3 | 20.3 |
| 7055 | 22.9 | 23.2 | 20.4 | 20.0 | 20.6 | 16.3 | 21.4 | 20.8 |
| 7056 | 22.9 | 23.2 | 20.4 | 20.0 | 20.6 | 16.3 | 21.4 | 20.8 |
| 7057 | 19.9 | 17.2 | 18.0 | 16.8 | 18.0 | 15.8 | 19.8 | 18.1 |
| 7058 | 19.9 | 17.2 | 18.0 | 16.8 | 18.0 | 15.8 | 19.8 | 18.1 |
| 7059 | 19.6 | 19.0 | 19.9 | 18.3 | 20.1 | 16.3 | 21.5 | 19.4 |
| 7060 | 19.6 | 19.0 | 19.9 | 18.3 | 20.1 | 16.3 | 21.5 | 19.4 |
| Mean | 21.05 | 19.30 | 19.45 | 18.47 | 19.35 | 15.97 | 21.08 | 19.40 |
| SD | 1.31 | 2.26 | 1.12 | 1.22 | 1.52 | 0.34 | 0.91 | 1.09 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

Individual Animal Mean Daily Food Consumption

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Mean Daily Food Consumption (g/day)

| 1536 mg/kg/day Group 4 | Day(s) Relative to Start Date | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 3 → 7 | 7 → 10 | 10 → 14 | 14 → 17 | 17 → 21 | 21 → 24 | 24 → 28 | 3 → 28 |
| 7071 | 19.8 | 17.2 | 17.0 | 17.8 | 18.1 | 14.7 | 20.8 | 18.1 |
| 7072 | 19.8 | 17.2 | 17.0 | 17.8 | 18.1 | 14.7 | 20.8 | 18.1 |
| 7073 | 21.1 | 19.2 | 19.6 | 17.0 | 19.9 | 16.2 | 19.6 | 19.1 |
| 7074 | 21.1 | 19.2 | 19.6 | 17.0 | 19.9 | 16.2 | 19.6 | 19.1 |
| 7075 | 20.5 | 19.3 | 19.5 | 19.5 | 19.0 | 16.0 | 21.1 | 19.4 |
| 7076 | 20.5 | 19.3 | 19.5 | 19.5 | 19.0 | 16.0 | 21.1 | 19.4 |
| 7077 | 20.5 | 19.8 | 19.4 | 19.7 | 19.6 | 15.7 | 20.1 | 19.4 |
| 7078 | 20.5 | 19.8 | 19.4 | 19.7 | 19.6 | 15.7 | 20.1 | 19.4 |
| 7079 | 19.0 | 19.0 | 19.9 | 19.7 | 19.0 | 15.7 | 20.6 | 19.1 |
| 7080 | 19.0 | 19.0 | 19.9 | 19.7 | 19.0 | 15.7 | 20.6 | 19.1 |
| Mean | 20.18 | 18.90 | 19.08 | 18.73 | 19.13 | 15.63 | 20.45 | 19.00 |
| SD | 0.77 | 0.96 | 1.11 | 1.17 | 0.64 | 0.55 | 0.55 | 0.52 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

# APPENDIX L: INDIVIDUAL ANIMAL FOOD EFFICIENCY[1,2]

## PRODUCT IDENTIFICATION

Soy Leghemoglobin Preparation

[1] Food efficiency = $\frac{\text{Mean Daily Body Weight Gain}}{\text{Mean Daily Food Consumption}}$

[2] Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient.
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

Individual Animal Mean Food Efficiency

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Food Efficiency

| 0 mg/kg/day Group 1 | Day(s) Relative to Start Date | | | |
|---|---|---|---|---|
| | 0 → 7 | 7 → 14 | 14 → 21 | 21 → 28 |
| 7001 | 0.36 | 0.25 | 0.26 | 0.18 |
| 7002 | 0.26 | 0.28 | 0.18 | 0.11 |
| 7003 | 0.32 | 0.26 | 0.26 | 0.13 |
| 7004 | 0.24 | 0.22 | 0.19 | 0.10 |
| 7005 | 0.24 | 0.22 | 0.19 | 0.10 |
| 7006 | 0.34 | 0.25 | 0.32 | 0.17 |
| 7007 | 0.36 | 0.26 | 0.23 | 0.17 |
| 7008 | 0.29 | 0.23 | 0.18 | 0.10 |
| 7009 | 0.31 | 0.24 | 0.21 | 0.11 |
| 7010 | 0.32 | 0.20 | 0.21 | 0.05 |
| Mean | 0.304 | 0.241 | 0.223 | 0.121 |
| SD | 0.046 | 0.025 | 0.044 | 0.040 |
| N | 10 | 10 | 10 | 10 |

Individual Animal Mean Food Efficiency

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Food Efficiency

| 512 mg/kg/day Group 2 | Day(s) Relative to Start Date | | | |
|---|---|---|---|---|
| | 0 → 7 | 7 → 14 | 14 → 21 | 21 → 28 |
| 7021 | 0.31 | 0.22 | 0.22 | 0.15 |
| 7022 | 0.35 | 0.27 | 0.21 | 0.11 |
| 7023 | 0.33 | 0.28 | 0.22 | 0.13 |
| 7024 | 0.31 | 0.25 | 0.20 | 0.10 |
| 7025 | 0.32 | 0.21 | 0.21 | 0.10 |
| 7026 | 0.33 | 0.30 | 0.20 | 0.12 |
| 7027 | 0.30 | 0.21 | 0.25 | 0.13 |
| 7028 | 0.27 | 0.20 | 0.18 | 0.08 |
| 7029 | 0.36 | 0.32 | 0.26 | 0.19 |
| 7030 | 0.23 | 0.23 | 0.22 | 0.11 |
| Mean | 0.312 | 0.248 | 0.217 | 0.123 |
| SD | 0.038 | 0.043 | 0.022 | 0.032 |
| N | 10 | 10 | 10 | 10 |



Case No.: IPR2023-00208
U.S. Patent No. 11,013,250

Individual Animal Mean Food Efficiency

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Food Efficiency

| 1024 mg/kg/day Group 3 | Day(s) Relative to Start Date | | | |
|---|---|---|---|---|
| | 0 → 7 | 7 → 14 | 14 → 21 | 21 → 28 |
| 7041 | 0.27 | 0.25 | 0.21 | 0.13 |
| 7042 | 0.35 | 0.30 | 0.25 | 0.15 |
| 7043 | 0.30 | 0.21 | 0.23 | 0.09 |
| 7044 | 0.38 | 0.30 | 0.25 | 0.18 |
| 7045 | 0.31 | 0.24 | 0.22 | 0.12 |
| 7046 | 0.37 | 0.31 | 0.24 | 0.17 |
| 7047 | 0.37 | 0.28 | 0.23 | 0.14 |
| 7048 | 0.35 | 0.28 | 0.26 | 0.18 |
| 7049 | 0.23 | 0.23 | 0.18 | 0.17 |
| 7050 | 0.27 | 0.19 | 0.20 | 0.06 |
| Mean | 0.319 | 0.258 | 0.227 | 0.139 |
| SD | 0.051 | 0.041 | 0.026 | 0.040 |
| N | 10 | 10 | 10 | 10 |

Individual Animal Mean Food Efficiency

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Food Efficiency

| 1536 mg/kg/day Group 4 | Day(s) Relative to Start Date | | | |
|---|---|---|---|---|
| | 0 → 7 | 7 → 14 | 14 → 21 | 21 → 28 |
| 7061 | 0.34 | 0.25 | 0.21 | 0.14 |
| 7062 | 0.34 | 0.25 | 0.22 | 0.16 |
| 7063 | 0.23 | 0.19 | 0.22 | 0.13 |
| 7064 | 0.40 | 0.31 | 0.30 | 0.16 |
| 7065 | 0.35 | 0.27 | 0.22 | 0.15 |
| 7066 | 0.34 | 0.26 | 0.23 | 0.13 |
| 7067 | 0.33 | 0.24 | 0.20 | 0.14 |
| 7068 | 0.29 | 0.22 | 0.19 | 0.12 |
| 7069 | 0.36 | 0.17 | 0.19 | 0.10 |
| 7070 | 0.30 | 0.24 | 0.20 | 0.16 |
| Mean | 0.329 | 0.241 | 0.217 | 0.139 |
| SD | 0.046 | 0.040 | 0.031 | 0.019 |
| N | 10 | 10 | 10 | 10 |

Individual Animal Mean Food Efficiency

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Food Efficiency

| 0 mg/kg/day Group 1 | Day(s) Relative to Start Date | | | |
|---|---|---|---|---|
| | 0 → 7 | 7 → 14 | 14 → 21 | 21 → 28 |
| 7011 | 0.12 | 0.08 | 0.13 | 0.03 |
| 7012 | 0.22 | 0.13 | 0.15 | 0.04 |
| 7013 | 0.10 | 0.33 | 0.14 | 0.04 |
| 7014 | 0.27 | -0.01 | 0.19 | 0.03 |
| 7015 | 0.19 | 0.09 | 0.19 | 0.07 |
| 7016 | 0.20 | 0.13 | 0.10 | 0.19 |
| 7017 | 0.16 | 0.13 | 0.13 | 0.11 |
| 7018 | 0.20 | 0.18 | 0.23 | 0.05 |
| 7019 | 0.25 | 0.19 | 0.04 | 0.14 |
| 7020 | 0.22 | 0.24 | 0.19 | 0.09 |
| Mean | 0.193 | 0.148 | 0.149 | 0.080 |
| SD | 0.055 | 0.093 | 0.057 | 0.052 |
| N | 10 | 10 | 10 | 10 |

Individual Animal Mean Food Efficiency

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Food Efficiency

| 512 mg/kg/day Group 2 | Day(s) Relative to Start Date | | | |
|---|---|---|---|---|
| | 0 → 7 | 7 → 14 | 14 → 21 | 21 → 28 |
| 7031 | 0.20 | 0.14 | 0.05 | 0.08 |
| 7032 | 0.16 | 0.09 | 0.11 | 0.09 |
| 7033 | 0.23 | 0.08 | 0.13 | 0.08 |
| 7034 | 0.18 | 0.12 | 0.07 | 0.08 |
| 7035 | 0.23 | 0.18 | 0.08 | 0.12 |
| 7036 | 0.29 | 0.12 | 0.11 | 0.12 |
| 7037 | 0.12 | 0.10 | 0.03 | 0.07 |
| 7038 | 0.21 | 0.12 | 0.10 | 0.12 |
| 7039 | 0.24 | 0.19 | -0.01 | 0.14 |
| 7040 | 0.28 | 0.14 | 0.08 | 0.21 |
| Mean | 0.215 | 0.128 | 0.077 | 0.111 |
| SD | 0.052 | 0.037 | 0.042 | 0.041 |
| N | 10 | 10 | 10 | 10 |

Individual Animal Mean Food Efficiency

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Food Efficiency

| 1024 mg/kg/day Group 3 | Day(s) Relative to Start Date | | | |
|---|---|---|---|---|
| | 0 → 7 | 7 → 14 | 14 → 21 | 21 → 28 |
| 7051 | 0.23 | 0.10 | 0.07 | 0.15 |
| 7052 | 0.25 | 0.19 | 0.07 | 0.11 |
| 7053 | 0.21 | 0.15 | 0.13 | 0.13 |
| 7054 | 0.21 | 0.16 | 0.11 | 0.09 |
| 7055 | 0.19 | 0.08 | 0.22 | 0.07 |
| 7056 | 0.28 | 0.17 | 0.13 | 0.07 |
| 7057 | 0.16 | 0.15 | 0.14 | 0.13 |
| 7058 | 0.25 | 0.14 | 0.11 | 0.07 |
| 7059 | 0.27 | 0.18 | 0.10 | 0.14 |
| 7060 | 0.20 | 0.14 | 0.06 | 0.14 |
| Mean | 0.226 | 0.146 | 0.112 | 0.109 |
| SD | 0.037 | 0.033 | 0.049 | 0.033 |
| N | 10 | 10 | 10 | 10 |



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Individual Animal Mean Food Efficiency

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Food Efficiency

| 1536 mg/kg/day Group 4 | Day(s) Relative to Start Date | | | |
|---|---|---|---|---|
| | 0 → 7 | 7 → 14 | 14 → 21 | 21 → 28 |
| 7071 | 0.23 | 0.12 | 0.22 | 0.06 |
| 7072 | 0.24 | 0.18 | 0.09 | 0.13 |
| 7073 | 0.23 | 0.18 | 0.09 | 0.15 |
| 7074 | 0.14 | 0.15 | 0.11 | 0.04 |
| 7075 | 0.19 | 0.13 | 0.08 | 0.09 |
| 7076 | 0.22 | 0.21 | 0.17 | 0.02 |
| 7077 | 0.23 | 0.19 | 0.14 | 0.09 |
| 7078 | 0.23 | 0.16 | 0.08 | 0.10 |
| 7079 | 0.15 | 0.23 | 0.09 | 0.03 |
| 7080 | 0.19 | 0.11 | 0.19 | 0.12 |
| Mean | 0.206 | 0.165 | 0.126 | 0.083 |
| SD | 0.038 | 0.040 | 0.052 | 0.044 |
| N | 10 | 10 | 10 | 10 |

# APPENDIX M: INDIVIDUAL ANIMAL MEAN DAILY DIETARY INTAKE OF SOY LEGHEMOGLOBIN PREPARATION[1]

## PRODUCT IDENTIFICATION

Soy Leghemoglobin Preparation

[1] Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient.
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

Individual Animal Mean Dietary Intake

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Dietary Intake Variable (mg/kg/day)

| 0 mg/kg/day Group 1 | Day(s) Relative to Start Date | | | | |
|---|---|---|---|---|---|
| | 0 → 7 | 7 → 14 | 14 → 21 | 21 → 28 | 0 → 28 |
| 7001 | 0 | 0 | 0 | 0 | 0 |
| 7002 | 0 | 0 | 0 | 0 | 0 |
| 7003 | 0 | 0 | 0 | 0 | 0 |
| 7004 | 0 | 0 | 0 | 0 | 0 |
| 7005 | 0 | 0 | 0 | 0 | 0 |
| 7006 | 0 | 0 | 0 | 0 | 0 |
| 7007 | 0 | 0 | 0 | 0 | 0 |
| 7008 | 0 | 0 | 0 | 0 | 0 |
| 7009 | 0 | 0 | 0 | 0 | 0 |
| 7010 | 0 | 0 | 0 | 0 | 0 |
| Mean | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| SD | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| N | 10 | 10 | 10 | 10 | 10 |



Case No.: IPR2023-00208
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Individual Animal Mean Dietary Intake

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Dietary Intake Variable (mg/kg/day)

| 512 mg/kg/day Group 2 | Day(s) Relative to Start Date | | | | |
|---|---|---|---|---|---|
| | 0 → 7 | 7 → 14 | 14 → 21 | 21 → 28 | 0 → 28 |
| 7021 | 482 | 544 | 512 | 492 | 480 |
| 7022 | 469 | 516 | 482 | 471 | 459 |
| 7023 | 468 | 526 | 476 | 458 | 456 |
| 7024 | 466 | 533 | 486 | 472 | 464 |
| 7025 | 480 | 551 | 500 | 511 | 484 |
| 7026 | 487 | 542 | 482 | 493 | 474 |
| 7027 | 474 | 521 | 493 | 492 | 468 |
| 7028 | 503 | 556 | 533 | 546 | 507 |
| 7029 | 489 | 519 | 492 | 468 | 463 |
| 7030 | 535 | 598 | 576 | 557 | 535 |
| Mean | 485.4 | 540.5 | 503.2 | 495.9 | 478.9 |
| SD | 20.9 | 24.5 | 30.7 | 33.2 | 24.7 |
| N | 10 | 10 | 10 | 10 | 10 |

Individual Animal Mean Dietary Intake.

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Dietary Intake Variable (mg/kg/day)

| 1024 mg/kg/day Group 3 | Day(s) Relative to Start Date | | | | |
|---|---|---|---|---|---|
| | 0 → 7 | 7 → 14 | 14 → 21 | 21 → 28 | 0 → 28 |
| 7041 | 928 | 1188 | 1129 | 1034 | 1009 |
| 7042 | 866 | 1083 | 1020 | 929 | 919 |
| 7043 | 989 | 1142 | 1089 | 1010 | 1001 |
| 7044 | 967 | 1065 | 993 | 905 | 925 |
| 7045 | 1011 | 1172 | 1012 | 1048 | 1003 |
| 7046 | 954 | 1079 | 921 | 946 | 919 |
| 7047 | 981 | 1079 | 998 | 948 | 946 |
| 7048 | 979 | 1081 | 992 | 929 | 937 |
| 7049 | 992 | 1032 | 954 | 975 | 934 |
| 7050 | 998 | 1037 | 965 | 1006 | 952 |
| Mean | 966.5 | 1095.9 | 1007.2 | 973.0 | 954.7 |
| SD | 42.5 | 53.5 | 61.7 | 49.1 | 36.0 |
| N | 10 | 10 | 10 | 10 | 10 |

Individual Animal Mean Dietary Intake.

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Dietary Intake Variable (mg/kg/day)

| 1536 mg/kg/day Group 4 | Day(s) Relative to Start Date | | | | |
|---|---|---|---|---|---|
| | 0 → 7 | 7 → 14 | 14 → 21 | 21 → 28 | 0 → 28 |
| 7061 | 1338 | 1587 | 1463 | 1411 | 1373 |
| 7062 | 1374 | 1623 | 1489 | 1424 | 1397 |
| 7063 | 1435 | 1745 | 1669 | 1576 | 1516 |
| 7064 | 1327 | 1504 | 1389 | 1303 | 1302 |
| 7065 | 1421 | 1569 | 1458 | 1417 | 1388 |
| 7066 | 1463 | 1617 | 1496 | 1450 | 1425 |
| 7067 | 1529 | 1631 | 1488 | 1471 | 1449 |
| 7068 | 1659 | 1776 | 1620 | 1603 | 1576 |
| 7069 | 1516 | 1625 | 1544 | 1565 | 1487 |
| 7070 | 1537 | 1638 | 1521 | 1518 | 1469 |
| Mean | 1459.8 | 1631.5 | 1513.7 | 1473.9 | 1438.2 |
| SD | 103.0 | 78.9 | 81.1 | 92.5 | 78.6 |
| N | 10 | 10 | 10 | 10 | 10 |



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Case No.: IPR2023-00208
U.S. Patent No. 11,013,250

Individual Animal Mean Dietary Intake

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female  Dietary Intake Variable (mg/kg/day)

| 0 mg/kg/day Group 1 | Day(s) Relative to Start Date | | | | |
|---|---|---|---|---|---|
| | 0 → 7 | 7 → 14 | 14 → 21 | 21 → 28 | 0 → 28 |
| 7011 | 0 | 0 | 0 | 0 | 0 |
| 7012 | 0 | 0 | 0 | 0 | 0 |
| 7013 | 0 | 0 | 0 | 0 | 0 |
| 7014 | 0 | 0 | 0 | 0 | 0 |
| 7015 | 0 | 0 | 0 | 0 | 0 |
| 7016 | 0 | 0 | 0 | 0 | 0 |
| 7017 | 0 | 0 | 0 | 0 | 0 |
| 7018 | 0 | 0 | 0 | 0 | 0 |
| 7019 | 0 | 0 | 0 | 0 | 0 |
| 7020 | 0 | 0 | 0 | 0 | 0 |
| Mean | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| SD | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| N | 10 | 10 | 10 | 10 | 10 |



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Case No.: IPR2023-00208
U.S. Patent No. 11,013,250

Individual Animal Mean Dietary Intake

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Dietary Intake Variable (mg/kg/day)

| 512 mg/kg/day Group 2 | Day(s) Relative to Start Date | | | | |
|---|---|---|---|---|---|
| | 0 → 7 | 7 → 14 | 14 → 21 | 21 → 28 | 0 → 28 |
| 7031 | 451 | 550 | 484 | 480 | 480 |
| 7032 | 498 | 622 | 543 | 523 | 532 |
| 7033 | 472 | 513 | 517 | 470 | 481 |
| 7034 | 510 | 552 | 557 | 513 | 521 |
| 7035 | 480 | 523 | 491 | 460 | 476 |
| 7036 | 470 | 513 | 487 | 451 | 469 |
| 7037 | 608 | 637 | 652 | 568 | 601 |
| 7038 | 474 | 490 | 495 | 422 | 458 |
| 7039 | 505 | 506 | 481 | 477 | 481 |
| 7040 | 513 | 513 | 481 | 458 | 477 |
| Mean | 498.0 | 541.9 | 518.8 | 482.4 | 497.8 |
| SD | 43.5 | 49.9 | 53.9 | 41.9 | 42.8 |
| N | 10 | 10 | 10 | 10 | 10 |

Individual Animal Mean Dietary Intake.

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female  Dietary Intake Variable (mg/kg/day)

| 1024 mg/kg/day Group 3 | Day(s) Relative to Start Date | | | | |
|---|---|---|---|---|---|
| | 0 → 7 | 7 → 14 | 14 → 21 | 21 → 28 | 0 → 28 |
| 7051 | 1013 | 1082 | 1046 | 1087 | 1022 |
| 7052 | 1004 | 1037 | 980 | 1033 | 982 |
| 7053 | 1003 | 1077 | 1041 | 968 | 986 |
| 7054 | 971 | 1044 | 1012 | 957 | 963 |
| 7055 | 957 | 1102 | 999 | 910 | 956 |
| 7056 | 1035 | 1119 | 1015 | 948 | 998 |
| 7057 | 1004 | 1066 | 1018 | 1018 | 988 |
| 7058 | 960 | 1004 | 977 | 1003 | 956 |
| 7059 | 975 | 1014 | 979 | 955 | 948 |
| 7060 | 1038 | 1104 | 1083 | 1061 | 1035 |
| Mean | 995.9 | 1064.6 | 1015.1 | 994.0 | 983.4 |
| SD | 29.2 | 39.2 | 34.3 | 56.0 | 29.0 |
| N | 10 | 10 | 10 | 10 | 10 |



Case No.: IPR2023-00208
U.S. Patent No. 11,013,250

Individual Animal Mean Dietary Intake

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Dietary Intake Variable (mg/kg/day)

| 1536 mg/kg/day Group 4 | Day(s) Relative to Start Date | | | | |
|---|---|---|---|---|---|
| | 0 → 7 | 7 → 14 | 14 → 21 | 21 → 28 | 0 → 28 |
| 7071 | 1411 | 1475 | 1479 | 1434 | 1402 |
| 7072 | 1431 | 1461 | 1496 | 1473 | 1418 |
| 7073 | 1350 | 1565 | 1455 | 1380 | 1388 |
| 7074 | 1405 | 1679 | 1560 | 1511 | 1489 |
| 7075 | 1504 | 1643 | 1597 | 1553 | 1524 |
| 7076 | 1610 | 1683 | 1548 | 1499 | 1534 |
| 7077 | 1391 | 1521 | 1456 | 1323 | 1376 |
| 7078 | 1584 | 1717 | 1670 | 1524 | 1573 |
| 7079 | 1421 | 1499 | 1421 | 1372 | 1384 |
| 7080 | 1703 | 1804 | 1690 | 1534 | 1618 |
| Mean | 1481.1 | 1604.6 | 1537.2 | 1460.2 | 1470.4 |
| SD | 115.0 | 116.7 | 92.3 | 79.0 | 88.2 |
| N | 10 | 10 | 10 | 10 | 10 |

# APPENDIX N: CLINICAL PATHOLOGY

## PRODUCT IDENTIFICATION

Soy Leghemoglobin Preparation

Submitted by:

Dupont Haskell Global Centers
for Health and Environmental Sciences
P.O. Box 30, Elkton Road
Newark, Delaware 19714

**STUDY TITLE:** Clinical Pathology Results for Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

**AUTHOR:** Denise Hoban, B.A., MLT (ASCP)

**CLINICAL PATHOLOGY RESULTS COMPLETED:** July 20, 2017

**PERFORMING LABORATORY:** E.I. du Pont de Nemours and Company
DuPont Haskell Global Centers for
Health & Environmental Sciences
P.O. Box 30
Newark, Delaware 19714
U.S.A.

**WORK REQUEST NUMBER:** 21641

**SERVICE CODE NUMBER:** 1611

**CLIENT:** Product Safety Labs
2394 U.S. Highway 130
Dayton, New Jersey 08810
U.S.A.

**CLIENT STUDY NUMBER:** 43166

## GOOD LABORATORY PRACTICE COMPLIANCE STATEMENT

The work performed at DuPont Haskell was conducted in compliance with U.S. FDA (21 CFR part 58) Good Laboratory Practice Standards, which are compatible with current OECD Good Laboratory Practices.

**Client:** Product Safety Labs
2394 U.S. Highway 130
Dayton, New Jersey 08810
U.S.A.

(b) (6)

**Reported by:** _____ 20 July 2017
Denise Hoban, B.A., MLT (ASCP) — Date
Senior Staff Toxicologist & Pathology Coordinator
E.I. du Pont de Nemours and Company

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

## QUALITY ASSURANCE STATEMENT

Work Request Number: 21641
Service Code Number: 1611
PSL Study Number: 43166

Key inspections for the above referenced clinical pathology study were completed by the Quality Assurance Unit of DuPont Haskell and the findings were submitted on the following dates:

| | *Date Reported to:* | | | |
|---|---|---|---|---|
| *Audit Dates* | *Principal Investigator (PI)* | *PI Management* | *Study Director (SD)* | *SD Management* |
| **Protocol/Conduct:** | | | | |
| 20 October 2016 | 21 October 2016 | 21 October 2016 | 21 October 2016 | 21 October 2016 |
| **Report/Records:** | | | | |
| 29-30 November 2016 | 30 November 2016 | 30 November 2016 | 30 November 2016 | 30 November 2016 |
| 9 December 2016 | 9 December 2016 | 9 December 2016 | 9 December 2016 | 9 December 2016 |

**Reported by:** (b) (6) 20 July 2017
Jessica Garcia-Arbulet
Quality Assurance Auditor
Dated

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

## CERTIFICATION

I, the undersigned, declare that these results provide accurate data obtained from this study.

**Issued by**
**Principal Investigator:** (b) (6) [redacted] 20 July 2017

Denise Hoban, B.A., MLT (ASCP)
Senior Staff Toxicologist & Pathology Coordinator

Date

## STUDY DESIGN

A 28-day dietary study in rats was conducted at Product Safety Labs (Dayton, New Jersey, U.S.A.) on behalf of Impossible Foods, Inc. (Redwood City, California, U.S.A.). Groups of 10 male and 10 female rats were fed 0, 512, 1024, 1536 mg/kg/day Soy Leghemoglobin Preparation which corresponds to 0, 250, 500 and 750 mg/kg/day of active ingredient Soy Leghemoglobin. Samples were collected for clinical pathology evaluation on test days 22 and 29/30 and were shipped to DuPont Haskell for analysis.

## MATERIALS AND METHODS

Clinical pathology analyses were conducted on samples collected on test days 22 (hematology, clinical chemistry, and urinalysis) and test days 29 (males) and 30 (females) (coagulation). Hematology measurements were conducted on whole blood on the day of collection. Clinical chemistry and coagulation measurements were conducted on samples that were frozen until analysis. All blood samples were evaluated for quality by visual examination. Urinalysis measurements were conducted on the day of collection.

1. Hematology and Coagulation

Complete blood counts, including reticulocytes, were determined on an Advia 120 Hematology Analyzer. Blood smears, stained with New Methylene-Blue or Wright-Giemsa, were prepared from each animal undergoing a hematology evaluation, but were not needed for examination. Coagulation times were determined on a Sysmex CA-1500 Coagulation Analyzer.

The following parameters were determined:

red blood cell count
hemoglobin
hematocrit
mean corpuscular (cell) volume
mean corpuscular (cell) hemoglobin
mean corpuscular (cell) hemoglobin concentration
red cell distribution width
absolute reticulocyte count
platelet count
white blood cell count
differential white blood cell count

prothrombin time
activated partial thromboplastin time

2. Clinical Chemistry

Serum clinical chemistry parameters were determined on an Olympus AU640 Clinical Chemistry Analyzer.

The following parameters were determined:

aspartate aminotransferase
alanine aminotransferase
glucose
total protein

| | |
|---|---|
| sorbitol dehydrogenase | albumin |
| alkaline phosphatase | globulin |
| total bilirubin | calcium |
| urea nitrogen | inorganic phosphorus |
| creatinine | sodium |
| cholesterol | potassium |
| triglycerides | chloride |

3. Urinalysis

Urine volume was measured, and appearance (quality, color, and clarity) was evaluated visually. Urine protein was measured on an Olympus AU640 Clinical Chemistry Analyzer. Other urine constituents were semi-quantitatively measured on a Clinitek Atlas Automated Urine Chemistry analyzer. Sediments from urine specimens were evaluated microscopically.

The following parameters were determined:

| | |
|---|---|
| quality | ketone |
| color | bilirubin |
| clarity | blood |
| volume | urobilinogen |
| specific gravity | protein |
| pH | microscopic urine sediment examination |
| glucose | |

## STATISTICAL ANALYSES

Significance was judged at $p < 0.05$. Separate analyses were performed on the data collected for each sex. Statistical analyses were performed by Provantis®.[1]

| | | Method of Statistical Analysis | |
|---|---|---|---|
| Parameter | Preliminary Test | If preliminary test is not significant | If preliminary test is significant |
| Clinical Pathology[a] | Levene's test for homogeneity[2] and Shapiro-Wilk test[3] for normality | One-way analysis of variance[4] followed by Dunnett's test[5] | Transforms of the data to achieve normality and variance homogeneity were used. The order of transforms attempted was log, square-root, and rank-order. If the log and square-root transforms failed, the rank-order was used. |

a When an individual observation was recorded as being less than a certain value, calculations were performed on half the recorded value. For example, if bilirubin was reported as <0.10, 0.05 was used for any calculations performed with those bilirubin data. When an individual observation was recorded as being greater than a certain value, calculations were performed on the recorded value. For example, if specific gravity was reported as >1.100, 1.100 was used for any calculations performed with those specific gravity data.

## RECORDS AND SAMPLE STORAGE

For the work conducted at DuPont Haskell, specimens (if applicable), raw data, and the clinical pathology report will be returned to the client within 6 months after the final report issues.

## REFERENCES

1. Provantis® (2012). Tables and Statistics (version 8). Instem LSS, Staffordshire, U.K.

2. Levene, H. (1960). Robust test for equality of variances. *Contributions to Probability and Statistics* (J. Olkin, ed.), pp 278-292. Stanford University Press, Palo Alto.

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4. Snedecor, G.W. and Cochran, W.G. (1967). *Statistical Methods*, 6th edition, pp 246-248 and 349-352. The Iowa State University Press, Iowa.

5. Dunnett, C.W. (1964). New tables for multiple comparisons with a control. *Biometrics* **20**, 482-491.

**TABLES**

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

TABLES

## EXPLANATORY NOTES

ABBREVIATIONS:

**General**

SD - standard deviation
N - number of values used in calculation
% Diff - percent difference from control
. or - - no data

**Summary of Hematology Values**

RBC - red blood cell count
HGB - hemoglobin
HCT - hematocrit
MCV - mean corpuscular (cell) volume
MCH - mean corpuscular (cell) hemoglobin
MCHC - mean corpuscular (cell) hemoglobin concentration
RDW - red cell distribution width
PLT - platelet count
WBC - white blood cell count
ANEU - absolute neutrophil (all forms)
ALYM - absolute lymphocyte
AMON - absolute monocyte
AEOS - absolute eosinophil
ABAS - absolute basophil
ALUC - absolute large unstained cell
ARET - absolute reticulocyte

**Summary of Coagulation Values**

PT - prothrombin time
APTT - activated partial thromboplastin time

**Summary of Clinical Chemistry Values**

AST - aspartate aminotransferase
ALT - alanine aminotransferase
SDH - sorbitol dehydrogenase
ALKP - alkaline phosphatase
BILI - total bilirubin
BUN - urea nitrogen
CREA - creatinine
CHOL - cholesterol
TRIG - triglycerides
GLUC - glucose
TP - total protein
ALB - albumin
GLOB - globulin
CALC - calcium
IPHS - inorganic phosphorous
NA - sodium
K - potassium
CL - chloride

**Summary of Urinalysis Values**

UVOL - volume
pH - the logarithm of the reciprocal of the hydrogen ion concentration
SG - specific gravity
URO - urobilinogen
UMTP - protein

TABLES

## EXPLANATORY NOTES (Continued)

ABBREVIATIONS: (Continued)

NOTES:

**Summary of Hematology Values**
**Summary of Coagulation Values**
**Summary of Clinical Chemistry Values**
**Summary of Urinalysis Values**

Groups with identical values may vary in statistical significance, because tabulated statistics are rounded to fewer decimal places than the values used for statistical determination.

The calculation for %Diff (deviation from control) is as follows:

%Diff = ((current group mean - control group mean) / control group mean) x 100

This calculation is performed upon full precision means and not the rounded values displayed within this report.

Calculation of mean, SD, and %Diff may vary from computer-generated values due to differences in rounding.

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## Table 1
## Summary of Hematology Values for Male Rats

| Sex: Male | Day(s) Relative to Start Date | | 0 mg/kg/day Group 1 | 512 mg/kg/day Group 2 | 1024 mg/kg/day Group 3 | 1536 mg/kg/day Group 4 |
|---|---|---|---|---|---|---|
| RBC (x10^6/µL) | 22 | Mean | 7.72 | 7.69 | 7.61 | 7.70 |
| | | SD | 0.23 | 0.34 | 0.35 | 0.27 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | | -1.6 | -1.5 | -0.3 |
| HGB (g/dL) | 22 | Mean | 15.6 | 15.4 | 15.5 | 15.9 |
| | | SD | 0.3 | 0.6 | 0.6 | 0.4 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | | -1.5 | -1.0 | 1.4 |
| HCT (%) | 22 | Mean | 45.5 | 45.1 | 45.1 | 45.9 |
| | | SD | 0.9 | 1.5 | 1.7 | 0.8 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | | -0.9 | -0.8 | 1.0 |
| MCV (fL) | 22 | Mean | 58.9 | 59.3 | 59.3 | 59.7 |
| | | SD | 1.0 | 2.3 | 1.5 | 1.9 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | | 0.7 | 0.7 | 1.3 |
| MCH (pg) | 22 | Mean | 20.3 | 20.3 | 20.4 | 20.6 |
| | | SD | 0.5 | 0.9 | 0.5 | 0.7 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | | 0.2 | 0.6 | 1.6 |
| MCHC (g/dL) | 22 | Mean | 34.4 | 34.2 | 34.4 | 34.5 |
| | | SD | 0.4 | 0.4 | 0.3 | 0.5 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | | -0.5 | -0.1 | 0.4 |
| RDW (%) | 22 | Mean | 12.1 | 12.5 | 12.5 | 12.3 |
| | | SD | 0.3 | 0.5 | 0.3 | 0.5 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | | 3.0 | 3.3 | 1.6 |
| PLT (x10^3/µL) | 22 | Mean | 1160 | 1202 | 1171 | 1227 |
| | | SD | 121 | 89 | 76 | 185 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | | 3.6 | 1.0 | 5.8 |

General Footnote: [Statistical Test: Anova and Dunnett's test Transformation: Automatic]

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient.
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

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Table 1
Summary of Hematology Values for Male Rats (Continued)

| Sex: Male | Day(s) Relative to Start Date | | 0 mg/kg/day Group 1 | 512 mg/kg/day Group 2 | 1024 mg/kg/day Group 3 | 1536 mg/kg/day Group 4 |
|---|---|---|---|---|---|---|
| WBC (x10^3/µL) | 22 | Mean | 13.00 | 14.41 | 11.13 | 13.45 |
| | | SD | 1.33 | 2.67 | 1.82 | 4.41 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | | 10.8 | -14.4 | 3.4 |
| ANEU (x10^3/µL) | 22 | Mean | 1.91 | 1.99 | 1.75 | 1.57 |
| | | SD | 0.67 | 0.43 | 0.43 | 0.62 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | | 4.1 | -8.1 | -17.8 |
| ALYM (x10^3/µL) | 22 | Mean | 10.49 | 11.79 | 8.86 | 11.29 |
| | | SD | 1.17 | 2.48 | 1.70 | 4.15 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | | 12.4 | -15.5 | 7.7 |
| AMON (x10^3/µL) | 22 | Mean | 0.31 | 0.34 | 0.28 | 0.30 |
| | | SD | 0.10 | 0.11 | 0.05 | 0.10 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | | 10.2 | -9.8 | -1.5 |
| AEOS (x10^3/µL) | 22 | Mean | 0.12 | 0.13 | 0.11 | 0.11 |
| | | SD | 0.04 | 0.08 | 0.04 | 0.05 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | | 4.4 | -7.2 | -7.6 |
| ABAS (x10^3/µL) | 22 | Mean | 0.09 | 0.09 | 0.07 | 0.10 |
| | | SD | 0.03 | 0.04 | 0.02 | 0.06 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | | -5.0 | -27.0 | 0.2 |
| ALUC (x10^3/µL) | 22 | Mean | 0.08 | 0.08 | 0.06 | 0.08 |
| | | SD | 0.03 | 0.03 | 0.02 | 0.04 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | | -8.1 | -27.0 | -2.4 |
| ARET (x10^3/µL) | 22 | Mean | 232.6 | 235.8 | 246.3 | 243.8 |
| | | SD | 31.2 | 40.7 | 24.1 | 41.1 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | | 1.4 | 5.9 | 4.8 |

General Footnote: [Statistical Test: Anova and Dunnett's test Transformation: Automatic]

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient.
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

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## Table 2
## Summary of Hematology Values for Female Rats

| Sex Female | Day(s) Relative to Start Date | | 0 mg/kg/day Group 1 | 512 mg/kg/day Group 2 | 1024 mg/kg/day Group 3 | 1536 mg/kg/day Group 4 |
|---|---|---|---|---|---|---|
| RBC (x10^6/µL) | 22 | Mean | 7.59 | 8.01 * | 7.86 | 7.63 |
| | | SD | 0.24 | 0.38 | 0.24 | 0.30 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | | 5.6 | 3.6 | 0.6 |
| HGB (g/dL) | 22 | Mean | 15.3 | 16.2 * | 15.7 | 15.5 |
| | | SD | 0.5 | 0.5 | 0.4 | 0.6 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | | 5.7 | 2.5 | 0.9 |
| HCT (%) | 22 | Mean | 43.6 | 45.9 * | 44.7 | 44.0 |
| | | SD | 1.2 | 1.2 | 1.3 | 1.7 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | | 5.2 | 2.4 | 0.9 |
| MCV (fL) | 22 | Mean | 57.5 | 57.4 | 56.8 | 57.7 |
| | | SD | 1.1 | 2.2 | 1.2 | 2.2 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | | -0.2 | -1.1 | 0.4 |
| MCH (pg) | 22 | Mean | 20.2 | 20.2 | 20.0 | 20.3 |
| | | SD | 0.3 | 0.7 | 0.5 | 0.7 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | | 0.1 | -1.0 | 0.3 |
| MCHC (g/dL) | 22 | Mean | 35.2 | 35.3 | 35.2 | 35.2 |
| | | SD | 0.7 | 0.3 | 0.4 | 0.5 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | | 0.3 | 0.1 | 0.0 |
| RDW (%) | 22 | Mean | 11.3 | 11.3 | 11.2 | 11.5 |
| | | SD | 0.4 | 0.5 | 0.3 | 0.5 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | | 0.1 | -0.4 | 1.7 |
| PLT (x10^3/µL) | 22 | Mean | 1190 | 1176 | 1230 | 1229 |
| | | SD | 108 | 127 | 115 | 114 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | | -1.1 | 3.4 | 3.3 |

General Footnote. [Statistical Test: Anova and Dunnett's test Transformation: Autoranks]
1 [#- Test: Dunnett 2 Sided p < 0.05]

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient.
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

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## Table 2
## Summary of Hematology Values for Female Rats (Continued)

| Sex Female | Day(s) Relative to Start Date | | 0 mg/kg/day Group 1 | 512 mg/kg/day Group 2 | 1024 mg/kg/day Group 3 | 1536 mg/kg/day Group 4 |
|---|---|---|---|---|---|---|
| WBC (x10^3/µL) | 22 | Mean | 10.08 | 11.67 | 11.59 | 10.19 |
| | | SD | 1.70 | 1.75 | 3.35 | 3.72 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | | 17.7 | 15.0 | 1.1 |
| ANEU (x10^3/µL) | 22 | Mean | 1.48 | 1.56 | 1.68 | 1.54 |
| | | SD | 0.30 | 0.58 | 0.85 | 1.10 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | | 5.3 | 13.9 | 4.0 |
| ALYM (x10^3/µL) | 22 | Mean | 8.15 | 9.74 | 9.29 | 8.71 |
| | | SD | 1.58 | 1.43 | 2.71 | 2.88 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | | 19.5 | 14.0 | 6.7 |
| AMON (x10^3/µL) | 22 | Mean | 0.25 | 0.29 | 0.33 | 0.22 |
| | | SD | 0.15 | 0.06 | 0.15 | 0.14 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | | 16.7 | 32.5 | -11.1 |
| AEOS (x10^3/µL) | 22 | Mean | 0.11 | 0.13 | 0.15 | 0.12 |
| | | SD | 0.03 | 0.04 | 0.05 | 0.06 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | | 21.4 | 35.8 | 9.0 |
| ABAS (x10^3/µL) | 22 | Mean | 0.04 | 0.07 # | 0.06 | 0.05 |
| | | SD | 0.01 | 0.03 | 0.03 | 0.04 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | | 93.2 | 64.1 | 46.7 |
| ALUG (x10^3/µL) | 22 | Mean | 0.05 | 0.07 | 0.07 | 0.06 |
| | | SD | 0.02 | 0.02 | 0.03 | 0.04 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | | 29.1 | 26.2 | 2.9 |
| ARET (x10^3/µL) | 22 | Mean | 205.8 | 182.4 | 169.1 # | 184.2 |
| | | SD | 33.9 | 32.9 | 30.9 | 33.7 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | | -11.3 | -17.8 | -10.5 |

General Footnote: [Statistical Test: Anova and Dunnett's test Transformation: Autoranks]
1 [#- Test: Dunnett 2 Sided p < 0.05]

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient.
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

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## Table 3
## Summary of Coagulation Values for Male Rats

| Sex: Male | Day(s) Relative to Start Date | | 0 mg/kg/day Group 1 | 512 mg/kg/day Group 2 | 1024 mg/kg/day Group 3 | 1536 mg/kg/day Group 4 |
|---|---|---|---|---|---|---|
| PT (sec) | 29 | Mean | 10.7 | 10.7 | 10.6 | 10.6 |
| | | SD | 0.3 | 0.4 | 0.2 | 0.2 |
| | | N | 10 | 10 | 10 | 10 |
| APTT (sec) | 29 | Mean | 20.2 | 21.8 | 24.9 @ | 23.9 @ |
| | | SD | 2.4 | 5.3 | 8.9 | 4.8 |
| | | N | 10 | 10 | 10 | 10 |

General Footnote: [Statistical Test: Anova and Dunnett's test Transformation: Automatic]
1 [@ - Test: Dunnett Non-Parametric 2 Sided p < 0.05]

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient.
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

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## Table 4
## Summary of Coagulation Values for Female Rats

| Sex: Female | Day(s) Relative to Start Date | | 0 mg/kg/day Group 1 | 512 mg/kg/day Group 2 | 1024 mg/kg/day Group 3 | 1536 mg/kg/day Group 4 |
|---|---|---|---|---|---|---|
| PT (sec) | 30 | Mean | 10.0 | 9.8 | 10.0 | 9.8 |
| | | SD | 0.2 | 0.2 | 0.3 | 0.2 |
| | | N | 10 | 10 | 10 | 10 |
| APTT (sec) | 30 | Mean | 21.9 | 20.0 | 20.8 | 19.4 |
| | | SD | 2.5 | 3.1 | 5.0 | 1.9 |
| | | N | 10 | 10 | 10 | 10 |

General Footnote [Statistical Test: Anova and Dunnett's test Transformation: Automatic]

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient.
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

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## Table 5
## Summary of Clinical Chemistry Values for Male Rats

| Ser. Male | Day(s) Relative to Start Date | | 0 mg/kg/day Group 1 | 512 mg/kg/day Group 2 | 1024 mg/kg/day Group 3 | 1536 mg/kg/day Group 4 |
|---|---|---|---|---|---|---|
| AST (U/L) | 22 | Mean | 73 | 76 | 79 | 78 |
| | | SD | 8 | 9 | 7 | 8 |
| | | N | 5 | 9 | 8 | 8 |
| | | %Diff | | 4.0 | 7.5 | 6.9 |
| ALT (U/L) | 22 | Mean | 29 | 28 | 28 | 30 |
| | | SD | 4 | 4 | 3 | 4 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | | -3.1 | -2.4 | 2.4 |
| SDH (U/L) | 22 | Mean | 8.2 | 8.1 | 8.4 | 8.0 |
| | | SD | 1.4 | 1.7 | 2.4 | 1.4 |
| | | N | 5 | 9 | 8 | 8 |
| | | %Diff | | -0.8 | 2.7 | -1.9 |
| ALKP (U/L) | 22 | Mean | 183 | 216 | 216 | 205 |
| | | SD | 24 | 29 | 44 | 42 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | | 18.6 | 18.5 | 12.3 |
| BILI (mg/dL) | 22 | Mean | 0.17 | 0.17 | 0.18 | 0.18 |
| | | SD | 0.02 | 0.02 | 0.02 | 0.02 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | | 1.2 | 4.1 | 5.9 |
| BUN (mg/dL) | 22 | Mean | 10 | 11 | 10 | 11 |
| | | SD | 1 | 1 | 1 | 2 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | | 4.8 | -3.8 | 1.0 |
| CREA (mg/dL) | 22 | Mean | 0.22 | 0.23 | 0.23 | 0.21 |
| | | SD | 0.01 | 0.02 | 0.02 | 0.02 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | | 3.6 | 4.1 | -5.9 |
| CHOL (mg/dL) | 22 | Mean | 76 | 73 | 72 | 67 |
| | | SD | 16 | 27 | 14 | 12 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | | -3.4 | -5.4 | -11.7 |

General Footnote [Statistical Test: Anova and Dunnett's test Transformation: Automatic]

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

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## Table 5
## Summary of Clinical Chemistry Values for Male Rats (Continued)

| Sex Male | Day(s) Relative to Start Date | | 0 mg/kg/day Group 1 | 512 mg/kg/day Group 2 | 1024 mg/kg/day Group 3 | 1536 mg/kg/day Group 4 |
|---|---|---|---|---|---|---|
| TRIG (mg/dL) | 22 | Mean | 68 | 67 | 67 | 68 |
| | | SD | 17 | 13 | 17 | 28 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | | 1.6 | 0.9 | 2.4 |
| GLUC (mg/dL) | 22 | Mean | 95 | 100 | 102 | 98 |
| | | SD | 12 | 9 | 13 | 8 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | | 5.4 | 7.1 | 2.6 |
| TP (g/dL) | 22 | Mean | 6.0 | 6.1 | 6.2 | 6.0 |
| | | SD | 0.2 | 0.2 | 0.2 | 0.2 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | | 0.7 | 2.8 | 0.2 |
| ALB (g/dL) | 22 | Mean | 3.1 | 3.2 | 3.3 * | 3.2 |
| | | SD | 0.1 | 0.1 | 0.1 | 0.1 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | | 2.2 | 4.1 | 1.9 |
| GLOB (g/dL) | 22 | Mean | 2.9 | 2.8 | 2.9 | 2.8 |
| | | SD | 0.1 | 0.2 | 0.1 | 0.2 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | | -1.0 | 1.4 | -1.7 |
| CALC (mg/dL) | 22 | Mean | 10.4 | 10.4 | 10.4 | 10.5 |
| | | SD | 0.2 | 0.2 | 0.2 | 0.2 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | | -0.1 | 0.1 | 0.8 |
| IPHS (mg/dL) | 22 | Mean | 8.8 | 8.7 | 8.8 | 8.6 |
| | | SD | 0.4 | 0.4 | 0.9 | 0.4 |
| | | N | 5 | 9 | 8 | 8 |
| | | %Diff | | 0.6 | 2.1 | -0.3 |
| NA (mmol/L) | 22 | Mean | 140.5 | 142.1 | 141.1 | 141.7 |
| | | SD | 4.2 | 0.6 | 0.7 | 0.8 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | | 1.1 | 0.4 | 0.9 |

General Footnote: [Statistical Test: Anova and Dunnett's test Transformation: Automatic]
1 [#: Test: Dunnett 2 Sided p < 0.05]

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

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Table 5
Summary of Clinical Chemistry Values for Male Rats (Continued)

| Sex: Male | Day(s) Relative to Start Date | | 0 mg/kg/day Group 1 | 512 mg/kg/day Group 2 | 1024 mg/kg/day Group 3 | 1536 mg/kg/day Group 4 |
|---|---|---|---|---|---|---|
| K (mmol/L) | 22 | Mean | 5.03 | 5.19 | 5.55 * | 5.10 |
| | | SD | 0.25 | 0.26 | 0.81 | 0.25 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | | 3.1 | 10.4 | 1.4 |
| CL (mmol/L) | 22 | Mean | 100.8 | 102.0 | 101.6 | 101.7 |
| | | SD | 2.4 | 1.0 | 0.9 | 1.2 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | | 1.2 | 0.8 | 0.9 |

General Footnote: [Statistical Test: Anova and Dunnett's test Transformation: Automatic]
1 [#- Test: Dunnett 2 Sided p < 0.05]

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

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## Table 6
## Summary of Clinical Chemistry Values for Female Rats

| Sex: Female | Day(s) Relative to Start Date | | 0 mg/kg/day Group 1 | 512 mg/kg/day Group 2 | 1024 mg/kg/day Group 3 | 1536 mg/kg/day Group 4 |
|---|---|---|---|---|---|---|
| AST (U/L) | 22 | Mean | 69 | 69 | 64 | 65 |
| | | SD | 6 | 10 | 8 | 6 |
| | | N | 9 | 9 | 10 | 10 |
| | | %Diff | | -0.3 | -7.4 | -6.5 |
| ALT (U/L) | 22 | Mean | 25 | 26 | 25 | 27 |
| | | SD | 4 | 5 | 6 | 5 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | | 2.8 | -0.4 | 5.2 |
| SDH (U/L) | 22 | Mean | 8.7 | 8.1 | 8.0 | 9.9 |
| | | SD | 2.2 | 1.2 | 0.9 | 2.5 |
| | | N | 9 | 9 | 10 | 10 |
| | | %Diff | | -7.4 | -8.0 | 12.9 |
| ALKP (U/L) | 22 | Mean | 137 | 107 * | 121 | 108 * |
| | | SD | 16 | 19 | 29 | 25 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | | -22.4 | -12.1 | -21.3 |
| BIU (mg/dL) | 22 | Mean | 0.18 | 0.19 | 0.20 | 0.19 |
| | | SD | 0.02 | 0.02 | 0.02 | 0.03 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | | 8.4 | 10.8 | 7.8 |
| BUN (mg/dL) | 22 | Mean | 12 | 11 | 12 | 12 |
| | | SD | 2 | 1 | 2 | 1 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | | -11.5 | -0.8 | 0.0 |
| CREA (mg/dL) | 22 | Mean | 0.28 | 0.28 | 0.27 | 0.29 |
| | | SD | 0.02 | 0.02 | 0.03 | 0.03 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | | -0.9 | -2.9 | 1.1 |
| CHOL (mg/dL) | 22 | Mean | 85 | 95 | 98 | 94 |
| | | SD | 11 | 18 | 19 | 22 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | | 12.2 | 15.6 | 11.2 |

General Footnote: [Statistical Test: Anova and Dunnett's test Transformation: Automatic]
1 [#- Test: Dunnett 2 Sided p < 0.05]

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

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## Table 6
## Summary of Clinical Chemistry Values for Female Rats (Continued)

| Sex Female | Day(s) Relative to Start Date | | 0 mg/kg/day Group 1 | 512 mg/kg/day Group 2 | 1024 mg/kg/day Group 3 | 1536 mg/kg/day Group 4 |
|---|---|---|---|---|---|---|
| TRIG (mg/dL) | 22 | Mean | 37 | 38 | 46 | 35 |
| | | SD | 6 | 9 | 15 | 8 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | | 3.5 | 24.9 | -4.3 |
| GLUC (mg/dL) | 22 | Mean | 118 | 103 * | 104 * | 110 |
| | | SD | 15 | 10 | 10 | 14 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | | -13.3 | -12.0 | -6.7 |
| TP (g/dL) | 22 | Mean | 6.4 | 6.7 | 6.8 | 6.7 |
| | | SD | 0.3 | 0.4 | 0.3 | 0.4 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | | 5.1 | 5.6 | 3.7 |
| ALB (g/dL) | 22 | Mean | 3.5 | 3.7 | 3.7 | 3.6 |
| | | SD | 0.2 | 0.2 | 0.2 | 0.3 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | | 4.0 | 4.6 | 3.4 |
| GLOB (g/dL) | 22 | Mean | 2.9 | 3.1 | 3.1 * | 3.0 |
| | | SD | 0.1 | 0.2 | 0.2 | 0.1 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | | 6.6 | 6.9 | 4.1 |
| CALC (mg/dL) | 22 | Mean | 10.5 | 10.9 * | 11.0 * | 10.7 |
| | | SD | 0.3 | 0.3 | 0.3 | 0.4 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | | 3.8 | 5.1 | 1.8 |
| IPHS (mg/dL) | 22 | Mean | 7.1 | 7.8 | 7.6 | 7.1 |
| | | SD | 0.5 | 0.6 | 0.4 | 0.8 |
| | | N | 9 | 9 | 10 | 10 |
| | | %Diff | | 9.7 | 6.5 | -0.6 |
| NA (mmol/L) | 22 | Mean | 140.3 | 140.6 | 140.3 | 140.2 |
| | | SD | 1.1 | 0.6 | 0.7 | 1.1 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | | 0.2 | 0.0 | 0.0 |

General Footnote [Statistical Test: Anova and Dunnett's test Transformation Automatic]
1 [* - Test Dunnett 2 Sided p < 0.05]

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
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Table 6
Summary of Clinical Chemistry Values for Female Rats (Continued)

| Sex: Female | Day(s) Relative to Start Date | | 0 mg/kg/day Group 1 | 512 mg/kg/day Group 2 | 1024 mg/kg/day Group 3 | 1536 mg/kg/day Group 4 |
|---|---|---|---|---|---|---|
| K (mmol/L) | 22 | Mean | 4.56 | 4.63 | 4.72 | 4.74 |
| | | SD | 0.33 | 0.38 | 0.21 | 0.38 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | | 1.5 | 3.5 | 4.0 |
| CL (mmol/L) | 22 | Mean | 102.8 | 101.3 #* | 101.1 #* | 102.1 |
| | | SD | 1.2 | 1.4 | 1.0 | 1.1 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | | -1.3 | -1.5 | -0.5 |

General Footnote: [Statistical Test: Anova and Dunnett's test Transformation: Automatic]
1 [#- Test: Dunnett 2 Sided p < 0.05]

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

Clinical Pathology Results for
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## Table 7
## Summary of Urinalysis Values for Male Rats

| Sex: Male | Day(s) Relative to Start Date | | 0 mg/kg/day Group 1 | 512 mg/kg/day Group 2 | 1024 mg/kg/day Group 3 | 1536 mg/kg/day Group 4 |
|---|---|---|---|---|---|---|
| UVOL (mL) | 22 | Mean | 11.7 | 11.5 | 12.3 | 14.3 |
| | | SD | 8.2 | 9.8 | 7.3 | 7.7 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | | -1.8 | 4.8 | 22.0 |
| pH | 22 | Mean | 6.5 | 6.5 | 6.6 | 6.6 |
| | | SD | 0.3 | 0.4 | 0.4 | 0.4 |
| | | N | 10 | 9 | 10 | 10 |
| | | %Diff | | 0.0 | 0.8 | 1.5 |
| SG | 22 | Mean | 1.027 | 1.027 | 1.026 | 1.024 |
| | | SD | 0.019 | 0.015 | 0.015 | 0.019 |
| | | N | 10 | 9 | 10 | 10 |
| | | %Diff | | 0.0 | -0.1 | -0.3 |
| URO (EU/dL) | 22 | Mean | 0.3 | 0.2 | 0.3 | 0.2 |
| | | SD | 0.3 | 0.0 | 0.3 | 0.0 |
| | | N | 10 | 9 | 10 | 10 |
| | | %Diff | | -28.6 | 0.0 | -28.6 |
| UMTP (mg/dL) | 22 | Mean | 104 | 241 | 124 | 111 |
| | | SD | 49 | 365 | 80 | 97 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | | 132.5 | 19.5 | 7.4 |

General Footnote: [Statistical Test: Anova and Dunnett's test Transformation: Autoscale]

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
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Table 8
Summary of Urinalysis Values for Female Rats

| Sex: Female | Day(s) Relative to Start Date | | 0 mg/kg/day Group 1 | 512 mg/kg/day Group 2 | 1024 mg/kg/day Group 3 | 1536 mg/kg/day Group 4 |
|---|---|---|---|---|---|---|
| UVOL (mL) | 22 | Mean | 7.9 | 6.8 | 6.5 | 6.8 |
| | | SD | 6.4 | 5.1 | 3.0 | 4.1 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | | -12.3 | -15.9 | -14.9 |
| pH | 22 | Mean | 6.4 | 6.2 | 6.6 | 6.5 |
| | | SD | 0.4 | 0.4 | 0.6 | 0.6 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | | -3.9 | 3.1 | 0.8 |
| SG | 22 | Mean | 1.037 | 1.035 | 1.028 | 1.030 |
| | | SD | 0.027 | 0.023 | 0.011 | 0.013 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | | -0.2 | -0.8 | -0.6 |
| URO (EU/dL) | 22 | Mean | 0.2 | 0.2 | 0.2 | 0.3 |
| | | SD | 0.0 | 0.0 | 0.0 | 0.3 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | | 0.0 | 0.0 | 40.0 |
| UMTP (mg/dL) | 22 | Mean | 43 | 41 | 34 | 44 |
| | | SD | 34 | 25 | 12 | 30 |
| | | N | 10 | 10 | 10 | 10 |
| | | %Diff | | -2.7 | -20.0 | 2.5 |

General Footnote: [Statistical Test: Anova and Dunnett's test Transformation: Automatic]

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

**Appendix A**
**Individual Animal Clinical Pathology Data**

Clinical Pathology Results for
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## INDIVIDUAL ANIMAL CLINICAL PATHOLOGY DATA

## EXPLANATORY NOTES

ABBREVIATIONS:

General:

| | | |
|---|---|---|
| - | - | not observed |
| . | - | not taken, not performed, not observed, or results not valid |
| Man | - | many |
| Mod | - | moderate |
| NPH | - | not performed due to hemolysis |
| OK | - | sample condition OK for testing |
| ppm | - | parts per million |
| QNS | - | sample quantity not sufficient for testing |

Individual Hematology Values:

| | | |
|---|---|---|
| WB | - | whole blood condition |
| RBC | - | red blood cell count |
| HGB | - | hemoglobin |
| HCT | - | hematocrit |
| MCV | - | mean corpuscular (cell) volume |
| MCH | - | mean corpuscular (cell) hemoglobin |
| MCHC | - | mean corpuscular (cell) hemoglobin concentration |
| RDW | - | red cell distribution width |
| PLT | - | platelet count |
| WBC | - | white blood cell count |
| ANEU | - | absolute neutrophil (all forms) |
| ALYM | - | absolute lymphocyte |
| AMON | - | absolute monocyte |
| AEOS | - | absolute eosinophil |
| ABAS | - | absolute basophil |
| ALUC | - | absolute large unstained cell |
| ARET | - | absolute reticulocyte |

Individual Coagulation Values:

| | | |
|---|---|---|
| PHEM | - | plasma hemolysis |
| PLIP | - | plasma lipemia |
| PICT | - | plasma icterus |
| PT | - | prothrombin time |
| APTT | - | activated partial thromboplastin time |

Clinical Pathology Results for
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## INDIVIDUAL ANIMAL CLINICAL PATHOLOGY DATA

### EXPLANATORY NOTES (Continued)

ABBREVIATIONS: (Continued)

Individual Clinical Chemistry Values:

| | | |
|---|---|---|
| HEM | - | hemolysis |
| LIP | - | lipemia |
| ICT | - | icterus |
| AST | - | aspartate aminotransferase |
| ALT | - | alanine aminotransferase |
| SDH | - | sorbitol dehydrogenase |
| ALKP | - | alkaline phospharase |
| BILI | - | total bilirubin |
| BUN | - | urea nitrogen |
| CREA | - | creatinine |
| CHOL | - | cholesterol |
| TRIG | - | triglycerides |
| GLUC | - | glucose |
| TP | - | total protein |
| ALB | - | albumin |
| GLOB | - | globulin |
| CALC | - | calcium |
| IPHS | - | inorganic phosphorous |
| NA | - | sodium |
| K | - | potassium |
| CL | - | chloride |

Individual Urinalysis Values:

| | | |
|---|---|---|
| QUAL | - | quality (modifies color) |
| COL | - | color |
| CLAR | - | clarity |
| UVOL | - | volume |
| pH | - | the logarithm of the reciprocal of the hydrogen ion concentration |
| SG | - | specific gravity |
| UGLC | - | Glucose |
| KET | - | ketone |
| UBIL | - | bilirubin |
| BLD | - | blood |
| URO | - | urobilinogen |
| UMTP | - | protein |

Individual Urine Microscopic Examination Values:

| | | |
|---|---|---|
| EPIT | - | epithelial cells |
| UWBC | - | urine white blood cells |
| URBC | - | urine red blood cells |
| NCRY | - | normal crystals |
| MICR | - | microorganisms |
| SPER | - | sperm |
| REPI | - | renal epithelial cell |
| MUC | - | mucus strand |

## INDIVIDUAL ANIMAL CLINICAL PATHOLOGY DATA

### EXPLANATORY NOTES (Continued)

NOTES:

When individual animal data are not reported, it may be due to one of the following reasons or other reasons:
the sample was clotted (CLOT)
there was insufficient sample for testing (QNS)
a valid result could not be obtained (RNV)
the sample was not suitable for testing
the animal died prior to sample collection
no sample was available for testing (NSR)

Only positive findings were recorded for special observations (e.g., additional cell types) or observations marked other.

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

[illegible]

Sex: Male Day(s) Relative to Start Date

| n mg/kg/day Group 1 | CBC/DIFF/RETIC Comp1 | | | | | | |
|---|---|---|---|---|---|---|---|
| | WB | RBC (x10^6/µL) | HGB (g/dL) | HCT (%) | MCV (fL) | MCH (pg) | MCHC (g/dL) |
| | 22 | 22 | 22 | 22 | 22 | 22 | 22 |
| 7001 | OK | 7.48 | 15.5 | 44.6 | 59.6 | 20.8 | 34.9 |
| 7002 | OK | 7.69 | 15.2 | 44.5 | 57.9 | 19.8 | 34.2 |
| 7003 | OK | 7.65 | 15.5 | 45.1 | 58.9 | 20.3 | 34.5 |
| 7004 | OK | 8.10 | 16.1 | 47.5 | 58.7 | 19.9 | 33.9 |
| 7005 | OK | 7.69 | 15.5 | 45.0 | 58.6 | 20.1 | 34.3 |
| 7006 | OK | 7.37 | 15.4 | 45.0 | 61.0 | 20.9 | 34.3 |
| 7007 | OK | 7.55 | 15.4 | 45.1 | 59.7 | 20.5 | 34.2 |
| 7008 | OK | 7.95 | 15.6 | 45.6 | 57.4 | 19.6 | 34.1 |
| 7009 | OK | 7.79 | 16.2 | 45.8 | 58.8 | 20.8 | 35.3 |
| 7010 | OK | 7.96 | 16.0 | 46.5 | 58.4 | 20.0 | 34.3 |

Sex: Male Day(s) Relative to Start Date

| n mg/kg/day Group 1 | CBC/DIFF/RETIC Comp1 | | | | | | |
|---|---|---|---|---|---|---|---|
| | RDW (%) | PLT (x10^3/µL) | WBC (x10^3/µL) | ANEU (x10^3/µL) | ALYM (x10^3/µL) | AMON (x10^3/µL) | ABOS (x10^3/µL) |
| | 22 | 22 | 22 | 22 | 22 | 22 | 22 |
| 7001 | 12.0 | 1128 | 15.34 | 2.24 | 12.17 | 0.31 | 0.11 |
| 7002 | 11.7 | 1118 | 11.88 | 1.52 | 9.71 | 0.31 | 0.21 |
| 7003 | 11.9 | 1217 | 10.89 | 1.20 | 9.30 | 0.16 | 0.08 |
| 7004 | 12.2 | 1078 | 13.86 | 3.17 | 10.19 | 0.29 | 0.11 |
| 7005 | 12.8 | 1229 | 14.23 | 1.34 | 12.39 | 0.18 | 0.07 |
| 7006 | 12.1 | 960 | 13.27 | 1.69 | 10.75 | 0.50 | 0.15 |
| 7007 | 12.0 | 1076 | 12.24 | 1.35 | 10.01 | 0.35 | 0.13 |
| 7008 | 12.2 | 1142 | 13.54 | 1.95 | 11.08 | 0.22 | 0.09 |
| 7009 | 12.0 | 1240 | 11.73 | 1.51 | 9.48 | 0.39 | 0.14 |
| 7010 | 12.3 | 1406 | 13.02 | 2.92 | 9.48 | 0.36 | 0.13 |

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

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Individual Animal Clinical Path Data

Sex: Male Days to Relative to Start Date

| D mg/kg/day Group 1 | AHAS (x10^3/uL) | ALT (x10^3/uL) | ARET (x10^3/uL) |
|---|---|---|---|
| | 22 | 22 | 22 |
| 7001 | 0.11 | 0.11 | 241.2 |
| 7002 | 0.06 | 0.06 | 225.6 |
| 7003 | 0.07 | 0.08 | 213.2 |
| 7004 | 0.06 | 0.06 | 233.5 |
| 7005 | 0.13 | 0.13 | 295.6 |
| 7006 | 0.04 | 0.13 | 268.3 |
| 7007 | 0.10 | 0.07 | 233.9 |
| 7008 | 0.14 | 0.07 | 197.9 |
| 7009 | 0.12 | 0.08 | 180.8 |
| 7010 | 0.10 | 0.04 | 226.2 |

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient.
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

Sex: Male  Days: Relative to Start Date

| 512 mg/kg/day Group 2 | CBC/DIFF/RETIC (cont) | | | | | | |
|---|---|---|---|---|---|---|---|
| | WB | RBC | HGB | HCT | MCV | MCH | MCHC |
| | | (x10^6/µL) | (g/dL) | (%) | (fL) | (pg) | (g/dL) |
| | 22 | 22 | 22 | 22 | 22 | 22 | 22 |
| 7021 | OK | 7.66 | 16.6 | 47.6 | 62.0 | 21.6 | 34.8 |
| 7022 | OK | 8.15 | 15.1 | 45.1 | 55.3 | 18.6 | 33.6 |
| 7023 | OK | 7.74 | 15.3 | 45.3 | 58.5 | 19.8 | 33.9 |
| 7024 | OK | 7.28 | 14.7 | 42.8 | 58.8 | 20.2 | 34.4 |
| 7025 | OK | 7.10 | 13.9 | 41.7 | 59.0 | 20.1 | 34.9 |
| 7026 | OK | 7.09 | 14.9 | 43.3 | 61.1 | 21.0 | 34.4 |
| 7027 | OK | 8.06 | 15.7 | 46.2 | 57.3 | 19.5 | 33.9 |
| 7028 | OK | 7.74 | 15.5 | 44.7 | 57.7 | 20.0 | 34.7 |
| 7029 | OK | 7.52 | 15.7 | 43.9 | 61.0 | 20.9 | 34.3 |
| 7030 | OK | 7.34 | 15.7 | 46.0 | 62.6 | 21.4 | 34.2 |

Sex: Male  Days: Relative to Start Date

| 512 mg/kg/day Group 2 | CBC/DIFF/RETIC (cont) | | | | | | |
|---|---|---|---|---|---|---|---|
| | RDW | PLT | WBC | ASEG | ALYM | AMON | ABSO |
| | (%) | (x10^3/µL) | (x10^3/µL) | (x10^3/µL) | (x10^3/µL) | (x10^3/µL) | (x10^3/µL) |
| | 22 | 22 | 22 | 22 | 22 | 22 | 22 |
| 7021 | 12.7 | 1315 | 13.10 | 1.55 | 11.99 | 0.28 | 0.10 |
| 7022 | 12.9 | 1136 | 16.79 | 2.38 | 13.33 | 0.44 | 0.35 |
| 7023 | 13.0 | 1207 | 11.65 | 1.13 | 10.08 | 0.27 | 0.07 |
| 7024 | 12.1 | 1265 | 13.53 | 1.36 | 11.28 | 0.26 | 0.11 |
| 7025 | 13.2 | 1195 | 12.75 | 2.30 | 9.74 | 0.28 | 0.08 |
| 7026 | 12.5 | 1172 | 13.87 | 1.79 | 11.60 | 0.24 | 0.10 |
| 7027 | 11.7 | 1358 | 11.49 | 2.09 | 8.76 | 0.54 | 0.10 |
| 7028 | 12.5 | 1301 | 23.57 | 2.16 | 17.81 | 0.25 | 0.12 |
| 7029 | 12.1 | 1229 | 14.95 | 2.26 | 11.96 | 0.45 | 0.13 |
| 7030 | 12.1 | 1185 | 14.36 | 2.34 | 11.34 | 0.41 | 0.15 |

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

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Individual Animal Clinical Pathology Data

Sex: Male Days: Relative to Start Date

| 512 mg/kg/day Group 2 | ABAS (x10^3/µL) | ALUC (x10^3/µL) | ARET (x10^3/µL) |
|---|---|---|---|
| | 22 | 22 | 22 |
| 7021 | 0.13 | 0.06 | 282.3 |
| 7022 | 0.13 | 0.13 | 224.6 |
| 7023 | 0.07 | 0.05 | 197.6 |
| 7024 | 0.07 | 0.05 | 225.0 |
| 7025 | 0.08 | 0.06 | 265.7 |
| 7026 | 0.08 | 0.07 | 220.8 |
| 7027 | 0.05 | 0.06 | 230.8 |
| 7028 | 0.14 | 0.08 | 167.9 |
| 7029 | 0.04 | 0.10 | 234.9 |
| 7030 | 0.07 | 0.09 | 308.3 |

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

[illegible]

Sex: Male Days(s) Relative to Start Date

| 1024 mg/kg/day Group 3 | CBC/DIFF/RETIC Compl | | | | | | |
|---|---|---|---|---|---|---|---|
| | WD | RBC (x10^6/µL) | HGD (g/dL) | HCT (%) | MCV (fL) | MCH (pg) | MCHC (g/dL) |
| | 22 | 22 | 22 | 22 | 22 | 22 | 22 |
| 7041 | OK | 7.74 | 15.2 | 44.6 | 57.6 | 19.6 | 34.1 |
| 7042 | OK | 7.77 | 16.1 | 46.7 | 60.2 | 20.8 | 34.5 |
| 7043 | OK | 7.76 | 15.4 | 45.3 | 58.4 | 19.9 | 34.1 |
| 7044 | OK | 7.72 | 15.9 | 46.7 | 60.5 | 20.6 | 34.1 |
| 7045 | OK | 7.87 | 16.1 | 46.2 | 58.7 | 20.4 | 34.8 |
| 7046 | OK | 6.75 | 14.1 | 40.7 | 59.9 | 20.8 | 34.8 |
| 7047 | OK | 7.45 | 15.5 | 45.5 | 61.1 | 20.8 | 34.1 |
| 7048 | OK | 7.25 | 15.2 | 44.4 | 61.2 | 21.0 | 34.3 |
| 7049 | OK | 7.91 | 15.7 | 45.0 | 56.9 | 19.8 | 34.8 |
| 7050 | OK | 7.81 | 15.7 | 46.0 | 58.9 | 20.2 | 34.2 |

Sex: Male Days(s) Relative to Start Date

| 1024 mg/kg/day Group 3 | CBC/DIFF/RETIC Compl | | | | | | |
|---|---|---|---|---|---|---|---|
| | RDW (%) | PLT (x10^3/µL) | WBC (x10^3/µL) | ANEU (x10^3/µL) | ALYM (x10^3/µL) | AMON (x10^3/µL) | ABOS (x10^3/µL) |
| | 22 | 22 | 22 | 22 | 22 | 22 | 22 |
| 7041 | 12.1 | 1286 | 11.55 | 1.64 | 9.45 | 0.25 | 0.08 |
| 7042 | 12.5 | 1167 | 14.92 | 2.07 | 12.20 | 0.28 | 0.16 |
| 7043 | 12.3 | 1228 | 12.44 | 2.31 | 9.52 | 0.37 | 0.11 |
| 7044 | 13.0 | 1133 | 10.33 | 1.87 | 7.96 | 0.26 | 0.12 |
| 7045 | 12.1 | 1007 | 9.46 | 1.94 | 7.03 | 0.26 | 0.11 |
| 7046 | 12.5 | 1209 | 11.47 | 1.89 | 8.91 | 0.32 | 0.19 |
| 7047 | 12.6 | 1159 | 10.04 | 1.58 | 7.95 | 0.31 | 0.10 |
| 7048 | 12.6 | 1232 | 12.44 | 1.08 | 10.95 | 0.25 | 0.05 |
| 7049 | 12.9 | 1123 | 8.79 | 1.03 | 7.34 | 0.22 | 0.07 |
| 7050 | 12.6 | 1169 | 9.86 | 2.12 | 7.29 | 0.25 | 0.13 |

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

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Individual Animal Clinical Pathology Data

Sex: Male Days Relative to Start Date

| 1024 mg/kg/day Group 3 | ABAS (x10^3/µL) | ALUC* (x10^3/µL) | AREF (x10^3/µL) |
|---|---|---|---|
| | 22 | 22 | 22 |
| 7041 | 0.05 | 0.08 | 270.7 |
| 7042 | 0.09 | 0.10 | 228.3 |
| 7043 | 0.06 | 0.06 | 293.3 |
| 7044 | 0.06 | 0.04 | 235.3 |
| 7045 | 0.08 | 0.05 | 222.1 |
| 7046 | 0.07 | 0.08 | 265.6 |
| 7047 | 0.07 | 0.05 | 243.9 |
| 7048 | 0.06 | 0.05 | 245.0 |
| 7049 | 0.09 | 0.04 | 211.8 |
| 7050 | 0.04 | 0.04 | 244.2 |

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

[illegible]

Sex: Male Days Relative to Start Date

| 1536 mg/kg/day Group 4 | CBC/DIFF/RETIC Comp C | | | | | | |
|---|---|---|---|---|---|---|---|
| | WB | RBC (x10^6/µL) | HGB (g/dL) | HCT (%) | MCV (fL) | MCH (pg) | MCHC (g/dL) |
| | 22 | 22 | 22 | 22 | 22 | 22 | 22 |
| 7061 | OK | 8.23 | 15.9 | 46.6 | 56.6 | 19.3 | 34.1 |
| 7062 | OK | 7.75 | 15.8 | 45.4 | 58.5 | 20.4 | 34.9 |
| 7063 | OK | 7.59 | 15.9 | 45.5 | 59.9 | 21.0 | 35.0 |
| 7064 | OK | 7.36 | 16.1 | 47.1 | 63.9 | 21.8 | 34.2 |
| 7065 | OK | 7.84 | 16.2 | 46.4 | 59.2 | 20.6 | 34.8 |
| 7066 | OK | 7.40 | 14.0 | 44.8 | 60.5 | 20.2 | 33.3 |
| 7067 | OK | 7.64 | 15.9 | 45.5 | 59.6 | 20.8 | 34.9 |
| 7068 | OK | 7.62 | 15.7 | 45.1 | 59.2 | 20.5 | 34.7 |
| 7069 | OK | 8.06 | 16.3 | 46.9 | 58.6 | 20.1 | 34.4 |
| 7070 | OK | 7.58 | 16.1 | 45.9 | 60.5 | 21.2 | 35.0 |

Sex: Male Days Relative to Start Date

| 1536 mg/kg/day Group 4 | CBC/DIFF/RETIC Comp C | | | | | | |
|---|---|---|---|---|---|---|---|
| | WB | RBC (x10^6/µL) | HGB (g/dL) | HCT (%) | MCV (fL) | MCH (pg) | MCHC (g/dL) |
| | 22 | 22 | 22 | 22 | 22 | 22 | 22 |
| 7061 | OK | 8.23 | 15.9 | 46.6 | 56.6 | 19.3 | 34.1 |
| 7062 | OK | 7.75 | 15.8 | 45.4 | 58.5 | 20.4 | 34.9 |
| 7063 | OK | 7.59 | 15.9 | 45.5 | 59.9 | 21.0 | 35.0 |
| 7064 | OK | 7.36 | 16.1 | 47.1 | 63.9 | 21.8 | 34.2 |
| 7065 | OK | 7.84 | 16.2 | 46.4 | 59.2 | 20.6 | 34.8 |
| 7066 | OK | 7.40 | 14.0 | 44.8 | 60.5 | 20.2 | 33.3 |
| 7067 | OK | 7.64 | 15.9 | 45.5 | 59.6 | 20.8 | 34.9 |
| 7068 | OK | 7.62 | 15.7 | 45.1 | 59.2 | 20.5 | 34.7 |
| 7069 | OK | 8.06 | 16.3 | 46.9 | 58.6 | 20.1 | 34.4 |
| 7070 | OK | 7.58 | 16.1 | 45.9 | 60.5 | 21.2 | 35.0 |

Group 2: 512 mg/kg/day of test substance corresponds to 290 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 580 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

Individual Animal Clinical Pathology Data

Sex: Male Days to Relative to Start Date

| 1536 mg/kg/day Group 4 | ABAS (x10^3/µL) | ALUC (x10^3/µL) | ARET (x10^3/µL) |
|---|---|---|---|
| | 22 | 22 | 22 |
| 7061 | 0.06 | 0.06 | 208.5 |
| 7062 | 0.09 | 0.04 | 238.4 |
| 7063 | 0.21 | 0.09 | 310.6 |
| 7064 | 0.10 | 0.10 | 319.9 |
| 7065 | 0.12 | 0.06 | 242.2 |
| 7066 | 0.05 | 0.07 | 224.8 |
| 7067 | 0.06 | 0.14 | 249.9 |
| 7068 | 0.17 | 0.15 | 194.5 |
| 7069 | 0.05 | 0.04 | 235.2 |
| 7070 | 0.05 | 0.06 | 214.2 |

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

[illegible]

Sex: Female Day(s) Relative to Start Date

| n mg/kg/day Group 1 | CBC/DIFF RETIC Comp1 | | | | | | |
|---|---|---|---|---|---|---|---|
| | WB | RBC (x10^6/µL) | HGB (g/dL) | HCT (%) | MCV (fL) | MCH (pg) | MCHC (g/dL) |
| | 22 | 22 | 22 | 22 | 22 | 22 | 22 |
| 7011 | OK | 7.71 | 15.7 | 43.5 | 56.4 | 20.4 | 36.1 |
| 7012 | OK | 7.82 | 15.7 | 44.8 | 57.2 | 20.1 | 35.2 |
| 7013 | OK | 7.22 | 14.8 | 42.4 | 58.8 | 20.5 | 34.9 |
| 7014 | OK | 7.72 | 15.6 | 44.4 | 57.5 | 20.2 | 35.1 |
| 7015 | OK | 7.33 | 15.0 | 43.3 | 59.2 | 20.5 | 34.7 |
| 7016 | OK | 7.41 | 14.6 | 42.4 | 57.3 | 19.7 | 34.4 |
| 7017 | OK | 7.93 | 16.1 | 44.5 | 56.1 | 20.4 | 36.3 |
| 7018 | OK | 7.76 | 15.6 | 45.5 | 58.6 | 20.1 | 34.3 |
| 7019 | OK | 7.67 | 15.4 | 43.5 | 56.7 | 20.1 | 35.5 |
| 7020 | OK | 7.33 | 14.7 | 41.6 | 56.7 | 20.0 | 35.3 |

Sex: Female Day(s) Relative to Start Date

| n mg/kg/day Group 1 | CBC/DIFF RETIC Comp1 | | | | | | |
|---|---|---|---|---|---|---|---|
| | RDW (%) | PLT (x10^3/µL) | WBC (x10^3/µL) | ANEU (x10^3/µL) | ALYM (x10^3/µL) | AMON (x10^3/µL) | ABOS (x10^3/µL) |
| | 22 | 22 | 22 | 22 | 22 | 22 | 22 |
| 7011 | 11.2 | 1268 | 9.60 | 1.42 | 7.95 | 0.16 | 0.08 |
| 7012 | 10.8 | 1173 | 8.81 | 1.49 | 6.96 | 0.21 | 0.10 |
| 7013 | 11.1 | 1262 | 9.63 | 1.65 | 7.43 | 0.36 | 0.11 |
| 7014 | 11.2 | 1084 | 10.65 | 1.35 | 8.92 | 0.14 | 0.10 |
| 7015 | 11.2 | 1217 | 8.53 | 2.00 | 6.24 | 0.13 | 0.09 |
| 7016 | 11.6 | 1126 | 11.48 | 1.80 | 9.02 | 0.40 | 0.17 |
| 7017 | 10.8 | 1123 | 8.94 | 0.87 | 7.73 | 0.13 | 0.13 |
| 7018 | 12.3 | 1004 | 11.97 | 1.38 | 10.14 | 0.19 | 0.13 |
| 7019 | 11.1 | 1371 | 13.21 | 1.48 | 10.90 | 0.58 | 0.09 |
| 7020 | 11.5 | 1269 | 7.89 | 1.33 | 6.20 | 0.21 | 0.10 |

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1025 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1526 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

Individual Animal Clinical Pathology Data

Sex: Female Day(s) Relative to Start Date

| 6 mg/kg/day Group 1 | ADAS (x10^3/µL) | ALUC (x10^3/µL) | ARET (x10^3/µL) |
|---|---|---|---|
| | 22 | 22 | 22 |
| 7011 | 0.05 | 0.03 | 151.8 |
| 7012 | 0.02 | 0.04 | 192.8 |
| 7013 | 0.02 | 0.06 | 205.3 |
| 7014 | 0.04 | 0.09 | 215.0 |
| 7015 | 0.03 | 0.03 | 243.8 |
| 7016 | 0.03 | 0.05 | 153.5 |
| 7017 | 0.03 | 0.04 | 226.8 |
| 7018 | 0.05 | 0.07 | 252.5 |
| 7019 | 0.07 | 0.09 | 194.2 |
| 7020 | 0.02 | 0.04 | 222.0 |

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

[illegible]

Sex: Female Day(s) Relative to Start Date

| 512 mg/kg/day Group 2 | CBC/DIFF/RETIC Compl. | | | | | | |
|---|---|---|---|---|---|---|---|
| | WB | RBC (x10^6/µL) | HGB (g/dL) | HCT (%) | MCV (fL) | MCH (pg) | MCHC (g/dL) |
| | 22 | 22 | 22 | 22 | 22 | 22 | 22 |
| 7031 | OK | 8.35 | 16.2 | 45.4 | 54.4 | 19.4 | 35.6 |
| 7032 | OK | 8.42 | 16.9 | 47.4 | 56.3 | 20.6 | 35.6 |
| 7033 | OK | 8.13 | 15.5 | 44.5 | 54.8 | 19.1 | 34.8 |
| 7034 | OK | 7.89 | 16.1 | 46.0 | 58.3 | 20.4 | 34.9 |
| 7035 | OK | 7.36 | 15.7 | 44.5 | 61.0 | 21.5 | 35.3 |
| 7036 | OK | 7.93 | 16.5 | 46.3 | 58.4 | 20.8 | 35.5 |
| 7037 | OK | 8.48 | 16.5 | 46.4 | 54.8 | 19.5 | 35.6 |
| 7038 | OK | 7.50 | 16.2 | 46.1 | 59.2 | 20.7 | 35.1 |
| 7039 | OK | 8.21 | 16.7 | 47.7 | 58.1 | 20.4 | 35.1 |
| 7040 | OK | 7.63 | 15.7 | 44.4 | 58.2 | 20.5 | 35.3 |

Sex: Female Day(s) Relative to Start Date

| 512 mg/kg/day Group 2 | CBC/DIFF/RETIC Compl. | | | | | | |
|---|---|---|---|---|---|---|---|
| | RDW (%) | PLT (x10^3/µL) | WBC (x10^3/µL) | ANEU (x10^3/µL) | ALYM (x10^3/µL) | AMOS (x10^3/µL) | ABOS (x10^3/µL) |
| | 22 | 22 | 22 | 22 | 22 | 22 | 22 |
| 7031 | 11.3 | 1067 | 11.94 | 0.92 | 10.44 | 0.32 | 0.11 |
| 7032 | 11.8 | 1387 | 10.43 | 0.99 | 9.05 | 0.19 | 0.08 |
| 7033 | 11.1 | 1159 | 16.00 | 2.26 | 13.15 | 0.32 | 0.10 |
| 7034 | 10.3 | 1172 | 9.70 | 1.45 | 7.97 | 0.21 | 0.09 |
| 7035 | 11.3 | 1368 | 12.45 | 2.38 | 9.47 | 0.37 | 0.69 |
| 7036 | 11.4 | 1276 | 11.46 | 1.99 | 8.80 | 0.36 | 0.19 |
| 7037 | 10.8 | 1107 | 12.95 | 1.79 | 10.55 | 0.26 | 0.17 |
| 7038 | 11.9 | 1075 | 10.91 | 0.74 | 9.50 | 0.32 | 0.16 |
| 7039 | 11.2 | 1048 | 10.62 | 1.20 | 8.78 | 0.34 | 0.17 |
| 7040 | 11.8 | 1069 | 12.10 | 1.84 | 9.70 | 0.24 | 0.17 |

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

Individual Animal Clinical Pathology Data

Sex: Female Days(s) Relative to Start Date

| 512 mg/kg/day Group 2 | ABAS (x10^3/µL) | ALUC (x10^3/µL) | ARET (x10^3/µL) |
|---|---|---|---|
| | 22 | 22 | 22 |
| 7031 | 0.07 | 0.06 | 155.8 |
| 7032 | 0.04 | 0.06 | 199.4 |
| 7033 | 0.10 | 0.10 | 205.1 |
| 7034 | 0.03 | 0.05 | 163.2 |
| 7035 | 0.06 | 0.06 | 214.8 |
| 7036 | 0.06 | 0.07 | 222.9 |
| 7037 | 0.09 | 0.09 | 133.1 |
| 7038 | 0.12 | 0.07 | 137.0 |
| 7039 | 0.07 | 0.05 | 184.7 |
| 7040 | 0.07 | 0.07 | 208.3 |

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Sow Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

[illegible]

Sex: Female  Day(s) Relative to Start Date

| 1024 mg/kg/day Group 3 | CBC/DIFF/RETIC Comp/C | | | | | | |
|---|---|---|---|---|---|---|---|
| | WB | RBC | HGB | HCT | MCV | MCH | MCHC |
| | | (x10^6/uL) | (g/dL) | (%) | (fL) | (pg) | (g/dL) |
| | 22 | 22 | 22 | 22 | 22 | 22 | 22 |
| 7051 | OK | 7.50 | 15.3 | 42.6 | 56.8 | 20.5 | 36.0 |
| 7052 | OK | 7.61 | 15.7 | 44.1 | 58.0 | 20.6 | 35.5 |
| 7053 | OK | 7.91 | 15.6 | 44.7 | 56.5 | 19.8 | 35.0 |
| 7054 | OK | 8.16 | 15.9 | 46.3 | 56.8 | 19.5 | 34.4 |
| 7055 | OK | 7.87 | 15.2 | 43.2 | 55.0 | 19.4 | 35.3 |
| 7056 | OK | 7.91 | 15.7 | 45.0 | 56.9 | 19.8 | 34.8 |
| 7057 | OK | 7.64 | 15.4 | 43.6 | 57.0 | 20.2 | 35.4 |
| 7058 | OK | 8.02 | 15.7 | 44.5 | 55.4 | 19.5 | 35.3 |
| 7059 | OK | 7.73 | 16.1 | 45.9 | 59.3 | 20.8 | 35.1 |
| 7060 | OK | 8.29 | 16.5 | 46.6 | 56.4 | 19.9 | 35.5 |

Sex: Female  Day(s) Relative to Start Date

| 1024 mg/kg/day Group 3 | CBC/DIFF/RETIC Comp/C | | | | | | |
|---|---|---|---|---|---|---|---|
| | RDW | PLT | WBC | ASPT | ALYM | ASS/N | ABOS |
| | (%) | (x10^3/uL) | (x10^3/uL) | (x10^3/uL) | (x10^3/uL) | (x10^3/uL) | (x10^3/uL) |
| | 22 | 22 | 22 | 22 | 22 | 22 | 22 |
| 7051 | 11.2 | 1288 | 7.91 | 1.06 | 6.09 | 0.22 | 0.13 |
| 7052 | 11.2 | 1253 | 8.44 | 1.37 | 6.68 | 0.21 | 0.13 |
| 7053 | 11.9 | 1206 | 12.97 | 2.97 | 9.03 | 0.66 | 0.19 |
| 7054 | 11.3 | 1063 | 11.78 | 2.33 | 8.91 | 0.32 | 0.06 |
| 7055 | 11.1 | 1334 | 8.29 | 1.24 | 6.65 | 0.25 | 0.08 |
| 7056 | 11.5 | 1162 | 15.10 | 2.02 | 12.16 | 0.50 | 0.23 |
| 7057 | 11.2 | 1178 | 12.42 | 0.88 | 11.03 | 0.21 | 0.15 |
| 7058 | 11.0 | 1305 | 17.73 | 3.05 | 13.88 | 0.37 | 0.18 |
| 7059 | 11.0 | 1046 | 13.10 | 0.89 | 11.46 | 0.38 | 0.20 |
| 7060 | 10.9 | 1303 | 8.10 | 1.02 | 6.70 | 0.15 | 0.15 |

Dosage 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Dosage 1: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

[illegible]

Sex: Female  Days on Relative to Start Date

| 1021 mg/kg/day Group 3 | ABAS (x10^3/µL) | ALGF (x10^3/µL) | ARET (x10^3/µL) |
|---|---|---|---|
| | 22 | 22 | 22 |
| 7051 | 0.03 | 0.03 | 98.9 |
| 7052 | 0.03 | 0.03 | 185.5 |
| 7053 | 0.06 | 0.05 | 170.5 |
| 7054 | 0.05 | 0.08 | 160.2 |
| 7055 | 0.05 | 0.03 | 169.8 |
| 7056 | 0.11 | 0.11 | 178.7 |
| 7057 | 0.07 | 0.07 | 203.0 |
| 7058 | 0.12 | 0.11 | 164.4 |
| 7059 | 0.05 | 0.10 | 173.4 |
| 7060 | 0.03 | 0.04 | 174.5 |

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1021 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1530 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

[illegible]

Sex: Female Day(s) Relative to Start Date

| 1536 mg/kg/day (Group 4) | CBC/DIFF/RETIC Comp1 | | | | | | |
|---|---|---|---|---|---|---|---|
| | WB | RBC (x10^6/µL) | HGB (g/dL) | HCT (%) | MCV (fL) | MCH (pg) | MCHC (g/dL) |
| | 22 | 22 | 22 | 22 | 22 | 22 | 22 |
| 7071 | OK | 7.57 | 14.7 | 42.2 | 55.7 | 19.4 | 34.9 |
| 7072 | OK | 7.54 | 15.4 | 44.3 | 56.4 | 19.7 | 34.8 |
| 7073 | OK | 7.32 | 15.4 | 44.8 | 61.2 | 21.0 | 34.4 |
| 7074 | OK | 7.45 | 15.0 | 42.3 | 56.8 | 20.2 | 35.6 |
| 7075 | OK | 7.95 | 15.6 | 44.0 | 55.4 | 19.7 | 35.5 |
| 7076 | OK | 7.27 | 15.7 | 43.9 | 60.4 | 21.6 | 35.8 |
| 7077 | OK | 8.12 | 16.7 | 47.1 | 58.0 | 20.6 | 35.5 |
| 7078 | OK | 7.67 | 16.0 | 46.2 | 60.2 | 20.8 | 34.6 |
| 7079 | OK | 7.82 | 15.2 | 43.1 | 55.1 | 19.4 | 35.3 |
| 7080 | OK | 7.31 | 14.9 | 42.0 | 57.5 | 20.3 | 35.4 |

Sex: Female Day(s) Relative to Start Date

| 1536 mg/kg/day (Group 4) | CBC/DIFF/RETIC Comp1 | | | | | | |
|---|---|---|---|---|---|---|---|
| | RDW (%) | PLT (x10^3/µL) | WBC (x10^3/µL) | ANEU (x10^3/µL) | ALYM (x10^3/µL) | AMON (x10^3/µL) | ABOS (x10^3/µL) |
| | 22 | 22 | 22 | 22 | 22 | 22 | 22 |
| 7071 | 12.4 | 1062 | 12.22 | 3.01 | 8.75 | 0.28 | 0.11 |
| 7072 | 11.0 | 1262 | 7.01 | 0.79 | 5.94 | 0.13 | 0.12 |
| 7073 | 11.3 | 1344 | 17.13 | 4.48 | 12.09 | 0.55 | 0.15 |
| 7074 | 11.6 | 1235 | 5.39 | 1.19 | 3.91 | 0.09 | 0.03 |
| 7075 | 11.0 | 1366 | 10.77 | 1.08 | 9.28 | 0.19 | 0.09 |
| 7076 | 10.9 | 1390 | 10.86 | 1.12 | 9.35 | 0.20 | 0.10 |
| 7077 | 11.7 | 1195 | 10.58 | 1.21 | 8.64 | 0.53 | 0.26 |
| 7078 | 10.9 | 1259 | 14.13 | 0.92 | 12.60 | 0.24 | 0.17 |
| 7079 | 11.9 | 1153 | 7.79 | 0.79 | 6.73 | 0.15 | 0.06 |
| 7080 | 12.0 | 1052 | 6.06 | 1.20 | 4.65 | 0.07 | 0.10 |

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

[illegible]

Sex: female Days: Relative to Start Date

| 1536 mg/kg/day Group 4 | ABAS (x10^3/µL) | ALUC (x10^3/µL) | ARET (x10^3/µL) |
|---|---|---|---|
| | 22 | 22 | 22 |
| 7071 | 0.05 | 0.04 | 2907 |
| 7072 | 0.02 | 0.01 | 1792 |
| 7073 | 0.14 | 0.14 | 2143 |
| 7074 | 0.01 | 0.03 | 1641 |
| 7075 | 0.05 | 0.06 | 1529 |
| 7076 | 0.05 | 0.04 | 1762 |
| 7077 | 0.06 | 0.06 | 1697 |
| 7078 | 0.10 | 0.10 | 1552 |
| 7079 | 0.03 | 0.04 | 1895 |
| 7080 | 0.02 | 0.02 | 2387 |

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

[illegible]

Sex: Male Days relative to Start Date

| 0 mg/kg/day Group 3 | PHEM | PLIP | PPCT | PT (sec) | APTT (sec) |
|---|---|---|---|---|---|
| | 29 | 29 | 29 | 29 | 29 |
| 7001 | None | None | None | 11.1 | 20.5 |
| 7002 | None | None | None | 10.6 | 18.6 |
| 7003 | None | None | None | 10.3 | 20.5 |
| 7004 | None | None | None | 10.6 | 25.4 |
| 7005 | None | None | None | 10.5 | [illegible] |
| 7006 | None | None | None | 10.1 | 22.5 |
| 7007 | None | None | None | 11.1 | 17.5 |
| 7008 | None | None | None | 10.9 | 20.2 |
| 7009 | None | None | None | 10.8 | 19.5 |
| 7010 | None | None | None | 10.6 | 19.1 |

Sex: Male Days relative to Start Date

| 512 mg/kg/day Group 2 | PHEM | PLIP | PPCT | PT (sec) | APTT (sec) |
|---|---|---|---|---|---|
| | 29 | 29 | 29 | 29 | 29 |
| 7021 | None | None | None | 11.1 | 21.7 |
| 7022 | None | None | None | 10.6 | 31.6 |
| 7023 | None | None | None | 10.5 | 26.1 |
| 7024 | None | None | None | 10.4 | 19.7 |
| 7025 | None | None | None | 10.8 | 31.0 |
| 7026 | None | None | None | 10.7 | 21.5 |
| 7027 | None | None | None | 10.5 | 21.2 |
| 7028 | None | None | None | 11.3 | 22.6 |
| 7029 | None | None | None | 10.7 | 22.4 |
| 7030 | None | None | None | 10.0 | 17.5 |

Group 2: 512 mg/kg/day of test substance corresponds to 29 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 50.0 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 75.0 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

[illegible]

Sex: Male Day(s) Relative to Start Date

| 1024 mg/kg/day Group 3 | PHEM | PLIP | PICT | PT (sec) | APTT (sec) |
|---|---|---|---|---|---|
| | 29 | 29 | 29 | 29 | 29 |
| 7041 | None | None | None | 10.5 | 41.9 |
| 7042 | None | None | None | 10.9 | 27.8 |
| 7043 | None | None | None | 10.5 | 21.9 |
| 7044 | None | None | None | 10.7 | 23.9 |
| 7045 | None | None | None | 10.9 | 27.1 |
| 7046 | None | None | None | 10.4 | 22.4 |
| 7047 | None | None | None | 10.3 | 17.0 |
| 7048 | None | None | None | 10.7 | 19.9 |
| 7049 | None | None | None | 10.6 | 29.8 |
| 7050 | None | None | None | 10.9 | 26.0 |

Sex: Male Day(s) Relative to Start Date

| 1536 mg/kg/day Group 4 | PHEM | PLIP | PICT | PT (sec) | APTT (sec) |
|---|---|---|---|---|---|
| | 29 | 29 | 29 | 29 | 29 |
| 7063 | None | None | None | 10.7 | 35.2 |
| 7062 | None | None | None | 10.5 | 28.0 |
| 7063 | None | None | None | 10.5 | 25.2 |
| 7064 | None | None | None | 10.1 | 23.0 |
| 7065 | None | None | None | 10.6 | 20.8 |
| 7066 | None | None | None | 10.2 | 21.8 |
| 7067 | None | None | None | 10.3 | 17.8 |
| 7068 | None | None | None | 10.3 | 20.9 |
| 7069 | None | None | None | 10.9 | 22.6 |
| 7070 | None | None | None | 10.7 | 23.3 |

Group 2: 512 mg/kg/day of test substance corresponds to 290 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 593 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 751 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

Individual Animal Data on Hematology Data

Sex: Female  Day(s) Relative to Start Date

| 0 mg/kg/day Group 1 | PHEM | PLIP | PLCT | PT (sec) | APTT (sec) |
|---|---|---|---|---|---|
| | 30 | 30 | 30 | 30 | 30 |
| 7001 | None | None | None | 9.8 | 22.6 |
| 7002 | None | None | None | 10.4 | 23.4 |
| 7003 | None | None | None | 10.0 | 18.6 |
| 7004 | None | None | None | 10.1 | 21.2 |
| 7005 | None | None | None | 10.0 | 23.8 |
| 7006 | None | None | None | 10.1 | 26.8 |
| 7007 | None | None | None | 9.9 | 19.6 |
| 7008 | None | None | None | 10.1 | 22.6 |
| 7009 | None | None | None | 9.8 | 19.2 |
| 7010 | None | None | None | 10.2 | 21.3 |

Sex: Female  Day(s) Relative to Start Date

| 512 mg/kg/day Group 2 | PHEM | PLIP | PLCT | PT (sec) | APTT (sec) |
|---|---|---|---|---|---|
| | 30 | 30 | 30 | 30 | 30 |
| 7001 | None | None | None | 10.0 | 17.3 |
| 7002 | None | None | None | 9.7 | 27.4 |
| 7003 | None | None | None | 9.9 | 16.3 |
| 7004 | None | None | None | 9.9 | 20.0 |
| 7005 | None | None | None | 9.5 | 18.1 |
| 7006 | None | None | None | 10.0 | 21.4 |
| 7007 | None | None | None | 9.6 | 19.4 |
| 7008 | None | None | None | 10.1 | 18.0 |
| 7009 | None | None | None | 9.6 | 19.0 |
| 7010 | None | None | None | 10.1 | 22.1 |

Group 2: 512 mg/kg/day of test substance corresponds to 290 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 581 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 870 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

Individual Animal Clinical Pathology Data

Sex: Female Day(s) Relative to Start Date

| 1024 mg/kg/day (Group 3) | PHEM | PLIP | PICT | PT (sec) | APTT (sec) |
|---|---|---|---|---|---|
| | 30 | 30 | 30 | 30 | 30 |
| 7051 | None | None | None | 10.6 | 29.7 |
| 7052 | None | None | None | 10.1 | 27.3 |
| 7053 | None | None | None | 9.8 | 14.9 |
| 7054 | None | None | None | 9.4 | 17.1 |
| 7055 | None | None | None | 10.0 | 23.3 |
| 7056 | None | None | None | 10.1 | 21.0 |
| 7057 | None | None | None | 9.9 | 23.8 |
| 7058 | None | None | None | 9.7 | 15.4 |
| 7059 | None | None | None | 10.2 | 18.3 |
| 7060 | None | None | None | 10.0 | 17.2 |

Sex: Female Day(s) Relative to Start Date

| 1536 mg/kg/day (Group 4) | PHEM | PLIP | PICT | PT (sec) | APTT (sec) |
|---|---|---|---|---|---|
| | 30 | 30 | 30 | 30 | 30 |
| 7071 | None | None | None | 9.7 | 18.2 |
| 7072 | None | None | None | 9.9 | 20.3 |
| 7073 | None | None | None | 9.4 | 17.6 |
| 7074 | None | None | None | 10.0 | 16.9 |
| 7075 | None | None | None | 9.7 | 18.3 |
| 7076 | None | None | None | 10.1 | 23.6 |
| 7077 | None | None | None | 9.7 | 20.1 |
| 7078 | None | None | None | 10.0 | 20.3 |
| 7079 | None | None | None | 9.9 | 18.8 |
| 7080 | None | None | None | 9.9 | 19.8 |

Group 2: 512 mg/kg/day of test substance corresponds to 290 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 580 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 870 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

[illegible]

Sex: Male Days(s) Relative to Start Date

| ID (mg/kg/day) Group 1 | Olympia Chem Plus | | | | | | |
|---|---|---|---|---|---|---|---|
| | HEM | LIP | ICT | AST (U/L) | ALT (U/L) | SDH (U/L) | ALKP (U/L) |
| | 22 | 22 | 22 | 22 | 22 | 22 | 22 |
| 7001 | Trace | None | None | NPH | 25 | NPH | 184 |
| 7002 | Trace | None | None | NPH | 33 | NPH | 162 |
| 7003 | Trace | None | None | NPH | 28 | NPH | 166 |
| 7004 | None | None | None | 72 | 26 | 10.3 | 241 |
| 7005 | None | None | None | 87 | 30 | 7.7 | 202 |
| 7006 | Trace | None | None | NPH | 29 | NPH | 181 |
| 7007 | None | None | None | 72 | 39 | 7.9 | 173 |
| 7008 | Trace | None | None | NPH | 28 | NPH | 186 |
| 7009 | None | None | None | 70 | 25 | 8.4 | 158 |
| 7010 | None | None | None | 65 | 26 | 6.6 | 172 |

Sex: Male Days(s) Relative to Start Date

| ID (mg/kg/day) Group 1 | Olympia Chem Plus | | | | | | |
|---|---|---|---|---|---|---|---|
| | BILI (mg/dL) | BUN (mg/dL) | CREA (mg/dL) | CHOL (mg/dL) | TRIG (mg/dL) | GLUC (mg/dL) | TP (g/dL) |
| | 22 | 22 | 22 | 22 | 22 | 22 | 22 |
| 7001 | 0.19 | 12 | 0.23 | 78 | 53 | 113 | 6.1 |
| 7002 | 0.18 | 11 | 0.23 | 106 | 82 | 82 | 6.6 |
| 7003 | 0.19 | 9 | 0.20 | 84 | 67 | 88 | 5.9 |
| 7004 | 0.16 | 12 | 0.24 | 73 | 90 | 87 | 6.2 |
| 7005 | 0.17 | 11 | 0.23 | 74 | 50 | 95 | 6.0 |
| 7006 | 0.20 | 10 | 0.23 | 89 | 90 | 120 | 6.0 |
| 7007 | 0.14 | 9 | 0.20 | 45 | 55 | 92 | 5.6 |
| 7008 | 0.17 | 8 | 0.22 | 68 | 72 | 81 | 6.0 |
| 7009 | 0.15 | 11 | 0.20 | 74 | 40 | 96 | 5.4 |
| 7010 | 0.14 | 11 | 0.22 | 69 | 62 | 93 | 5.9 |

Group 2: 512 mg/kg/day of raw substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of raw substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of raw substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

[illegible]

Sex: Male  Day(s) Relative to Start Date

| 0 mg/kg/day Group 1 | Olympus Chem Plus | | | | | | |
|---|---|---|---|---|---|---|---|
| | ALB g/dL | GLOB g/dL | CALC mg/dL | IPHS mg/dL | NA mmol/L | K mmol/L | CL mmol/L |
| | 22 | 22 | 22 | 22 | 22 | 22 | 22 |
| 7/01 | 3.2 | 2.9 | 10.7 | NPH | 143.7 | 4.91 | 102.3 |
| 7/02 | 3.1 | 2.9 | 10.4 | NPH | 141.6 | 5.47 | 101.5 |
| 7/03 | 3.1 | 2.8 | 10.5 | NPH | 140.9 | 5.02 | 100.8 |
| 7/04 | 3.1 | 3.1 | 10.4 | 8.6 | 142.0 | 4.96 | 101.5 |
| 7/05 | 3.2 | 2.8 | 10.2 | 9.9 | 142.5 | 4.95 | 101.1 |
| 7/06 | 3.1 | 2.9 | 10.5 | NPH | 140.8 | 5.32 | 101.8 |
| 7/07 | 3.0 | 2.6 | 10.0 | 8.1 | 128.9 | 4.91 | 94.6 |
| 7/08 | 3.2 | 2.8 | 10.4 | NPH | 141.9 | 4.65 | 102.2 |
| 7/09 | 3.3 | 3.1 | 10.8 | 8.4 | 141.4 | 5.29 | 101.1 |
| 7/10 | 3.1 | 2.8 | 10.4 | 8.9 | 141.5 | 4.82 | 101.4 |

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

[illegible]

Sex: Male  Day(s) Relative to Start Date

| 512 mg/kg/day Group 2 | Otherwise Clean Plus | | | | | | |
|---|---|---|---|---|---|---|---|
| | HEM | LIP | ICT | AST (U/L) | ALT (U/L) | SDH (U/L) | ALKP (U/L) |
| | 22 | 22 | 22 | 22 | 22 | 22 | 22 |
| 7/21 | None | None | None | 70 | 30 | 8.0 | 192 |
| 7/22 | None | None | None | 85 | 25 | 10 | 243 |
| 7/23 | None | None | None | NPH | 26 | NPH | 218 |
| 7/24 | None | None | None | 76 | 24 | 7.6 | 194 |
| 7/25 | None | None | None | 82 | 29 | 11.6 | 182 |
| 7/26 | None | None | None | 74 | 27 | 7.4 | 204 |
| 7/27 | None | None | None | 81 | 35 | 8.4 | 264 |
| 7/28 | None | None | None | 68 | 24 | 7.8 | 208 |
| 7/29 | None | None | None | 63 | 27 | 9.1 | 350 |
| 7/30 | None | None | None | 92 | 33 | 8.2 | 237 |

Sex: Male  Day(s) Relative to Start Date

| 512 mg/kg/day Group 2 | Otherwise Clean Plus | | | | | | |
|---|---|---|---|---|---|---|---|
| | BILI (mg/dL) | BUN (mg/dL) | CREA (mg/dL) | CHOL (mg/dL) | TRIG (mg/dL) | GLUC (mg/dL) | TP (g/dL) |
| | 22 | 22 | 22 | 22 | 22 | 22 | 22 |
| 7/21 | 0.17 | 11 | 0.23 | 86 | 73 | 105 | 5.2 |
| 7/22 | 0.20 | 11 | 0.20 | 72 | [illegible] | 89 | 5.7 |
| 7/23 | 0.17 | 9 | 0.23 | 97 | 65 | 114 | 5.4 |
| 7/24 | 0.18 | 13 | 0.21 | 51 | 39 | 109 | 6.1 |
| 7/25 | 0.18 | 11 | 0.24 | 53 | 65 | 86 | 6.0 |
| 7/26 | 0.15 | 12 | 0.20 | 118 | 69 | 90 | 5.9 |
| 7/27 | 0.15 | 12 | 0.23 | 55 | 61 | 108 | 6.0 |
| 7/28 | 0.15 | 9 | 0.23 | 59 | 92 | 91 | 6.3 |
| 7/29 | 0.19 | 9 | 0.24 | 95 | 65 | 94 | 6.2 |
| 7/30 | 0.17 | 12 | 0.23 | 78 | 66 | 111 | 5.7 |

Group 2: 512 mg/kg/day of test substance corresponds to 290 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 580 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 870 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

[illegible]

Sex: Male Day(s) Relative to Start Date

| 512 mg/kg/day Group 2 | Clinical Chem Plus | | | | | | |
|---|---|---|---|---|---|---|---|
| | ALB (g/dL) | GLOB (g/dL) | CALC (mg/dL) | IPHS (mg/dL) | NA (mmol/L) | K (mmol/L) | CL (mmol/L) |
| | 22 | 22 | 22 | 22 | 22 | 22 | 22 |
| 7021 | 3.4 | 2.8 | 11.0 | 9.3 | 142.5 | 4.90 | 100.8 |
| 7022 | 3.1 | 2.6 | 10.5 | 8.3 | 141.6 | 5.05 | 101.2 |
| 7023 | 3.3 | 3.1 | 10.5 | NFH | 141.7 | 5.27 | 101.5 |
| 7024 | 3.2 | 2.9 | 10.3 | 8.1 | 141.3 | 5.33 | 103.8 |
| 7025 | 3.1 | 2.9 | 10.3 | 9.9 | 141.9 | 5.35 | 102.6 |
| 7026 | 3.1 | 2.8 | 10.4 | 8.6 | 142.0 | 5.34 | 102.6 |
| 7027 | 3.0 | 3.0 | 10.1 | 8.8 | 142.4 | 5.25 | 102.8 |
| 7028 | 3.4 | 2.9 | 10.3 | 8.5 | 143.2 | 5.06 | 102.2 |
| 7029 | 3.3 | 2.9 | 10.5 | 8.9 | 141.5 | 4.73 | 100.7 |
| 7030 | 3.2 | 2.9 | 10.3 | 8.4 | 143.0 | 5.28 | 103.9 |

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

[illegible]

Sex: Male Days(s) Relative to Start Date

| 1024 mg/kg/day Group 3 | Olympus Chem Plus | | | | | | |
|---|---|---|---|---|---|---|---|
| | HEM | LIP | ICT | AST (U/L) | ALT (U/L) | SDH (U/L) | ALKP (U/L) |
| | 22 | 22 | 22 | 22 | 22 | 22 | 22 |
| 7041 | None | None | None | 81 | 24 | 7.3 | 181 |
| 7042 | None | None | None | 76 | 28 | 7.2 | 266 |
| 7043 | Trace | None | None | NPH | 24 | NPH | 193 |
| 7044 | None | None | None | 86 | 28 | 13.0 | 227 |
| 7045 | Trace | None | None | NPH | 30 | NPH | 295 |
| 7046 | None | None | None | 69 | 32 | 8.8 | 236 |
| 7047 | Trace | None | None | NPH | 29 | NPH | 157 |
| 7048 | None | None | None | 87 | 25 | 6.9 | 207 |
| 7049 | Trace | None | None | NPH | 31 | NPH | 244 |
| 7050 | None | None | None | 73 | 31 | 7.0 | 164 |

Sex: Male Days(s) Relative to Start Date

| 1024 mg/kg/day Group 3 | Olympus Chem Plus | | | | | | |
|---|---|---|---|---|---|---|---|
| | BILI (mg/dL) | BUN (mg/dL) | CREA (mg/dL) | CHOL (mg/dL) | TRIG (mg/dL) | GLUC (mg/dL) | TP (g/dL) |
| | 22 | 22 | 22 | 22 | 22 | 22 | 22 |
| 7041 | 0.18 | 10 | 0.22 | 71 | 72 | 90 | 6.2 |
| 7042 | 0.17 | 9 | 0.22 | 85 | 90 | 107 | 6.3 |
| 7043 | 0.17 | 9 | 0.25 | 70 | 62 | 101 | 6.5 |
| 7044 | 0.18 | 10 | 0.23 | 73 | 96 | 86 | 6.2 |
| 7045 | 0.15 | 11 | 0.26 | 61 | 65 | 109 | 6.0 |
| 7046 | 0.20 | 12 | 0.25 | 94 | 74 | 124 | 6.6 |
| 7047 | 0.17 | 9 | 0.23 | 71 | 58 | 102 | 6.4 |
| 7048 | 0.15 | 12 | 0.23 | 76 | 64 | 83 | 6.0 |
| 7049 | 0.19 | 8 | 0.20 | 40 | 41 | 99 | 6.1 |
| 7050 | 0.20 | 10 | 0.20 | 75 | 47 | 116 | 6.1 |

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

[illegible]

Sex: Male  Days relative to Start Date

| 1024 mg/kg/day Group 3 | Vitreous Chem Plus | | | | | | |
|---|---|---|---|---|---|---|---|
| | ALB (g/dL) | GLOB (g/dL) | CALC (mg/dL) | IPHS (mg/dL) | NA (mmol/L) | K (mmol/L) | CL (mmol/L) |
| | 22 | 22 | 22 | 22 | 22 | 22 | 22 |
| 7041 | 3.3 | 2.9 | 10.3 | 7.5 | 141.6 | 5.30 | 101.2 |
| 7042 | 3.3 | 3.0 | 10.9 | 8.8 | 140.7 | 4.79 | 100.4 |
| 7043 | 3.4 | 3.1 | 10.4 | NPH | 142.1 | 4.96 | 101.3 |
| 7044 | 3.3 | 2.9 | 10.5 | 8.4 | 140.3 | 6.83 | 101.9 |
| 7045 | 3.2 | 2.8 | 10.2 | NPH | 140.7 | 5.47 | 100.9 |
| 7046 | 3.1 | 2.9 | 10.2 | 8.6 | 139.9 | 5.72 | 101.8 |
| 7047 | 3.3 | 3.1 | 10.6 | NPH | 140.8 | 5.92 | 100.4 |
| 7048 | 3.3 | 2.7 | 10.4 | 10.0 | 142.9 | 5.11 | 101.7 |
| 7049 | 3.3 | 2.8 | 10.1 | NPH | 141.3 | 6.28 | 102.9 |
| 7050 | 3.2 | 2.9 | 10.3 | 9.4 | 141.4 | 5.55 | 102.6 |

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1538 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation A 28-Day Dietary Study in Rats

[illegible]

Sex: Male Day(s) Relative to Start Date

| 1536 mg/kg/day Group 4 | Olympus Clam Plus | | | | | | |
|---|---|---|---|---|---|---|---|
| | HEM | LIP | HCT | AST (IU/L) | ALT (IU/L) | SDH (IU/L) | ALKP (IU/L) |
| | 22 | 22 | 22 | 22 | 22 | 22 | 22 |
| 7061 | None | None | None | 81 | 33 | 7.9 | 198 |
| 7062 | Trace | None | None | NPH | 32 | NPH | 188 |
| 7063 | None | None | None | 84 | 33 | 7.9 | 267 |
| 7064 | None | None | None | [illegible] | 33 | 8.6 | 235 |
| 7065 | None | None | None | 93 | 32 | 5.2 | 181 |
| 7066 | None | None | None | 65 | 24 | 8.4 | 186 |
| 7067 | Trace | None | None | NPH | 25 | NPH | 222 |
| 7068 | None | None | None | 73 | 27 | 10.2 | 257 |
| 7069 | None | None | None | [illegible] | 23 | 7.0 | 128 |
| 7070 | None | None | None | 76 | 33 | 8.7 | 196 |

Sex: Male Day(s) Relative to Start Date

| 1536 mg/kg/day Group 4 | Olympus Clam Plus | | | | | | |
|---|---|---|---|---|---|---|---|
| | BILI (mg/dL) | BUN (mg/dL) | CREA (mg/dL) | CHOL (mg/dL) | TRIG (mg/dL) | GLUC (mg/dL) | TP (g/dL) |
| | 22 | 22 | 22 | 22 | 22 | 21 | 22 |
| 7061 | 0.12 | 11 | 0.21 | 52 | 56 | 105 | 6.1 |
| 7062 | 0.19 | 9 | 0.23 | 61 | 45 | 92 | 6.1 |
| 7063 | 0.20 | 11 | 0.21 | 71 | 88 | 148 | 6.3 |
| 7064 | 0.19 | [illegible] | 0.19 | 70 | 78 | 139 | 6.0 |
| 7065 | 0.20 | 11 | 0.21 | 68 | 54 | 81 | 5.8 |
| 7066 | 0.18 | 12 | 0.22 | 73 | 92 | 102 | 6.1 |
| 7067 | 0.18 | 12 | 0.22 | 85 | 116 | 101 | 6.1 |
| 7068 | 0.20 | 10 | 0.20 | 36 | 47 | 92 | 6.3 |
| 7069 | 0.16 | 11 | 0.17 | 62 | 33 | 103 | 5.4 |
| 7070 | 0.17 | 11 | 0.18 | 83 | 65 | 91 | 6.1 |

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

Individual Animal Clinical Pathology Data

Sex: Male  Days to Relative to Start Date

| 1536 mg/kg/day Group 4 | Clinical Chem Plus | | | | | | |
|---|---|---|---|---|---|---|---|
| | ALB (g/dL) | GLOB (g/dL) | CALC (mg/dL) | IPHS (mg/dL) | NA (mmol/L) | K (mmol/L) | CL (mmol/L) |
| | 22 | 22 | 22 | 22 | 22 | 22 | 22 |
| 7061 | 3.2 | 2.9 | 10.3 | 7.8 | 142.2 | 4.83 | 101.7 |
| 7062 | 3.3 | 2.8 | 10.3 | NPH | 142.6 | 5.41 | 102.2 |
| 7063 | 3.3 | 2.8 | 10.3 | 8.8 | 142.1 | 5.04 | 100.9 |
| 7064 | 3.3 | 2.7 | 10.5 | 8.9 | 142.3 | 5.29 | 103.6 |
| 7065 | 3.1 | 2.7 | 10.8 | 8.9 | 140.1 | 5.23 | 100.4 |
| 7066 | 3.6 | 3.1 | 10.8 | 8.6 | 140.9 | 5.07 | 101.5 |
| 7067 | 3.1 | 3.0 | 10.7 | NPH | 140.6 | 5.09 | 101.6 |
| 7068 | 3.4 | 2.9 | 10.7 | 8.8 | 141.8 | 4.85 | 100.3 |
| 7069 | 3.1 | 2.4 | 10.1 | 8.4 | 142.2 | 5.42 | 104.3 |
| 7071 | 3.2 | 2.9 | 10.6 | 8.4 | 141.6 | 4.71 | 101.3 |

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient.
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

[illegible]

Sex: Female  Day(s) Relative to Start Date

| [illegible] (mg/kg/day) (Group) | Olympus Chem Plus | | | | | | |
|---|---|---|---|---|---|---|---|
| | HEM | LIP | PCT | AST (U/L) | ALT (U/L) | SDH (U/L) | ALKP (U/L) |
| | 22 | 22 | 22 | 22 | 22 | 22 | 22 |
| 7011 | None | None | None | 78 | 33 | 7.9 | 152 |
| 7012 | None | None | None | 66 | 26 | 5.8 | 112 |
| 7013 | None | None | None | 78 | 25 | 6.7 | 134 |
| 7014 | None | None | None | 74 | 21 | 9.5 | 112 |
| 7015 | None | None | None | 66 | 23 | 7.6 | 114 |
| 7016 | None | None | None | 59 | 25 | 11.0 | 151 |
| 7017 | None | None | None | 69 | 23 | 8.5 | 131 |
| 7018 | None | None | None | 68 | 25 | 8.6 | 155 |
| 7019 | Trace | None | None | NPH | 27 | NPH | 140 |
| 7020 | None | None | None | 66 | 28 | 13.0 | 139 |

Sex: Female  Day(s) Relative to Start Date

| [illegible] (mg/kg/day) (Group) | Olympus Chem Plus | | | | | | |
|---|---|---|---|---|---|---|---|
| | BILI (mg/dL) | BUN (mg/dL) | CREA (mg/dL) | CHOL (mg/dL) | TRIG (mg/dL) | GLUC (mg/dL) | TP (g/dL) |
| | 22 | 22 | 22 | 22 | 22 | 22 | 22 |
| 7011 | 0.18 | 12 | 0.29 | 82 | 31 | 116 | 6.5 |
| 7012 | 0.18 | 13 | 0.26 | 87 | 31 | 116 | 6.7 |
| 7013 | 0.23 | 12 | 0.29 | 85 | 47 | 125 | 6.8 |
| 7014 | 0.16 | 15 | 0.29 | 76 | 33 | 150 | 6.8 |
| 7015 | 0.17 | 14 | 0.32 | 71 | 41 | 126 | 6.3 |
| 7016 | 0.19 | 11 | 0.29 | 90 | 39 | 99 | 6.3 |
| 7017 | 0.15 | 12 | 0.25 | 98 | 34 | 105 | 6.0 |
| 7018 | 0.16 | 12 | 0.26 | 85 | 32 | 121 | 6.5 |
| 7019 | 0.26 | 12 | 0.27 | 102 | 32 | 103 | 6.2 |
| 7020 | 0.19 | 9 | 0.24 | 102 | 36 | 138 | 5.6 |

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

Individual Animal Clinical Pathology Data

Sex: Female Day(s) Relative to Start Date

| ID mg/kg/day Group 1 | Olympus Chem Plus | | | | | | |
|---|---|---|---|---|---|---|---|
| | ALB (g/dL) | GLOB (g/dL) | CALC (mg/dL) | IPHS (mg/dL) | NA (mmol/L) | K (mmol/L) | CL (mmol/L) |
| | 22 | 22 | 22 | 22 | 22 | 22 | 22 |
| 7011 | 3.6 | 2.9 | 10.3 | 7.3 | 139.4 | 4.64 | 102.0 |
| 7012 | 3.7 | 3.0 | 10.7 | 6.8 | 140.8 | 4.15 | 102.7 |
| 7013 | 3.8 | 3.0 | 10.8 | 7.3 | 139.4 | 4.90 | 101.5 |
| 7014 | 3.2 | 3.1 | 10.4 | 6.6 | 141.6 | 4.21 | 105.2 |
| 7015 | 3.5 | 2.8 | 9.9 | 6.8 | 139.8 | 4.14 | 102.0 |
| 7016 | 3.4 | 2.9 | 10.6 | 7.1 | 138.5 | 4.45 | 101.2 |
| 7017 | 3.3 | 2.7 | 10.7 | 7.9 | 140.9 | 5.14 | 103.8 |
| 7018 | 3.5 | 3.0 | 10.8 | 7.6 | 141.5 | 4.63 | 103.0 |
| 7019 | 3.3 | 2.9 | 10.5 | NFH | 139.6 | 4.71 | 102.0 |
| 7020 | 3.3 | 2.7 | 10.3 | 6.6 | 141.2 | 4.62 | 102.6 |

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

[illegible]

Sex: Female  Days Relative to Start Date

| 512 mg/kg/day Group 2 | Observed Clinical Path | | | | | | |
|---|---|---|---|---|---|---|---|
| | HEM | LIP | ICT | AST (IU/L) | ALT (IU/L) | SERI (IU/L) | ALKP (IU/L) |
| | 22 | 22 | 22 | 22 | 22 | 22 | 22 |
| 7031 | None | None | None | 71 | 54 | 8.2 | 97 |
| 7032 | None | None | None | 58 | 22 | 8.6 | 111 |
| 7033 | None | None | None | 78 | 27 | 9.7 | 121 |
| 7034 | None | None | None | 59 | 26 | 8.3 | 115 |
| 7035 | None | None | None | 63 | 39 | 9.4 | 98 |
| 7036 | None | None | None | 58 | 24 | 6.1 | 135 |
| 7037 | None | None | None | 87 | 32 | 7.4 | 102 |
| 7038 | None | None | None | 70 | 31 | 8.3 | 127 |
| 7039 | Trace | None | None | NEH | 20 | NEH | 90 |
| 7040 | None | None | None | 58 | 24 | 6.8 | 70 |

Sex: Female  Days Relative to Start Date

| 512 mg/kg/day Group 2 | Observed Clinical Path | | | | | | |
|---|---|---|---|---|---|---|---|
| | BILI (mg/dL) | BUN (mg/dL) | CREA (mg/dL) | CHOL (mg/dL) | TRIG (mg/dL) | GLUC (mg/dL) | TP (g/dL) |
| | 22 | 22 | 22 | 22 | 22 | 22 | 22 |
| 7031 | 0.20 | 10 | 0.24 | 93 | 29 | 91 | 6.8 |
| 7032 | 0.19 | 9 | 0.25 | 117 | 47 | 89 | 6.9 |
| 7033 | 0.20 | 11 | 0.26 | 73 | 25 | 131 | 7.1 |
| 7034 | 0.21 | 11 | 0.26 | 95 | 44 | 105 | 7.4 |
| 7035 | 0.16 | 11 | 0.28 | 78 | 30 | 95 | 6.4 |
| 7036 | 0.20 | 12 | 0.26 | 91 | 34 | 97 | 6.7 |
| 7037 | 0.20 | 9 | 0.22 | 89 | 51 | 95 | 6.1 |
| 7038 | 0.18 | 11 | 0.27 | 85 | 42 | 115 | 6.4 |
| 7039 | 0.21 | 10 | 0.25 | 137 | 45 | 138 | 6.3 |
| 7040 | 0.19 | 14 | 0.28 | 86 | 32 | 106 | 7.0 |

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

Individual Animal Data in Pathology Data

Sex: Female Day(s) Relative to Start Date

| 512 mg/kg/day Group 2 | Olympus Chem Plus | | | | | | |
|---|---|---|---|---|---|---|---|
| | ALB (g/dL) | GLOB (g/dL) | CALC (mg/dL) | IPHS (mg/dL) | NA (mmol/L) | K (mmol/L) | CL (mmol/L) |
| | 22 | 22 | 22 | 22 | 22 | 22 | 22 |
| 7031 | 3.7 | 3.1 | 11.1 | 7.6 | 140.3 | 4.28 | 101.2 |
| 7032 | 3.5 | 3.4 | 11.0 | 8.4 | 141.0 | 5.18 | 99.7 |
| 7033 | 3.9 | 3.2 | 11.0 | 8.4 | 139.9 | 4.76 | 99.6 |
| 7034 | 4.2 | 3.2 | 11.2 | 8.4 | 140.1 | 4.78 | 99.6 |
| 7035 | 3.5 | 2.9 | 10.5 | 7.5 | 141.8 | 4.23 | 103.3 |
| 7036 | 3.7 | 3.0 | 11.2 | 8.3 | 140.7 | 4.48 | 101.2 |
| 7037 | 3.5 | 2.9 | 10.6 | 7.8 | 140.8 | 4.68 | 101.1 |
| 7038 | 3.5 | 2.9 | 10.4 | 7.1 | 139.9 | 5.08 | 102.9 |
| 7039 | 3.5 | 2.8 | 11.2 | NPH | 141.4 | 4.82 | 103.0 |
| 7040 | 3.5 | 3.5 | 10.8 | 6.7 | 140.2 | 3.99 | 101.0 |

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient.
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

[illegible]

Sex: Female  Day(s) Relative to Start Date

| 1024 mg/kg/day Group 3 | Otherwise Clinic Plus | | | | | | |
|---|---|---|---|---|---|---|---|
| | HEM | LIP | RCT | AST (IU/L) | ALT (IU/L) | SDH (IU/L) | ALKP (IU/L) |
| | 22 | 22 | 22 | 22 | 22 | 22 | 22 |
| 7/61 | None | None | None | 73 | 33 | 8.2 | 131 |
| 7/62 | None | None | None | 75 | 36 | 7.6 | 152 |
| 7/63 | None | None | None | 67 | 25 | 8.1 | 102 |
| 7/64 | None | None | None | 56 | 17 | 7.6 | 64 |
| 7/65 | None | None | None | 67 | 23 | 8.9 | 113 |
| 7/66 | None | None | None | 49 | 20 | 6.1 | 107 |
| 7/67 | None | None | None | 60 | 25 | 7.9 | 151 |
| 7/68 | None | None | None | 60 | 28 | 7.3 | 104 |
| 7/69 | None | None | None | 69 | 23 | 8.7 | 131 |
| 7/70 | None | None | None | 66 | 23 | 7.8 | 136 |

Sex: Female  Day(s) Relative to Start Date

| 1024 mg/kg/day Group 3 | Otherwise Clinic Plus | | | | | | |
|---|---|---|---|---|---|---|---|
| | BILI (mg/dL) | BUN (mg/dL) | CREA (mg/dL) | CHOL (mg/dL) | TRIG (mg/dL) | GLUC (mg/dL) | TP (g/dL) |
| | 22 | 22 | 22 | 22 | 22 | 22 | 22 |
| 7/61 | 0.21 | 13 | 0.27 | 96 | 52 | 98 | 6.5 |
| 7/62 | 0.19 | 15 | 0.25 | 71 | 21 | 97 | 6.8 |
| 7/63 | 0.17 | 16 | 0.26 | 136 | 50 | 98 | 7.3 |
| 7/64 | 0.19 | 12 | 0.33 | 108 | 13 | 107 | 6.8 |
| 7/65 | 0.20 | 11 | 0.26 | 82 | 66 | 127 | 6.9 |
| 7/66 | 0.25 | 14 | 0.27 | 90 | 41 | 113 | 6.8 |
| 7/67 | 0.20 | 13 | 0.23 | 106 | 38 | 101 | 6.4 |
| 7/68 | 0.20 | 10 | 0.28 | 117 | 72 | 96 | 7.2 |
| 7/69 | 0.17 | 12 | 0.28 | 101 | 57 | 98 | 6.6 |
| 7/70 | 0.20 | 11 | 0.23 | 129 | 42 | 103 | 6.6 |

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation - A 28-Day Dietary Study in Rats

[illegible]

Sex: Female  Day(s) Relative to Start Date

| D024 mg/kg/day Group 3 | Albumin Chem Plus | | | | | | |
|---|---|---|---|---|---|---|---|
| | ALB (g/dL) | GLOB (g/dL) | CALC (mg/dL) | IPHS (mg/dL) | NA (mmol/L) | K (mmol/L) | CL (mmol/L) |
| | 22 | 22 | 22 | 22 | 22 | 22 | 22 |
| 7051 | 3.6 | 2.9 | 10.5 | 7.4 | 139.7 | 4.52 | 100.3 |
| 7052 | 3.7 | 3.1 | 10.7 | 7.9 | 140.3 | 4.50 | 102.4 |
| 7053 | 3.8 | 3.5 | 11.4 | 7.8 | 140.5 | 4.38 | 100.9 |
| 7054 | 3.6 | 3.2 | 11.3 | 7.7 | 140.1 | 4.78 | 100.7 |
| 7055 | 3.8 | 3.1 | 10.8 | 7.9 | 140.9 | 4.78 | 101.1 |
| 7056 | 3.6 | 3.0 | 11.1 | 8.1 | 140.0 | 4.53 | 100.4 |
| 7057 | 3.3 | 2.9 | 10.9 | 7.5 | 139.7 | 4.51 | 101.2 |
| 7058 | 3.6 | 3.2 | 11.5 | 7.4 | 140.3 | 4.69 | 100.9 |
| 7059 | 3.5 | 3.1 | 11.0 | 8.2 | 141.7 | 4.80 | 103.3 |
| 7060 | 3.6 | 3.0 | 11.2 | 7.6 | 139.5 | 5.02 | 99.7 |

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

[illegible]

Sex: Female Day(s) Relative to Start Date

| 1536 mg/kg/day Group 1 | Olympus Chem Plus | | | | | | |
|---|---|---|---|---|---|---|---|
| | HEM | LIP | ICT | AST (U/L) | ALT (U/L) | SDH (U/L) | ALKP (U/L) |
| | 22 | 22 | 22 | 22 | 22 | 22 | 22 |
| 7071 | None | None | None | 70 | 24 | 7.5 | 88 |
| 7072 | None | None | None | 69 | 31 | 8.7 | 148 |
| 7073 | None | None | None | 74 | 38 | 12.7 | 78 |
| 7074 | None | None | None | 64 | 17 | 8.9 | 78 |
| 7075 | None | None | None | 61 | 28 | 8.2 | 115 |
| 7076 | None | None | None | 57 | 24 | 11.4 | 94 |
| 7077 | None | None | None | 62 | 27 | 8.3 | 110 |
| 7078 | None | None | None | 56 | 26 | 7.5 | 104 |
| 7079 | None | None | None | 68 | 27 | 15.2 | 149 |
| 7080 | None | None | None | 67 | 23 | 10.2 | 117 |

Sex: Female Day(s) Relative to Start Date

| 1536 mg/kg/day Group 1 | Olympus Chem Plus | | | | | | |
|---|---|---|---|---|---|---|---|
| | BILI (mg/dL) | BUN (mg/dL) | CREA (mg/dL) | CHOL (mg/dL) | TRIG (mg/dL) | GLUC (mg/dL) | TP (g/dL) |
| | 22 | 22 | 22 | 22 | 22 | 22 | 22 |
| 7071 | 0.20 | 11 | 0.25 | 81 | 29 | 103 | 6.5 |
| 7072 | 0.18 | 12 | 0.26 | 79 | 29 | 95 | 6.6 |
| 7073 | 0.20 | 12 | 0.32 | 128 | 43 | 106 | 7.3 |
| 7074 | 0.19 | 13 | 0.31 | 100 | 41 | 157 | 7.2 |
| 7075 | 0.22 | 13 | 0.26 | 110 | 36 | 100 | 6.9 |
| 7076 | 0.20 | 11 | 0.25 | 61 | 27 | 103 | 6.1 |
| 7077 | 0.19 | 10 | 0.25 | 127 | 52 | 106 | 6.6 |
| 7078 | 0.13 | 13 | 0.26 | 89 | 31 | 100 | 6.3 |
| 7079 | 0.22 | 13 | 0.31 | 80 | 35 | 130 | 6.5 |
| 7080 | 0.20 | 14 | 0.32 | 94 | 31 | 123 | 6.5 |

Group 2: 512 mg/kg/day of raw substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of raw substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of raw substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

Individual Animal Clinical Pathology Data

Sex: Female Day(s) Relative to Start Date

| 1536 mg/kg/day Group 4 | Chemistry Chem Plus | | | | | | |
|---|---|---|---|---|---|---|---|
| | ALB g/dL | GLOB g/dL | CALC mg/dL | IPHS mg/dL | NA mmol/L | K mmol/L | CL mmol/L |
| | 22 | 22 | 22 | 22 | 22 | 22 | 22 |
| 7021 | 3.6 | 2.9 | 10.5 | 6.9 | 140.3 | 5.21 | 102.8 |
| 7022 | 3.5 | 3.1 | 10.5 | 6.9 | 138.0 | 5.18 | 101.8 |
| 7023 | 4.1 | 3.2 | 11.1 | 7.3 | 139.9 | 4.66 | 101.3 |
| 7024 | 3.9 | 3.3 | 10.8 | 6.3 | 141.2 | 4.29 | 102.9 |
| 7025 | 3.9 | 3.0 | 11.1 | 6.9 | 140.7 | 4.37 | 101.3 |
| 7026 | 3.3 | 2.8 | 10.6 | 7.6 | 140.3 | 4.99 | 103.3 |
| 7027 | 3.6 | 3.0 | 11.1 | 8.0 | 139.8 | 5.23 | 99.8 |
| 7028 | 3.3 | 3.0 | 10.9 | 8.6 | 142.3 | 4.61 | 103.0 |
| 7029 | 3.5 | 3.0 | 10.3 | 5.7 | 139.7 | 4.54 | 102.1 |
| 7030 | 3.6 | 2.9 | 10.0 | 6.5 | 140.2 | 4.29 | 102.8 |

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation A 28-Day Dietary Study in Rats

[illegible]

Sex: Male Days in Relative to Start Date

| 0 mg/kg/day Group 1 | uvol/ATLAS | | | | | | |
|---|---|---|---|---|---|---|---|
| | QUAL | COL | CLAR | UVOL (mL) | pH | SG | UGLC (mg/dL) |
| | 22 | 22 | 22 | 22 | 22 | 22 | 22 |
| 7001 | Light | Yellow | Clear | 2.4 | 6.0 | 1.072 | NEGATIVE |
| 7002 | Light | Yellow | Hazy | 8.2 | 6.0 | 1.029 | NEGATIVE |
| 7003 | Light | Yellow | Clear | 9.6 | 6.5 | 1.024 | NEGATIVE |
| 7004 | Light | Yellow | Clear | 6.0 | 6.5 | 1.027 | NEGATIVE |
| 7005 | Light | Yellow | Clear | 16.8 | 6.5 | 1.013 | NEGATIVE |
| 7006 | Light | Yellow | Clear | 7.2 | 6.5 | 1.026 | NEGATIVE |
| 7007 | Light | Yellow | Clear | 18.2 | 7.0 | 1.016 | NEGATIVE |
| 7008 | Light | Yellow | Clear | 14.0 | 6.5 | 1.016 | NEGATIVE |
| 7009 | Medium | Yellow | Hazy | 5.6 | 6.5 | 1.043 | NEGATIVE |
| 7010 | Light | Yellow | Clear | 30.0 | 7.0 | 1.008 | NEGATIVE |

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation A 28-Day Dietary Study in Rats

[illegible]

Sex: Male Day(s) Relative to Start Date

| 0 mg/kg/day Group 1 | nvol-ATLAS | | | | Olympus Chem Plu |
|---|---|---|---|---|---|
| | KET (mg/dL) | UBL | BLD | UBG (EU/dL) | UMTP (mg/dL) |
| | 22 | 22 | 22 | 22 | 22 |
| 7001 | TRACE | NEGATIVE | NEGATIVE | 1.0 | 190 |
| 7002 | TRACE | NEGATIVE | NEGATIVE | 0.2 | 115 |
| 7003 | 15 | NEGATIVE | NEGATIVE | 0.2 | 84 |
| 7004 | 15 | NEGATIVE | NEGATIVE | 0.2 | 85 |
| 7005 | NEGATIVE | NEGATIVE | LARGE | 0.2 | 46 |
| 7006 | 15 | NEGATIVE | NEGATIVE | 0.2 | 129 |
| 7007 | NEGATIVE | NEGATIVE | TRACE | 0.2 | 65 |
| 7008 | TRACE | NEGATIVE | LARGE | 0.2 | 50 |
| 7009 | 15 | NEGATIVE | TRACE | 0.2 | 175 |
| 7010 | NEGATIVE | NEGATIVE | NEGATIVE | 0.2 | 98 |

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation - A 28-Day Dietary Study in Rats

[illegible]

Sex: Male Days in Relative to Start Date

| 512 mg/kg/day (Group 2) | URINALYSIS | | | | | | |
|---|---|---|---|---|---|---|---|
| | QUAL | COL | CLAR | VOL | pH | SG | UGLU |
| | | | | ml. | | | mg/dL |
| | 22 | 22 | 22 | 22 | 22 | 22 | 22 |
| 7021 | Light | Yellow | Hazy | 4.8 | 6.0 | 1.042 | NEGATIVE |
| 7022 | Light | Yellow | Cloudy | 9.6 | 7.0 | 1.024 | NEGATIVE |
| 7023 | Light | Yellow | Hazy | 6.0 | 6.5 | 1.031 | NEGATIVE |
| 7024 | Light | Yellow | Clear | 4.0 | 6.0 | 1.052 | NEGATIVE |
| 7025 | Light | Yellow | Clear | 15.4 | 7.0 | 1.015 | NEGATIVE |
| 7026 | Light | Yellow | Clear | 29.0 | 6.5 | 1.011 | NEGATIVE |
| 7027 | Light | Yellow | Clear | 15.8 | 6.5 | 1.017 | NEGATIVE |
| 7028 | Light | Yellow | Clear | 0.1 | QNS | QNS | QNS |
| 7029 | Light | Yellow | Hazy | 26.0 | 7.0 | 1.013 | NEGATIVE |
| 7030 | Light | Yellow | Clear | 4.6 | 6.0 | 1.040 | NEGATIVE |

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

Individual Animal Clinical Pathology Data

Sex: Male Day(s) Relative to Start Date

| 512 mg/kg/day (Group 2) | nvol-ALAS | | | | Olympus Chem Plu |
|---|---|---|---|---|---|
| | KET (mg/dL) | UBIL | BLD | URO (EU/dL) | UMTP (mg/dL) |
| | 22 | 22 | 22 | 22 | 22 |
| 7021 | TRACE | NEGATIVE | TRACE | 0.2 | 122 |
| 7022 | TRACE | NEGATIVE | LARGE | 0.2 | 116 |
| 7023 | 15 | NEGATIVE | NEGATIVE | 0.2 | 205 |
| 7024 | NEGATIVE | NEGATIVE | NEGATIVE | 0.2 | 250 |
| 7025 | NEGATIVE | NEGATIVE | NEGATIVE | 0.2 | 133 |
| 7026 | NEGATIVE | NEGATIVE | TRACE | 0.2 | 38 |
| 7027 | TRACE | NEGATIVE | NEGATIVE | 0.2 | 78 |
| 7028 | QNS | QNS | QNS | QNS | 1260 |
| 7029 | TRACE | NEGATIVE | NEGATIVE | 0.2 | 24 |
| 7030 | TRACE | NEGATIVE | NEGATIVE | 0.2 | 185 |

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Chemical Pathology Results for
Soy Leghemoglobin Preparation - A 28-Day Dietary Study in Rats

[illegible]

Sex: Male  Days in Relative to Start Date

| 1024 mg/kg/day (Group 3) | uvoFATLAS | | | | | | |
|---|---|---|---|---|---|---|---|
| | QUAL | COL | CLAR | UWGL (mL) | pH | SG | UGLU (mg/dL) |
| | 22 | 22 | 22 | 22 | 22 | 22 | 22 |
| 7041 | Light | Yellow | Clear | 24.0 | 7.0 | 1.011 | NEGATIVE |
| 7042 | Light | Yellow | Clear | 9.0 | 6.5 | 1.024 | NEGATIVE |
| 7043 | Light | Yellow | Clear | 4.2 | 6.0 | 1.042 | NEGATIVE |
| 7044 | Light | Yellow | Clear | 19.0 | 6.5 | 1.017 | NEGATIVE |
| 7045 | Light | Yellow | Hazy | 22.0 | 7.0 | 1.012 | NEGATIVE |
| 7046 | Light [1] | Brown [1] | Cloudy [1] | 3.6 [1] | 6.5 [1] | 1.063 [1] | NEGATIVE [1] |
| 7047 | Light | Yellow | Clear | 13.0 | 6.0 | 1.022 | NEGATIVE |
| 7048 | Light | Yellow | Hazy | 11.0 | 6.5 | 1.026 | NEGATIVE |
| 7049 | Light | Yellow | Clear | 7.0 | 6.5 | 1.023 | NEGATIVE |
| 7050 | Light | Yellow | Clear | 9.0 | 7.0 | 1.024 | NEGATIVE |

[1] [illegible] Fecal contamination observed.

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation A 28-Day Dietary Study in Rats

Individual Analysis Data on Pathology Data

Sex: Male Day(s) Relative to Start Date

| 1021 mg/kg/day Group 3 | uvol-ATLAS | | | | Olympus Chem Pla |
|---|---|---|---|---|---|
| | KET (mg/dL) | UBIL | BLD | URO (EU/dL) | UMPP (mg/dL) |
| | 22 | 22 | 22 | 22 | 22 |
| 7041 | TRACE | NEGATIVE | TRACE | 0.2 | 34 |
| 7042 | TRACE | NEGATIVE | NEGATIVE | 0.2 | 61 |
| 7043 | TRACE | NEGATIVE | SMALL | 0.2 | 230 |
| 7044 | NEGATIVE | NEGATIVE | SMALL | 0.2 | 103 |
| 7045 | TRACE | NEGATIVE | MODERATE | 0.2 | 65 |
| 7046 | 15 # | SMALL # | LARGE # | 1.0 # | 290 |
| 7047 | TRACE | NEGATIVE | NEGATIVE | 0.2 | 159 |
| 7048 | 15 | NEGATIVE | MODERATE | 0.2 | 166 |
| 7049 | TRACE | NEGATIVE | TRACE | 0.2 | 98 |
| 7050 | TRACE | NEGATIVE | MODERATE | 0.2 | 93 |

1 ISC Fecal contamination observed 1
Group 2 312 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3 1021 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation A 28-Day Dietary Study in Rats

[illegible]

Sex: Male Day(s) Relative to Start Date

| 1536 mg/kg/day Group 4 | uvol/ATLAS | | | | | | |
|---|---|---|---|---|---|---|---|
| | QUAL | COL | CLAR | UVOL (mL) | pH | SG | UGLC (mg/dL) |
| | 22 | 22 | 22 | 22 | 22 | 22 | 22 |
| 7061 | Light | Yellow | Hazy | 15.8 | 6.5 | 1.020 | NEGATIVE |
| 7062 | Light | Yellow | Clear | 11.8 | 6.5 | 1.019 | NEGATIVE |
| 7063 | Light | Yellow | Clear | 10.2 | 6.5 | 1.024 | NEGATIVE |
| 7064 | Light | Yellow | Clear | 31.0 | 7.0 | 1.011 | NEGATIVE |
| 7065 | Light | Yellow | Clear | 16.0 | 6.0 | 1.018 | NEGATIVE |
| 7066 | Light | Yellow | Hazy | 15.4 | 7.0 | 1.017 | NEGATIVE |
| 7067 | Medium # | Yellow # | Cloudy # | 9.6 # | 7.0 # | 1.022 # | NEGATIVE # |
| 7068 | Light | Yellow | Clear | 12.8 | 6.5 | 1.019 | NEGATIVE |
| 7069 | Light | Yellow | Clear | 1.0 | 6.0 | 1.026 | NEGATIVE |
| 7070 | Light | Yellow | Hazy | 19.6 | 7.0 | 1.015 | NEGATIVE |

[ USC Fecal contamination observed ]
Group 2 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

[illegible]

Sex: Male Days in Relative to Start Date

| 1536 mg/kg/day (Group 4) | uvol/ATLAS | | | | Olympus Chem Pla |
|---|---|---|---|---|---|
| | KET (mg/dL) | UHB | BLD | URO (EU/dL) | UMTP (mg/dL) |
| | 22 | 22 | 22 | 22 | 22 |
| 7061 | TRACE | NEGATIVE | SMALL | 0.2 | 77 |
| 7062 | NEGATIVE | NEGATIVE | NEGATIVE | 0.2 | 84 |
| 7063 | 15 | NEGATIVE | NEGATIVE | 0.2 | 120 |
| 7064 | NEGATIVE | NEGATIVE | MODERATE | 0.2 | 48 |
| 7065 | NEGATIVE | NEGATIVE | SMALL | 0.2 | 53 |
| 7066 | NEGATIVE | NEGATIVE | LARGE | 0.2 | 97 |
| 7067 | 15 P | NEGATIVE P | LARGE P | 0.2 P | 108 |
| 7068 | TRACE | NEGATIVE | SMALL | 0.2 | 92 |
| 7069 | NEGATIVE | NEGATIVE | NEGATIVE | 0.2 | 380 |
| 7070 | TRACE | NEGATIVE | LARGE | 0.2 | 55 |

1 ISC Fecal contamination observed.
Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

[illegible]

Sex: Female Day(s) Relative to Start Date

| 0 mg/kg/day (Group 1) | uvol/ATLAS | | | | | | |
|---|---|---|---|---|---|---|---|
| | QUAL | COL | CLAR | UVOL (mL) | pH | SG | UGLC (mg/dL) |
| | 22 | 22 | 22 | 22 | 22 | 22 | 22 |
| 7011 | Light | Yellow | Clear | 0.5 | 6.0 | 1.100 [1] | NEGATIVE |
| 7012 | Light | Yellow | Clear | 1.2 | 6.0 | 1.039 | NEGATIVE |
| 7013 | Light | Yellow | Hazy | 7.6 | 6.5 | 1.025 | NEGATIVE |
| 7014 | Light | Yellow | Hazy | 3.6 | 7.0 | 1.038 | NEGATIVE |
| 7015 | Light | Yellow | Clear | 3.8 | 6.0 | 1.047 | NEGATIVE |
| 7016 | Light | Yellow | Clear | 18.2 | 6.5 | 1.012 | NEGATIVE |
| 7017 | Light | Yellow | Clear | 15.4 | 6.5 | 1.010 | NEGATIVE |
| 7018 | Light | Yellow | Clear | 0.9 | 6.5 | 1.058 | NEGATIVE |
| 7019 | Light | Yellow | Clear | 15.0 | 6.0 | 1.013 | NEGATIVE |
| 7020 | Medium | Yellow | Cloudy | 8.6 | 7.0 | 1.025 | NEGATIVE |

1 IRC Specific gravity result is >1.100

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results Ice
Soy Leghemoglobin Preparation A 28-Day Dietary Study in Rats

[illegible]

Sex: Female Day(s) Relative to Start Date

| n mg/kg/day (Group 1 | uvol/ATLAS | | | | Olympus Chem Phi |
|---|---|---|---|---|---|
| | KET (mg/dL) | UHIL | BLD | URO (EU/dL) | UMTP (mg/dL) |
| | 22 | 22 | 22 | 22 | 22 |
| 7011 | NEGATIVE | SMALL | NEGATIVE | 0.2 | 127 |
| 7012 | NEGATIVE | NEGATIVE | NEGATIVE | 0.2 | 34 |
| 7013 | NEGATIVE | NEGATIVE | TRACE | 0.2 | 35 |
| 7014 | NEGATIVE | NEGATIVE | SMALL | 0.2 | 37 |
| 7015 | NEGATIVE | NEGATIVE | NEGATIVE | 0.2 | 47 |
| 7016 | NEGATIVE | NEGATIVE | NEGATIVE | 0.2 | 11 |
| 7017 | NEGATIVE | NEGATIVE | NEGATIVE | 0.2 | 9 |
| 7018 | NEGATIVE | NEGATIVE | LARGE | 0.2 | 69 |
| 7019 | NEGATIVE | NEGATIVE | NEGATIVE | 0.2 | 22 |
| 7020 | NEGATIVE | NEGATIVE | MODERATE | 0.2 | 38 |

Group 2 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

[illegible]

Sex: Female Day(s) Relative to Start Date

| 512 mg/kg/day Group 2 | uroMALAS | | | | | | |
|---|---|---|---|---|---|---|---|
| | QUAL | COL | CLAR | UVOL ml/L | pH | SG | UGLC mg/dL |
| | 22 | 22 | 22 | 22 | 22 | 22 | 22 |
| 7031 | Light | Yellow | Clear | 5.8 | 6.0 | 1.031 | NEGATIVE |
| 7032 | Light | Yellow | Hazy | 12.4 | 7.0 | 1.013 | NEGATIVE |
| 7033 | Light | Yellow | Clear | 1.0 | 6.0 | 1.026 | NEGATIVE |
| 7034 | Light | Yellow | Hazy | 7.6 | 6.5 | 1.020 | NEGATIVE |
| 7035 | Light | Yellow | Clear | 11.2 | 6.0 | 1.013 | NEGATIVE |
| 7036 | Light | Yellow | Clear | 16.8 | 6.5 | 1.011 | NEGATIVE |
| 7037 | Light | Yellow | Clear | 2.8 | 6.0 | 1.040 | NEGATIVE |
| 7038 | Medium | Yellow | Hazy | 3.6 | 6.6 | 1.053 | NEGATIVE |
| 7039 | Light | Yellow | Clear | 1.0 | 6.0 | 1.036 | NEGATIVE |
| 7040 | Light | Yellow | Clear | 3.0 | 5.5 | 1.062 | NEGATIVE |

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

[illegible]

Sex: Female Day(s) Relative to Start Date

| 512 mg/kg/day Group 2 | nvol-ATLAS | | | | Olympus Chem Phi |
|---|---|---|---|---|---|
| | KET (mg/dL) | UBL | BLD | URO (EU/dL) | UMTP (mg/dL) |
| | 22 | 22 | 22 | 22 | 22 |
| 7031 | TRACE | NEGATIVE | NEGATIVE | 0.2 | 35 |
| 7032 | NEGATIVE | NEGATIVE | MODERATE | 0.2 | 17 |
| 7033 | NEGATIVE | NEGATIVE | NEGATIVE | 0.2 | 90 |
| 7034 | NEGATIVE | NEGATIVE | MODERATE | 0.2 | 29 |
| 7035 | NEGATIVE | NEGATIVE | NEGATIVE | 0.2 | 16 |
| 7036 | NEGATIVE | NEGATIVE | NEGATIVE | 0.2 | 14 |
| 7037 | TRACE | SMALL | SMALL | 0.2 | 45 |
| 7038 | TRACE | SMALL | MODERATE | 0.2 | 61 |
| 7039 | TRACE | NEGATIVE | NEGATIVE | 0.2 | 41 |
| 7040 | NEGATIVE | NEGATIVE | MODERATE | 0.2 | 65 |

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation A 28-Day Dietary Study in Rats

[illegible]

Sex: Female Day(s) Relative to Start Date

| 1021 mg/kg/day Group 3 | uvol-ATLAS | | | | | | |
|---|---|---|---|---|---|---|---|
| | QUAL | COL | CLAR | UVOL (mL) | pH | SG | UGLC (mg/dL) |
| | 22 | 22 | 22 | 22 | 22 | 22 | 22 |
| 7051 | Medium | Yellow | Hazy | 3.0 | 6.0 | 1.046 | NEGATIVE |
| 7052 | Light | Yellow | Clear | 3.6 | 6.0 | 1.043 | NEGATIVE |
| 7053 | Light | Yellow | Cloudy | 8.0 | 7.0 | 1.021 | NEGATIVE |
| 7054 | Light | Yellow | Clear | 10.8 | 6.0 | 1.017 | NEGATIVE |
| 7055 | Light | Yellow | Clear | 3.0 | 6.5 | 1.040 | NEGATIVE |
| 7056 | Light | Yellow | Clear | 10.2 | 6.5 | 1.020 | NEGATIVE |
| 7057 | Medium ♂ | Brown ♂ | Turbid ♂ | 4.0 ♂ | 7.5 ♂ | 1.028 ♂ | NEGATIVE ♂ |
| 7058 | Medium | Yellow | Cloudy | 7.0 | 7.0 | 1.022 | NEGATIVE |
| 7059 | Light ♂ | Brown ♂ | Cloudy ♂ | 9.6 ♂ | 7.5 ♂ | 1.017 ♂ | NEGATIVE ♂ |
| 7060 | Light | Yellow | Clear | 6.2 | 6.0 | 1.027 | NEGATIVE |

[ ISC Fecal contamination observed ]
Group 2 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation A 28-Day Dietary Study in Rats

Individual Animal Clinical Pathology Data

Sex: Female Day(s) Relative to Start Date

| 1021 mg/kg/day Group 3 | nvolATLAS | | | | Olympus Chem Plu |
|---|---|---|---|---|---|
| | KET (mg/dL) | UBIL | BLD | URO (EU/dL) | UMTP (mg/dL) |
| | 22 | 22 | 22 | 22 | 22 |
| 7051 | TRACE | SMALL | LARGE | 0.2 | 43 |
| 7052 | NEGATIVE | NEGATIVE | NEGATIVE | 0.2 | 41 |
| 7053 | TRACE | NEGATIVE | LARGE | 0.2 | 31 |
| 7054 | NEGATIVE | NEGATIVE | NEGATIVE | 0.2 | 15 |
| 7055 | NEGATIVE | NEGATIVE | NEGATIVE | 0.2 | 40 |
| 7056 | NEGATIVE | NEGATIVE | NEGATIVE | 0.2 | 20 |
| 7057 | TRACE [1] | SMALL [1] | LARGE [1] | 0.2 [1] | 56 |
| 7058 | NEGATIVE | NEGATIVE | LARGE | 0.2 | 32 |
| 7059 | NEGATIVE [1] | NEGATIVE [1] | LARGE [1] | 0.2 [1] | 35 |
| 7060 | NEGATIVE | NEGATIVE | LARGE | 0.2 | 30 |

[1] ISC Fecal contamination observed.]
Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation - A 28-Day Dietary Study in Rats

[illegible]

Sex: Female Day(s) Relative to Start Date

| 1536 mg/kg/day (Group 4) | uvol/ATLAS | | | | | | |
|---|---|---|---|---|---|---|---|
| | QUAL | COL | CLAR | UVOL (mL) | pH | SG | UGLC (mg/dL) |
| | 22 | 22 | 22 | 22 | 22 | 22 | 22 |
| 7071 | Light [1] | Brown [1] | Cloudy [1] | 7.8 [1] | 7.0 [1] | 1.024 [1] | NEGATIVE [1] |
| 7072 | Light | Yellow | Clear | 7.8 | 6.0 | 1.022 | NEGATIVE |
| 7073 | Light | Yellow | Clear | 5.0 | 6.0 | 1.026 | NEGATIVE |
| 7074 | Light | Yellow | Clear | 2.6 | 6.0 | 1.046 | NEGATIVE |
| 7075 | Light | Yellow | Clear | 12.8 | 6.0 | 1.015 | NEGATIVE |
| 7076 | Light | Yellow | Clear | 3.0 | 6.0 | 1.056 | NEGATIVE |
| 7077 | Medium | Yellow | Hazy | 7.0 | 6.5 | 1.027 | NEGATIVE |
| 7078 | Light | Yellow | Clear | 14.0 | 6.5 | 1.014 | NEGATIVE |
| 7079 | Dark [1] | Brown [1] | Turbid [1] | 4.0 [1] | 8.0 [1] | 1.031 [1] | NEGATIVE [1] |
| 7080 | Light | Yellow | Clear | 2.2 | 6.5 | 1.039 | NEGATIVE |

[1] ISC Fecal contamination observed.
Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation - A 28-Day Dietary Study in Rats

Individual Animal Clinical Pathology Data

Sex: Female Day(s) Relative to Start Date

| 1536 mg/kg/day Group 4 | nvolATLAS | | | | Olympus Chem Pla |
|---|---|---|---|---|---|
| | KET (mg/dL) | UBIL | BLD | URO (EU/dL) | UMTP (mg/dL) |
| | 22 | 22 | 22 | 22 | 22 |
| 7071 | NEGATIVE [1] | NEGATIVE [1] | LARGE [1] | 0.2 [1] | 47 |
| 7072 | NEGATIVE | NEGATIVE | SMALL | 0.2 | 23 |
| 7073 | NEGATIVE | NEGATIVE | TRACE | 0.2 | 42 |
| 7074 | NEGATIVE | NEGATIVE | MODERATE | 0.2 | 49 |
| 7075 | NEGATIVE | NEGATIVE | SMALL | 0.2 | 15 |
| 7076 | NEGATIVE | NEGATIVE | NEGATIVE | 0.2 | 59 |
| 7077 | NEGATIVE | NEGATIVE | LARGE | 0.2 | 38 |
| 7078 | NEGATIVE | NEGATIVE | LARGE | 0.2 | 15 |
| 7079 | TRACE [1] | MODERATE [1] | LARGE [1] | 1.0 [1] | 118 |
| 7080 | NEGATIVE | NEGATIVE | MODERATE | 0.2 | 38 |

1 ISC Fecal contamination observed

Group 2 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation A 28-Day Dietary Study in Rats

Individual Animal Clinical Pathology Data

Sex Male Day(s) Relative to Start Date

| (-) mg/kg/day Group 1 | Urine Microscopic | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | EPIT (-hpf) | UWBC (-hpf) | URBC (-hpf) | NCRY (-hpf) | MICR (-hpf) | SPER (-lpf) | REPI (-hpf) | MUC (-lpf) |
| | 22 | 22 | 22 | 22 | 22 | 22 | 22 | 22 |
| 7001 | Few (+) | - (+) | - (+) | Few (+) | Few (+) | Mod (+) | - (+) | - (+) |
| 7002 | Few | Few | - | Few | Mod | Mod | - | Few |
| 7003 | Few | - | - | Few | Few | Mod | - | - |
| 7004 | Few | | - | Few | Few | Few | - | - |
| 7005 | Few | - | - | Few | Mod | Few | - | - |
| 7006 | Few | - | - | Mod | Mod | Mod | | |
| 7007 | - | - | - | Few | Few | Few | - | - |
| 7008 | - | - | - | - | Few | Few | - | - |
| 7009 | Few | Few | - | Mod | Mod | Mod | | |
| 7010 | Few | - | - | Few | Few | Few | - | - |

[ ISC urine below recommended volume ]

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.
Group 3: 1021 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 3536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

Sex: Male  Day(s) Relative to Start Date

| 512 mg/kg/day Group 2 | Urine Microscopy | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | EPIT (/hpf) | UWBC (/hpf) | URBC (/hpf) | SQRY (/hpf) | MICR (/hpf) | SPER (/hpf) | RESP (/hpf) | MUC (/hpf) |
| | 22 | 22 | 22 | 22 | 22 | 22 | 22 | 22 |
| 7021 | Few | - | - | Few | Few | Few | - | |
| 7022 | Few | Few | - | Mod | Mod | Mod | - | - |
| 7023 | Few | Few | - | Few | Few | Man | - | - |
| 7024 | | - | - | Few | Few | Few | - | - |
| 7025 | Few | - | - | Few | Few | Few | - | - |
| 7026 | - | - | - | Few | Few | Few | | - |
| 7027 | Few | Few | - | Few | Mod | Few | - | - |
| 7028 | QNS | | | | | | | |
| 7029 | Few | - | - | Few | Few | Few | | |
| 7030 | Few | - | - | Few | Few | Few | - | - |

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient.
Group 4: 2536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

Clinical Pathology Results for
Soy Leghemoglobin Preparation A 28-Day Dietary Study in Rats

[illegible]

Sex Male Day(s) Relative to Start Date

| 1024 mg/kg/day Group 3 | Urine Microscopic | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | EPIT (/hpf) | UWBC (/hpf) | URBC (/hpf) | NCRY (/hpf) | MICR (/hpf) | SPER (/hpf) | REPI (/hpf) | MUC (/hpf) |
| | 22 | 22 | 22 | 22 | 22 | 22 | 22 | 22 |
| 7041 | Few | - | - | Few | Few | Few | - | - |
| 7042 | Few | - | - | - | Few | Few | - | - |
| 7043 | Few | Few | - | Few | Few | Few | - | - |
| 7044 | Few | Few | | Few | Mod | Mod | - | - |
| 7045 | Few | Few | - | Mod | Mod | Mod | - | - |
| 7046 | Few | Few | - | Man | Mod | Mod | | - |
| 7047 | - | - | - | - | Few | Few | - | - |
| 7048 | Few | Few | - | Mod | Mod | Mod | - | - |
| 7049 | Few | - | - | Few | Few | Few | - | |
| 7050 | Few | - | - | Few | Few | Few | - | - |

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 2556 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

Individual Animal Clinical Pathology Data

Sex: Male  Day(s) Relative to Start Date

| 153b mg/kg/day Group 4 | Urine Macroscopic | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | EPIT (/hpf) | UWBC (/hpf) | URBC (/hpf) | NCRY (/hpf) | MICR (/hpf) | SPER (/hpf) | REPI (/hpf) | MUC (/hpf) |
| | 22 | 22 | 22 | 22 | 22 | 22 | 22 | 22 |
| 7061 | - | - | - | - | Few | Few | - | - |
| 7062 | Few | - | - | Few | Few | Few | - | - |
| 7063 | Few | - | - | Few | Few | Few | - | - |
| 7064 | Few | | | Few | Mod | Few | - | - |
| 7065 | Few | Few | - | Few | Few | Mod | Few | - |
| 7066 | Few | - | - | Few | Few | Few | - | - |
| 7067 | Few | - | - | Mod | Mod | Mod | - | - |
| 7068 | - | - | - | - | Few | Few | - | - |
| 7069 | Few (1) | Few (1) | - (1) | Few (1) | Mod (1) | Mod (1) | (1) | (1) |
| 7070 | Few | Few | - | Few | Few | Few | - | - |

(1) SC urine below recommended volume)

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1021 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

Individual Animal Clinical Pathology Data

Sex: Female  Day(s) Relative to Start Date

| Group (mg/kg/day) | Urine Microscopic | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | EPIT (/hpf) | UWBC (/hpf) | URBC (/hpf) | NCRY (/hpf) | MICR (/hpf) | SPER (/lpf) | REPI (/hpf) | MUC (/lpf) |
| | 22 | 22 | 22 | 22 | 22 | 22 | 22 | 22 |
| 7011 | Few | Few | - | Few | Mod | - | - | - |
| 7012 | Few | - | - | Few | Few | - | Few | |
| 7013 | Few | Few | - | Mod | Mod | - | - | - |
| 7014 | Few | Few | - | Mod | Mod | - | - | - |
| 7015 | Few | Few | - | - | Few | - | - | - |
| 7016 | Few | - | - | Few | Few | - | - | - |
| 7017 | Few | | - | - | Few | - | - | |
| 7018 | Few (1) | (1) | - (1) | Few (1) | Few (1) | - (1) | - (1) | - (1) |
| 7019 | Few | - | - | Few | Few | - | - | - |
| 7020 | Few | Few | - | Few | Mod | - | - | - |

[TSC urine below recommended volume]

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

Individual Animal Clinical Pathology Data

Sex: Female  Day(s) Relative to Start Date

| 512 mg kg/day Group 2 | Urine Microscopic | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | EPIT (/hpf) | UWBC (/hpf) | URBC (/hpf) | NCRY (/hpf) | MICR (/hpf) | SPER (/hpf) | REPI (/hpf) | MUC (/hpf) |
| | 22 | 22 | 22 | 22 | 22 | 22 | 22 | 22 |
| 7031 | Few | Few | - | Few | Few | - | - | - |
| 7032 | Few | - | - | Mod | Mod | - | | |
| 7033 | Few | Few | - | Few | Few | - | - | - |
| 7034 | - | - | - | Few | Mod | - | - | - |
| 7035 | Few | Few | - | Few | Mod | - | - | - |
| 7036 | - | - | - | Few | Few | - | - | - |
| 7037 | Few [1] | Few [1] | - [1] | Few [1] | Mod [1] | - [1] | [1] | - [1] |
| 7038 | Few | - | - | Mod | Mod | - | - | - |
| 7039 | - | - | - | Few | Few | - | - | - |
| 7040 | Few | - | - | Few | Few | - | - | - |

[1] [SC urine below recommended volume]

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient.
Group 4: 2048 mg/kg/day of test substance corresponds to 1000 mg/kg/day of the active ingredient.

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

[illegible]

Sex: Female  Day(s) Relative to Start Date

| 1024 mg/kg/day Group 3 | Urine Microscopic | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | EPIT (/hpf) | UWBC (/hpf) | URBC (/hpf) | NCRY (/hpf) | MCRK (/hpf) | SPER (/hpf) | REPI (/hpf) | MUC (/hpf) |
| | 22 | 22 | 22 | 22 | 22 | 22 | 22 | 22 |
| 7051 | Few | Few | - | Few | Mod | - | - | - |
| 7052 | Few | | - | Few | Mod | - | | |
| 7053 | Few | Few | - | Mod | Mod | - | - | - |
| 7054 | Few | Few | - | Mod | Mod | - | - | - |
| 7055 | Few | Few | - | Few | Few | - | - | - |
| 7056 | Few | - | - | Few | Few | - | - | - |
| 7057 | Few | Few | Few | Man | Man | - | | |
| 7058 | Few | Few | Few | Mod | Man | - | - | - |
| 7059 | Few | Few | Few | Man | Man | - | - | - |
| 7060 | Few | - | - | Mod | Mod | - | - | - |

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 2048 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

Clinical Pathology Results for
Soy Leghemoglobin Preparation: A 28-Day Dietary Study in Rats

Individual Animal Clinical Pathology Data

Sex: Female  Day(s) Relative to Start Date

| 1536 mg/kg/day Group 4 | Urine Microscopic | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | EPIT (/hpf) | UWBC (/hpf) | URBC (/hpf) | NCRY (/hpf) | MICR (/hpf) | SPER (/hpf) | REPI (/hpf) | MUC (/hpf) |
| | 22 | 22 | 22 | 22 | 22 | 22 | 22 | 22 |
| 7071 | Few | Few | - | Mod | Mod | - | - | Few |
| 7072 | Few | | - | Few | Few | - | | |
| 7073 | Few | - | - | Few | Few | - | - | - |
| 7074 | Few [1] | - [1] | - [1] | Few [1] | Mod [1] | - [1] | - [1] | - [1] |
| 7075 | Few | Few | - | Few | Few | - | - | - |
| 7076 | Few | - | - | Few | Few | - | - | - |
| 7077 | Few | - | - | Few | Mod | - | | |
| 7078 | Few | | - | Few | Few | - | - | |
| 7079 | Few | Few | Few | Mod | Mod | - | - | - |
| 7080 | Few | - | - | Few | Few | - | - | - |

[1] SC urine below recommended volume]

Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient

# APPENDIX O: ANIMAL NUMBERS, DOSE GROUPS, AND FATES[1]

## PRODUCT IDENTIFICATION

Soy Leghemoglobin Preparation

[1] Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient.
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

Individual Animal Fates

PSL Study Number 43166
A 28-Day Dietary Study in Rats

| Group | Dose Level | Sex | Animal | Cage | Removal Day | Removal Week | Removal Date | Removal Time | Time Slot | Removal Symptom | Pathology Reason |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 0 mg/kg/day | Male | 7001 | 1 | 29 | 4 | 27/10/16 | 6:50 | . | Term | Term |
| | | | 7002 | 1 | 29 | 4 | 27/10/16 | 6:51 | . | Term | Term |
| | | | 7003 | 2 | 29 | 4 | 27/10/16 | 6:51 | . | Term | Term |
| | | | 7004 | 2 | 29 | 4 | 27/10/16 | 6:51 | . | Term | Term |
| | | | 7005 | 3 | 29 | 4 | 27/10/16 | 6:52 | . | Term | Term |
| | | | 7006 | 3 | 29 | 4 | 27/10/16 | 6:52 | . | Term | Term |
| | | | 7007 | 4 | 29 | 4 | 27/10/16 | 6:52 | . | Term | Term |
| | | | 7008 | 4 | 29 | 4 | 27/10/16 | 6:53 | . | Term | Term |
| | | | 7009 | 5 | 29 | 4 | 27/10/16 | 6:53 | . | Term | Term |
| | | | 7010 | 5 | 29 | 4 | 27/10/16 | 6:53 | . | Term | Term |
| 1 | 0 mg/kg/day | Female | 7011 | 6 | 30 | 4 | 28/10/16 | 6:50 | . | Term | Term |
| | | | 7012 | 6 | 30 | 4 | 28/10/16 | 6:50 | . | Term | Term |
| | | | 7013 | 7 | 30 | 4 | 28/10/16 | 6:50 | . | Term | Term |
| | | | 7014 | 7 | 30 | 4 | 28/10/16 | 6:51 | . | Term | Term |
| | | | 7015 | 8 | 30 | 4 | 28/10/16 | 6:51 | . | Term | Term |
| | | | 7016 | 8 | 30 | 4 | 28/10/16 | 6:51 | . | Term | Term |
| | | | 7017 | 9 | 30 | 4 | 28/10/16 | 6:52 | . | Term | Term |
| | | | 7018 | 9 | 30 | 4 | 28/10/16 | 6:52 | . | Term | Term |
| | | | 7019 | 10 | 30 | 4 | 28/10/16 | 6:53 | . | Term | Term |
| | | | 7020 | 10 | 30 | 4 | 28/10/16 | 6:53 | . | Term | Term |
| 2 | 512 mg/kg/day | Male | 7021 | 11 | 29 | 4 | 27/10/16 | 6:56 | . | Term | Term |
| | | | 7022 | 11 | 29 | 4 | 27/10/16 | 6:57 | . | Term | Term |
| | | | 7023 | 12 | 29 | 4 | 27/10/16 | 6:57 | . | Term | Term |
| | | | 7024 | 12 | 29 | 4 | 27/10/16 | 6:57 | . | Term | Term |
| | | | 7025 | 13 | 29 | 4 | 27/10/16 | 6:58 | . | Term | Term |
| | | | 7026 | 13 | 29 | 4 | 27/10/16 | 6:58 | . | Term | Term |
| | | | 7027 | 14 | 29 | 4 | 27/10/16 | 6:59 | . | Term | Term |
| | | | 7028 | 14 | 29 | 4 | 27/10/16 | 6:59 | . | Term | Term |
| | | | 7029 | 15 | 29 | 4 | 27/10/16 | 6:59 | . | Term | Term |

Individual Animal Fates

PSL Study Number 43166
A 28-Day Dietary Study in Rats

| Group | Dose Level | Sex | Animal | Cage | Removal Day | Removal Week | Removal Date | Removal Time | Time Slot | Removal Symptom | Pathology Reason |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 2 | 512 mg/kg/day | Male | 7030 | 15 | 29 | 4 | 27/10/16 | 7:00 | . | Term | Term |
| 2 | 512 mg/kg/day | Female | 7031 | 16 | 30 | 4 | 28/10/16 | 6:54 | . | Term | Term |
| | | | 7032 | 16 | 30 | 4 | 28/10/16 | 6:54 | . | Term | Term |
| | | | 7033 | 17 | 30 | 4 | 28/10/16 | 6:55 | . | Term | Term |
| | | | 7034 | 17 | 30 | 4 | 28/10/16 | 6:55 | . | Term | Term |
| | | | 7035 | 18 | 30 | 4 | 28/10/16 | 6:55 | . | Term | Term |
| | | | 7036 | 18 | 30 | 4 | 28/10/16 | 6:56 | . | Term | Term |
| | | | 7037 | 19 | 30 | 4 | 28/10/16 | 6:56 | . | Term | Term |
| | | | 7038 | 19 | 30 | 4 | 28/10/16 | 6:56 | . | Term | Term |
| | | | 7039 | 20 | 30 | 4 | 28/10/16 | 6:57 | . | Term | Term |
| | | | 7040 | 20 | 30 | 4 | 28/10/16 | 6:57 | . | Term | Term |
| 3 | 1024 mg/kg/day | Male | 7041 | 21 | 29 | 4 | 27/10/16 | 7:00 | . | Term | Term |
| | | | 7042 | 21 | 29 | 4 | 27/10/16 | 7:00 | . | Term | Term |
| | | | 7043 | 22 | 29 | 4 | 27/10/16 | 7:01 | . | Term | Term |
| | | | 7044 | 22 | 29 | 4 | 27/10/16 | 7:01 | . | Term | Term |
| | | | 7045 | 23 | 29 | 4 | 27/10/16 | 7:02 | . | Term | Term |
| | | | 7046 | 23 | 29 | 4 | 27/10/16 | 7:02 | . | Term | Term |
| | | | 7047 | 24 | 29 | 4 | 27/10/16 | 7:03 | . | Term | Term |
| | | | 7048 | 24 | 29 | 4 | 27/10/16 | 7:03 | . | Term | Term |
| | | | 7049 | 25 | 29 | 4 | 27/10/16 | 7:04 | . | Term | Term |
| | | | 7050 | 25 | 29 | 4 | 27/10/16 | 7:04 | . | Term | Term |
| 3 | 1024 mg/kg/day | Female | 7051 | 26 | 30 | 4 | 28/10/16 | 6:58 | . | Term | Term |
| | | | 7052 | 26 | 30 | 4 | 28/10/16 | 6:58 | . | Term | Term |
| | | | 7053 | 27 | 30 | 4 | 28/10/16 | 6:58 | . | Term | Term |
| | | | 7054 | 27 | 30 | 4 | 28/10/16 | 6:59 | . | Term | Term |
| | | | 7055 | 28 | 30 | 4 | 28/10/16 | 6:59 | . | Term | Term |
| | | | 7056 | 28 | 30 | 4 | 28/10/16 | 6:59 | . | Term | Term |
| | | | 7057 | 29 | 30 | 4 | 28/10/16 | 6:59 | . | Term | Term |

Individual Animal Fates

PSL Study Number 43166
A 28-Day Dietary Study in Rats

| Group | Dose Level | Sex | Animal | Cage | Removal Day | Removal Week | Removal Date | Removal Time | Time Slot | Removal Symptom | Pathology Reason |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 3 | 1024 mg/kg/day | Female | 7058 | 29 | 30 | 4 | 28/10/16 | 7:00 | . | Term | Term |
| | | | 7059 | 30 | 30 | 4 | 28/10/16 | 7:00 | . | Term | Term |
| | | | 7060 | 30 | 30 | 4 | 28/10/16 | 7:01 | . | Term | Term |
| 4 | 1536 mg/kg/day | Male | 7061 | 31 | 29 | 4 | 27/10/16 | 7:05 | . | Term | Term |
| | | | 7062 | 31 | 29 | 4 | 27/10/16 | 7:05 | . | Term | Term |
| | | | 7063 | 32 | 29 | 4 | 27/10/16 | 7:05 | . | Term | Term |
| | | | 7064 | 32 | 29 | 4 | 27/10/16 | 7:06 | . | Term | Term |
| | | | 7065 | 33 | 29 | 4 | 27/10/16 | 7:06 | . | Term | Term |
| | | | 7066 | 33 | 29 | 4 | 27/10/16 | 7:06 | . | Term | Term |
| | | | 7067 | 34 | 29 | 4 | 27/10/16 | 7:07 | . | Term | Term |
| | | | 7068 | 34 | 29 | 4 | 27/10/16 | 7:07 | . | Term | Term |
| | | | 7069 | 35 | 29 | 4 | 27/10/16 | 7:07 | . | Term | Term |
| | | | 7070 | 35 | 29 | 4 | 27/10/16 | 7:08 | . | Term | Term |
| 4 | 1536 mg/kg/day | Female | 7071 | 36 | 30 | 4 | 28/10/16 | 7:01 | . | Term | Term |
| | | | 7072 | 36 | 30 | 4 | 28/10/16 | 7:01 | . | Term | Term |
| | | | 7073 | 37 | 30 | 4 | 28/10/16 | 7:02 | . | Term | Term |
| | | | 7074 | 37 | 30 | 4 | 28/10/16 | 7:02 | . | Term | Term |
| | | | 7075 | 38 | 30 | 4 | 28/10/16 | 7:02 | . | Term | Term |
| | | | 7076 | 38 | 30 | 4 | 28/10/16 | 7:03 | . | Term | Term |
| | | | 7077 | 39 | 30 | 4 | 28/10/16 | 7:03 | . | Term | Term |
| | | | 7078 | 39 | 30 | 4 | 28/10/16 | 7:03 | . | Term | Term |
| | | | 7079 | 40 | 30 | 4 | 28/10/16 | 7:04 | . | Term | Term |
| | | | 7080 | 40 | 30 | 4 | 28/10/16 | 7:04 | . | Term | Term |

# APPENDIX P: INDIVIDUAL ANIMAL NECROPSY OBSERVATIONS[1]

## PRODUCT IDENTIFICATION

Soy Leghemoglobin Preparation

[1] Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient.
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

Individual Animal Necropsy Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Animal: 7001 Group: 1 Sex: Male
Dose: 0
Necropsy Date: 10/27/2016

**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7002 Group: 1 Sex: Male
Dose: 0
Necropsy Date: 10/27/2016

**Gross Pathology Observations [Correlation]:**

testes-combined : size: 1 x 1.5 cm
testes-combined : right; small; soft
epididymides-combined : size: 3 x 0.5 cm
epididymides-combined : right; small

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7003 Group: 1 Sex: Male
Dose: 0
Necropsy Date: 10/27/2016

**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7004 Group: 1 Sex: Male
Dose: 0
Necropsy Date: 10/27/2016

**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7005 Group: 1 Sex: Male
Dose: 0
Necropsy Date: 10/27/2016

**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7006 Group: 1 Sex: Male
Dose: 0
Necropsy Date: 10/27/2016

Individual Animal Necropsy Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7007 Group: 1 Sex: Male
Dose: 0
Necropsy Date: 10/27/2016

**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7008 Group: 1 Sex: Male
Dose: 0
Necropsy Date: 10/27/2016

**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7009 Group: 1 Sex: Male
Dose: 0
Necropsy Date: 10/27/2016

**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7010 Group: 1 Sex: Male
Dose: 0
Necropsy Date: 10/27/2016

**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7011 Group: 1 Sex: Female
Dose: 0
Necropsy Date: 10/28/2016

**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7012 Group: 1 Sex: Female
Dose: 0
Necropsy Date: 10/28/2016

Individual Animal Necropsy Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7013 Group: 1 Sex: Female
Dose: 0
Necropsy Date: 10/28/2016

**Gross Pathology Observations [Correlation]:**

uterus : fluid filled

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7014 Group: 1 Sex: Female
Dose: 0
Necropsy Date: 10/28/2016

**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7015 Group: 1 Sex: Female
Dose: 0
Necropsy Date: 10/28/2016

**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7016 Group: 1 Sex: Female
Dose: 0
Necropsy Date: 10/28/2016

**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7017 Group: 1 Sex: Female
Dose: 0
Necropsy Date: 10/28/2016

**Gross Pathology Observations [Correlation]:**

uterus : fluid filled

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7018 Group: 1 Sex: Female
Dose: 0

Individual Animal Necropsy Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Necropsy Date: 10/28/2016

**Gross Pathology Observations [Correlation]:**

uterus : fluid filled

Any remaining protocol required tissues, which have been examined, have no visible lesions

| Animal: | 7019 | Group: | 1 | Sex: | Female |
|---|---|---|---|---|---|
| | | Dose: | 0 | | |

Necropsy Date: 10/28/2016

**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

| Animal: | 7020 | Group: | 1 | Sex: | Female |
|---|---|---|---|---|---|
| | | Dose: | 0 | | |

Necropsy Date: 10/28/2016

**Gross Pathology Observations [Correlation]:**

uterus : fluid filled

Any remaining protocol required tissues, which have been examined, have no visible lesions

| Animal: | 7021 | Group: | 2 | Sex: | Male |
|---|---|---|---|---|---|
| | | Dose: | 512 | | |

Necropsy Date: 10/27/2016

**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

| Animal: | 7022 | Group: | 2 | Sex: | Male |
|---|---|---|---|---|---|
| | | Dose: | 512 | | |

Necropsy Date: 10/27/2016

**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

| Animal: | 7023 | Group: | 2 | Sex: | Male |
|---|---|---|---|---|---|
| | | Dose: | 512 | | |

Necropsy Date: 10/27/2016

**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

| Animal: | 7024 | Group: | 2 | Sex: | Male |
|---|---|---|---|---|---|

Individual Animal Necropsy Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Dose: 512

Necropsy Date: 10/27/2016

**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7025 Group: 2 Sex: Male
Dose: 512

Necropsy Date: 10/27/2016

**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7026 Group: 2 Sex: Male
Dose: 512

Necropsy Date: 10/27/2016

**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7027 Group: 2 Sex: Male
Dose: 512

Necropsy Date: 10/27/2016

**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7028 Group: 2 Sex: Male
Dose: 512

Necropsy Date: 10/27/2016

**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7029 Group: 2 Sex: Male
Dose: 512

Necropsy Date: 10/27/2016

**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Individual Animal Necropsy Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Animal: 7030 Group: 2 Dose: 512 Sex: Male

Necropsy Date: 10/27/2016

**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7031 Group: 2 Dose: 512 Sex: Female

Necropsy Date: 10/28/2016

**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7032 Group: 2 Dose: 512 Sex: Female

Necropsy Date: 10/28/2016

**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7033 Group: 2 Dose: 512 Sex: Female

Necropsy Date: 10/28/2016

**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7034 Group: 2 Dose: 512 Sex: Female

Necropsy Date: 10/28/2016

**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7035 Group: 2 Dose: 512 Sex: Female

Necropsy Date: 10/28/2016

**Last Clinical Observations:**

Alopecia, Left Forelimb, Moderate
Alopecia, Right Forelimb, Moderate

Individual Animal Necropsy Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

**Gross Pathology Observations [Correlation]:**

non correlated finding : no correlated finding [Alopecia, Left Forelimb, Moderate (C) | Alopecia, Right Forelimb, Moderate (C)]

Any remaining protocol required tissues, which have been examined, have no visible lesions

| Animal: 7036 | Group: 2 | Sex: Female |
|---|---|---|
| | Dose: 512 | |
| Necropsy Date: 10/28/2016 | | |

**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

| Animal: 7037 | Group: 2 | Sex: Female |
|---|---|---|
| | Dose: 512 | |
| Necropsy Date: 10/28/2016 | | |

**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

| Animal: 7038 | Group: 2 | Sex: Female |
|---|---|---|
| | Dose: 512 | |
| Necropsy Date: 10/28/2016 | | |

**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

| Animal: 7039 | Group: 2 | Sex: Female |
|---|---|---|
| | Dose: 512 | |
| Necropsy Date: 10/28/2016 | | |

**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

| Animal: 7040 | Group: 2 | Sex: Female |
|---|---|---|
| | Dose: 512 | |
| Necropsy Date: 10/28/2016 | | |

**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

| Animal: 7041 | Group: 3 | Sex: Male |
|---|---|---|
| | Dose: 1024 | |
| Necropsy Date: 10/27/2016 | | |

Individual Animal Necropsy Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7042 Group: 3 Sex: Male
Dose: 1024
Necropsy Date: 10/27/2016

**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7043 Group: 3 Sex: Male
Dose: 1024
Necropsy Date: 10/27/2016

**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7044 Group: 3 Sex: Male
Dose: 1024
Necropsy Date: 10/27/2016

**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7045 Group: 3 Sex: Male
Dose: 1024
Necropsy Date: 10/27/2016

**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7046 Group: 3 Sex: Male
Dose: 1024
Necropsy Date: 10/27/2016

**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7047 Group: 3 Sex: Male
Dose: 1024
Necropsy Date: 10/27/2016

Individual Animal Necropsy Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

**Gross Pathology Observations [Correlation]:**

brain : focal depressed area on left hemisphere. Possible prosection damage

Any remaining protocol required tissues, which have been examined, have no visible lesions

| Animal: | 7048 | Group: | 3 | Sex: | Male |
|---|---|---|---|---|---|
| | | Dose: | 1024 | | |

Necropsy Date: 10/27/2016

**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

| Animal: | 7049 | Group: | 3 | Sex: | Male |
|---|---|---|---|---|---|
| | | Dose: | 1024 | | |

Necropsy Date: 10/27/2016

**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

| Animal: | 7050 | Group: | 3 | Sex: | Male |
|---|---|---|---|---|---|
| | | Dose: | 1024 | | |

Necropsy Date: 10/27/2016

**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

| Animal: | 7051 | Group: | 3 | Sex: | Female |
|---|---|---|---|---|---|
| | | Dose: | 1024 | | |

Necropsy Date: 10/28/2016

**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

| Animal: | 7052 | Group: | 3 | Sex: | Female |
|---|---|---|---|---|---|
| | | Dose: | 1024 | | |

Necropsy Date: 10/28/2016

**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

| Animal: | 7053 | Group: | 3 | Sex: | Female |
|---|---|---|---|---|---|
| | | Dose: | 1024 | | |

Individual Animal Necropsy Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Necropsy Date: 10/28/2016

**Gross Pathology Observations [Correlation]:**

uterus : fluid filled

Any remaining protocol required tissues, which have been examined, have no visible lesions

| Animal: | 7054 | Group: | 3 | Sex: | Female |
|---|---|---|---|---|---|
| | | Dose: | 1024 | | |

Necropsy Date: 10/28/2016

**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

| Animal: | 7055 | Group: | 3 | Sex: | Female |
|---|---|---|---|---|---|
| | | Dose: | 1024 | | |

Necropsy Date: 10/28/2016

**Gross Pathology Observations [Correlation]:**

spleen : stricture

Any remaining protocol required tissues, which have been examined, have no visible lesions

| Animal: | 7056 | Group: | 3 | Sex: | Female |
|---|---|---|---|---|---|
| | | Dose: | 1024 | | |

Necropsy Date: 10/28/2016

**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

| Animal: | 7057 | Group: | 3 | Sex: | Female |
|---|---|---|---|---|---|
| | | Dose: | 1024 | | |

Necropsy Date: 10/28/2016

**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

| Animal: | 7058 | Group: | 3 | Sex: | Female |
|---|---|---|---|---|---|
| | | Dose: | 1024 | | |

Necropsy Date: 10/28/2016

**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

| Animal: | 7059 | Group: | 3 | Sex: | Female |
|---|---|---|---|---|---|

Individual Animal Necropsy Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Dose: 1024

Necropsy Date: 10/28/2016

**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7060 Group: 3 Sex: Female
Dose: 1024

Necropsy Date: 10/28/2016

**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7061 Group: 4 Sex: Male
Dose: 1536

Necropsy Date: 10/27/2016

**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7062 Group: 4 Sex: Male
Dose: 1536

Necropsy Date: 10/27/2016

**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7063 Group: 4 Sex: Male
Dose: 1536

Necropsy Date: 10/27/2016

**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7064 Group: 4 Sex: Male
Dose: 1536

Necropsy Date: 10/27/2016

**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Individual Animal Necropsy Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Animal: 7065 Group: 4 Sex: Male
Dose: 1536
Necropsy Date: 10/27/2016

**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7066 Group: 4 Sex: Male
Dose: 1536
Necropsy Date: 10/27/2016

**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7067 Group: 4 Sex: Male
Dose: 1536
Necropsy Date: 10/27/2016

**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7068 Group: 4 Sex: Male
Dose: 1536
Necropsy Date: 10/27/2016

**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7069 Group: 4 Sex: Male
Dose: 1536
Necropsy Date: 10/27/2016

**Last Clinical Observations:**

Eschar, Head, Superficial

**Gross Pathology Observations [Correlation]:**

non correlated finding : no correlated finding [Eschar, Head, Superficial (C)]

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7070 Group: 4 Sex: Male
Dose: 1536
Necropsy Date: 10/27/2016

Individual Animal Necropsy Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7071 Group: 4 Sex: Female
Dose: 1536
Necropsy Date: 10/28/2016

**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7072 Group: 4 Sex: Female
Dose: 1536
Necropsy Date: 10/28/2016

**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7073 Group: 4 Sex: Female
Dose: 1536
Necropsy Date: 10/28/2016

**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7074 Group: 4 Sex: Female
Dose: 1536
Necropsy Date: 10/28/2016

**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7075 Group: 4 Sex: Female
Dose: 1536
Necropsy Date: 10/28/2016

**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7076 Group: 4 Sex: Female
Dose: 1536
Necropsy Date: 10/28/2016

Individual Animal Necropsy Observations

PSL Study Number 43166
A 28-Day Dietary Study in Rats

**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7077 Group: 4 Sex: Female
Dose: 1536
Necropsy Date: 10/28/2016

**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7078 Group: 4 Sex: Female
Dose: 1536
Necropsy Date: 10/28/2016

**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7079 Group: 4 Sex: Female
Dose: 1536
Necropsy Date: 10/28/2016

**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7080 Group: 4 Sex: Female
Dose: 1536
Necropsy Date: 10/28/2016

**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

# APPENDIX Q: INDIVIDUAL ANIMAL TERMINAL BODY AND ORGAN WEIGHTS[1]

## PRODUCT IDENTIFICATION

Soy Leghemoglobin Preparation

[1] Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient.
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

Individual Animal Terminal Body and Organ Weights

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

| 0 mg/kg/day Group 1 | Terminal BW (g) | Adrenal Glands Wt (g) | Brain Wt (g) | Epididymides Wt (g) | Heart Wt (g) | Kidneys Wt (g) | Liver Wt (g) |
|---|---|---|---|---|---|---|---|
| | -- | -- | -- | -- | -- | -- | -- |
| 7001 | 399 | 0.073 | 2.19 | 1.14 | 1.31 | 3.19 | 11.08 |
| 7002 | 359 | 0.071 | 2.16 | 0.94 | 1.13 | 2.81 | 14.06 |
| 7003 | 376 | 0.071 | 2.15 | 0.94 | 1.19 | 2.66 | 12.53 |
| 7004 | 337 | 0.056 | 1.98 | 0.82 | 1.06 | 2.26 | 11.00 |
| 7005 | 329 | 0.063 | 2.10 | 1.04 | 1.07 | 2.20 | 8.44 |
| 7006 | 401 | 0.066 | 2.20 | 1.20 | 1.30 | 2.54 | 11.90 |
| 7007 | 395 | 0.068 | 2.13 | 1.17 | 1.35 | 2.83 | 11.68 |
| 7008 | 355 | 0.071 | 2.21 | 1.04 | 1.18 | 2.59 | 9.44 |
| 7009 | 370 | 0.062 | 2.00 | 0.93 | 1.11 | 2.47 | 9.76 |
| 7010 | 354 | 0.053 | 2.29 | 1.10 | 1.25 | 2.86 | 12.29 |
| Mean | 367.5 | 0.0654 | 2.141 | 1.032 | 1.195 | 2.641 | 11.218 |
| SD | 25.3 | 0.0068 | 0.095 | 0.123 | 0.104 | 0.297 | 1.657 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

Individual Animal Terminal Body and Organ Weights

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

| 0 mg/kg/day Group 1 | Spleen Wt (g) | Testes Wt (g) | Thymus Wt (g) |
|---|---|---|---|
| | -- | -- | -- |
| 7001 | 0.86 | 3.65 | 0.845 |
| 7002 | 0.78 | 2.18 | 0.583 |
| 7003 | 0.85 | 3.27 | 0.495 |
| 7004 | 0.72 | 2.43 | 0.385 |
| 7005 | 0.76 | 2.91 | 0.633 |
| 7006 | 0.98 | 3.12 | 0.397 |
| 7007 | 1.05 | 3.96 | 0.659 |
| 7008 | 0.91 | 3.34 | 0.414 |
| 7009 | 0.77 | 3.23 | 0.474 |
| 7010 | 0.63 | 3.39 | 0.320 |
| Mean | 0.831 | 3.148 | 0.5205 |
| SD | 0.125 | 0.531 | 0.1595 |
| N | 10 | 10 | 10 |

Individual Animal Terminal Body and Organ Weights

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

| 512 mg/kg/day Group 2 | Terminal BW (g) | Adrenal Glands Wt (g) | Brain Wt (g) | Epididymides Wt (g) | Heart Wt (g) | Kidneys Wt (g) | Liver Wt (g) |
|---|---|---|---|---|---|---|---|
| | -- | -- | -- | -- | -- | -- | -- |
| 7021 | 363 | 0.076 | 1.96 | 1.17 | 1.14 | 2.68 | 11.05 |
| 7022 | 374 | 0.074 | 2.21 | 1.10 | 1.28 | 3.01 | 11.54 |
| 7023 | 386 | 0.054 | 2.22 | 1.19 | 1.29 | 2.47 | 10.80 |
| 7024 | 374 | 0.067 | 2.31 | 1.08 | 1.28 | 2.57 | 10.74 |
| 7025 | 362 | 0.069 | 2.09 | 1.05 | 1.12 | 2.42 | 10.75 |
| 7026 | 378 | 0.053 | 2.17 | 1.17 | 1.26 | 2.86 | 12.25 |
| 7027 | 366 | 0.087 | 2.15 | 1.01 | 1.28 | 2.65 | 10.57 |
| 7028 | 336 | 0.058 | 2.14 | 1.06 | 1.13 | 2.67 | 10.68 |
| 7029 | 428 | 0.062 | 2.21 | 0.92 | 1.54 | 3.01 | 12.52 |
| 7030 | 358 | 0.055 | 1.97 | 1.13 | 1.22 | 2.44 | 10.92 |
| Mean | 372.5 | 0.0655 | 2.143 | 1.088 | 1.254 | 2.678 | 11.182 |
| SD | 23.8 | 0.0112 | 0.110 | 0.083 | 0.121 | 0.219 | 0.691 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

Individual Animal Terminal Body and Organ Weights

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

| 512 mg/kg/day Group 2 | Spleen Wt (g) | Testes Wt (g) | Thymus Wt (g) |
|---|---|---|---|
| | -- | -- | -- |
| 7021 | 0.80 | 3.39 | 0.359 |
| 7022 | 0.84 | 3.09 | 0.623 |
| 7023 | 0.78 | 2.95 | 0.521 |
| 7024 | 0.73 | 3.39 | 0.639 |
| 7025 | 0.86 | 3.16 | 0.406 |
| 7026 | 0.92 | 3.96 | 0.648 |
| 7027 | 0.68 | 3.42 | 0.715 |
| 7028 | 1.04 | 3.63 | 0.614 |
| 7029 | 0.72 | 3.56 | 0.643 |
| 7030 | 0.76 | 3.26 | 0.493 |
| Mean | 0.813 | 3.381 | 0.5661 |
| SD | 0.107 | 0.292 | 0.1162 |
| N | 10 | 10 | 10 |

Individual Animal Terminal Body and Organ Weights

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex Male Day(s) Relative to Start Date

| 1024 mg/kg/day Group 3 | Terminal BW (g) | Adrenal Glands Wt (g) | Brain Wt (g) | Epididymides Wt (g) | Heart Wt (g) | Kidneys Wt (g) | Liver Wt (g) |
|---|---|---|---|---|---|---|---|
| | -- | -- | -- | -- | -- | -- | -- |
| 7041 | 375 | 0.068 | 2.20 | 1.14 | 1.15 | 2.89 | 13.47 |
| 7042 | 421 | 0.074 | 2.29 | 1.07 | 1.38 | 2.91 | 13.21 |
| 7043 | 355 | 0.056 | 2.14 | 0.93 | 1.21 | 2.50 | 10.42 |
| 7044 | 406 | 0.067 | 2.33 | 1.35 | 1.36 | 2.96 | 13.78 |
| 7045 | 377 | 0.064 | 2.25 | 0.94 | 1.27 | 2.45 | 11.88 |
| 7046 | 418 | 0.060 | 2.27 | 0.96 | 1.46 | 3.11 | 13.24 |
| 7047 | 404 | 0.046 | 1.87 | 0.98 | 1.30 | 2.79 | 12.54 |
| 7048 | 413 | 0.066 | 2.31 | 1.06 | 1.32 | 3.10 | 15.05 |
| 7049 | 328 | 0.035 | 2.12 | 0.93 | 1.13 | 2.51 | 9.59 |
| 7050 | 343 | 0.057 | 2.08 | 0.99 | 1.14 | 2.67 | 9.99 |
| Mean | 384.0 | 0.0593 | 2.186 | 1.035 | 1.272 | 2.789 | 12.317 |
| SD | 33.4 | 0.0116 | 0.140 | 0.131 | 0.113 | 0.246 | 1.804 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

Individual Animal Terminal Body and Organ Weights

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

| 1024 mg/kg/day Group 3 | Spleen Wt (g) | Testes Wt (g) | Thymus Wt (g) |
|---|---|---|---|
| | -- | -- | -- |
| 7041 | 0.82 | 3.57 | 0.513 |
| 7042 | 0.78 | 2.99 | 0.534 |
| 7043 | 0.77 | 3.43 | 0.441 |
| 7044 | 0.75 | 3.76 | 0.502 |
| 7045 | 0.68 | 3.30 | 0.559 |
| 7046 | 0.82 | 3.15 | 0.841 |
| 7047 | 0.83 | 3.12 | 0.552 |
| 7048 | 0.78 | 3.18 | 0.612 |
| 7049 | 0.78 | 3.16 | 0.409 |
| 7050 | 0.68 | 3.00 | 0.503 |
| Mean | 0.769 | 3.266 | 0.5466 |
| SD | 0.053 | 0.251 | 0.1185 |
| N | 10 | 10 | 10 |

Individual Animal Terminal Body and Organ Weights

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

| 1536 mg/kg/day Group 4 | Terminal BW (g) | Adrenal Glands Wt (g) | Brain Wt (g) | Epididymides Wt (g) | Heart Wt (g) | Kidneys Wt (g) | Liver Wt (g) |
|---|---|---|---|---|---|---|---|
| | -- | -- | -- | -- | -- | -- | -- |
| 7061 | 381 | 0.064 | 2.09 | 1.04 | 1.22 | 2.61 | 10.92 |
| 7062 | 379 | 0.058 | 2.14 | 0.88 | 1.26 | 2.83 | 10.89 |
| 7063 | 353 | 0.063 | 1.99 | 1.13 | 1.08 | 2.78 | 12.40 |
| 7064 | 413 | 0.064 | 2.27 | 0.87 | 1.29 | 3.05 | 12.47 |
| 7065 | 405 | 0.075 | 2.24 | 0.91 | 1.36 | 3.21 | 13.51 |
| 7066 | 394 | 0.069 | 2.15 | 1.10 | 1.29 | 2.77 | 14.23 |
| 7067 | 389 | 0.073 | 2.10 | 1.05 | 1.13 | 2.48 | 11.20 |
| 7068 | 361 | 0.084 | 2.22 | 1.12 | 1.20 | 2.77 | 12.87 |
| 7069 | 350 | 0.049 | 2.02 | 0.94 | 1.12 | 2.48 | 9.43 |
| 7070 | 368 | 0.073 | 2.30 | 1.04 | 1.24 | 3.02 | 13.01 |
| Mean | 379.3 | 0.0672 | 2.152 | 1.008 | 1.219 | 2.800 | 12.093 |
| SD | 21.4 | 0.0098 | 0.105 | 0.100 | 0.088 | 0.241 | 1.452 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

Individual Animal Terminal Body and Organ Weights

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

| 1536 mg/kg/day Group 4 | Spleen Wt (g) | Testes Wt (g) | Thymus Wt (g) |
|---|---|---|---|
| | -- | -- | -- |
| 7061 | 0.82 | 3.22 | 0.476 |
| 7062 | 0.77 | 3.00 | 0.366 |
| 7063 | 0.87 | 3.25 | 0.510 |
| 7064 | 0.86 | 3.66 | 0.437 |
| 7065 | 0.82 | 3.25 | 0.715 |
| 7066 | 0.75 | 3.00 | 0.548 |
| 7067 | 0.73 | 2.99 | 0.549 |
| 7068 | 1.01 | 3.56 | 0.702 |
| 7069 | 0.61 | 3.55 | 0.461 |
| 7070 | 0.85 | 3.24 | 0.512 |
| Mean | 0.809 | 3.272 | 0.5276 |
| SD | 0.105 | 0.246 | 0.1097 |
| N | 10 | 10 | 10 |

Individual Animal Terminal Body and Organ Weights

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

| 0 mg/kg/day Group 1 | Terminal BW (g) | Adrenal Glands Wt (g) | Brain Wt (g) | Heart Wt (g) | Kidneys Wt (g) | Liver Wt (g) | Ovaries with Oviducts Wt (g) |
|---|---|---|---|---|---|---|---|
| | - | - | - | - | - | - | - |
| 7011 | 194 | 0.061 | 1.83 | 0.73 | 1.59 | 6.61 | 0.124 |
| 7012 | 206 | 0.075 | 1.94 | 0.74 | 1.68 | 6.20 | 0.128 |
| 7013 | 266 | 0.084 | 2.14 | 1.00 | 2.07 | 7.83 | 0.152 |
| 7014 | 227 | 0.076 | 2.09 | 0.90 | 1.83 | 6.79 | 0.145 |
| 7015 | 236 | 0.069 | 2.08 | 0.90 | 1.65 | 7.32 | 0.139 |
| 7016 | 227 | 0.068 | 1.94 | 0.83 | 1.68 | 8.19 | 0.124 |
| 7017 | 205 | 0.067 | 1.94 | 0.71 | 1.50 | 6.05 | 0.104 |
| 7018 | 241 | 0.070 | 2.02 | 0.91 | 1.85 | 7.23 | 0.156 |
| 7019 | 240 | 0.079 | 2.05 | 0.85 | 1.86 | 7.74 | 0.108 |
| 7020 | 250 | 0.068 | 2.04 | 0.83 | 1.81 | 7.60 | 0.129 |
| Mean | 229.2 | 0.0717 | 2.007 | 0.840 | 1.752 | 7.156 | 0.1309 |
| SD | 22.3 | 0.0067 | 0.093 | 0.092 | 0.164 | 0.720 | 0.0173 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

Individual Animal Terminal Body and Organ Weights

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

| 0 mg/kg/day Group 1 | Spleen Wt (g) | Thymus Wt (g) | Uterus Wt (g) |
|---|---|---|---|
| | - | - | - |
| 7011 | 0.39 | 0.369 | 0.57 |
| 7012 | 0.42 | 0.258 | 0.60 |
| 7013 | 0.60 | 0.480 | 0.96 |
| 7014 | 0.49 | 0.460 | 0.65 |
| 7015 | 0.42 | 0.491 | 0.56 |
| 7016 | 0.56 | 0.481 | 0.48 |
| 7017 | 0.47 | 0.385 | 0.87 |
| 7018 | 0.53 | 0.373 | 0.97 |
| 7019 | 0.66 | 0.413 | 0.44 |
| 7020 | 0.44 | 0.633 | 1.17 |
| Mean | 0.498 | 0.4343 | 0.727 |
| SD | 0.088 | 0.0998 | 0.247 |
| N | 10 | 10 | 10 |

Individual Animal Terminal Body and Organ Weights

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

| 512 mg/kg/day Group 2 | Terminal BW (g) | Adrenal Glands Wt (g) | Brain Wt (g) | Heart Wt (g) | Kidneys Wt (g) | Liver Wt (g) | Ovaries with Oviducts Wt (g) |
|---|---|---|---|---|---|---|---|
| | - | - | - | - | - | - | - |
| 7031 | 234 | 0.072 | 2.02 | 0.88 | 1.88 | 7.87 | 0.118 |
| 7032 | 216 | 0.074 | 2.05 | 0.80 | 1.91 | 7.42 | 0.119 |
| 7033 | 217 | 0.085 | 2.01 | 0.79 | 1.95 | 7.54 | 0.141 |
| 7034 | 199 | 0.061 | 1.92 | 0.75 | 1.61 | 6.34 | 0.113 |
| 7035 | 233 | 0.068 | 1.92 | 0.85 | 1.61 | 7.63 | 0.142 |
| 7036 | 228 | 0.063 | 1.86 | 0.82 | 1.76 | 8.83 | 0.129 |
| 7037 | 182 | 0.059 | 1.88 | 0.75 | 1.57 | 5.93 | 0.096 |
| 7038 | 247 | 0.083 | 1.88 | 0.87 | 1.83 | 7.05 | 0.133 |
| 7039 | 243 | 0.070 | 2.16 | 0.87 | 2.00 | 8.62 | 0.124 |
| 7040 | 257 | 0.078 | 2.06 | 0.92 | 2.08 | 9.13 | 0.157 |
| Mean | 225.6 | 0.0713 | 1.976 | 0.830 | 1.820 | 7.636 | 0.1272 |
| SD | 22.7 | 0.0089 | 0.099 | 0.057 | 0.177 | 1.037 | 0.0172 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

Individual Animal Terminal Body and Organ Weights

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

| 512 mg/kg/day Group 2 | Spleen Wt (g) | Thymus Wt (g) | Uterus Wt (g) |
|---|---|---|---|
| | - | - | - |
| 7031 | 0.61 | 0.473 | 0.46 |
| 7032 | 0.43 | 0.446 | 0.54 |
| 7033 | 0.54 | 0.532 | 0.54 |
| 7034 | 0.39 | 0.492 | 0.41 |
| 7035 | 0.43 | 0.411 | 0.38 |
| 7036 | 0.60 | 0.480 | 0.43 |
| 7037 | 0.39 | 0.370 | 0.54 |
| 7038 | 0.44 | 0.625 | 0.45 |
| 7039 | 0.61 | 0.396 | 0.41 |
| 7040 | 0.74 | 0.429 | 0.41 |
| Mean | 0.518 | 0.4654 | 0.457 |
| SD | 0.119 | 0.0741 | 0.061 |
| N | 10 | 10 | 10 |

Individual Animal Terminal Body and Organ Weights

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

| 1024 mg/kg/day Group 3 | Terminal BW (g) | Adrenal Glands Wt (g) | Brain Wt (g) | Heart Wt (g) | Kidneys Wt (g) | Liver Wt (g) | Ovaries with Oviducts Wt (g) |
|---|---|---|---|---|---|---|---|
| | - | - | - | - | - | - | - |
| 7051 | 217 | 0.056 | 2.14 | 0.82 | 1.71 | 7.05 | 0.134 |
| 7052 | 227 | 0.067 | 1.94 | 0.83 | 1.81 | 8.34 | 0.108 |
| 7053 | 247 | 0.061 | 2.07 | 0.85 | 1.62 | 7.54 | 0.116 |
| 7054 | 246 | 0.077 | 2.01 | 0.86 | 1.52 | 7.11 | 0.122 |
| 7055 | 257 | 0.065 | 2.03 | 0.92 | 1.98 | 7.85 | 0.140 |
| 7056 | 250 | 0.066 | 2.11 | 0.81 | 1.81 | 7.24 | 0.107 |
| 7057 | 222 | 0.051 | 1.97 | 0.82 | 1.75 | 7.31 | 0.134 |
| 7058 | 224 | 0.065 | 2.07 | 0.86 | 1.70 | 6.82 | 0.105 |
| 7059 | 248 | 0.077 | 1.96 | 0.89 | 1.94 | 6.57 | 0.144 |
| 7060 | 225 | 0.079 | 2.16 | 0.84 | 1.85 | 7.55 | 0.121 |
| Mean | 236.3 | 0.0664 | 2.046 | 0.850 | 1.769 | 7.338 | 0.1231 |
| SD | 14.5 | 0.0092 | 0.077 | 0.034 | 0.140 | 0.512 | 0.0143 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

Individual Animal Terminal Body and Organ Weights

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female  Day(s) Relative to Start Date

| 1024 mg/kg/day Group 3 | Spleen Wt (g) | Thymus Wt (g) | Uterus Wt (g) |
|---|---|---|---|
| | - | - | - |
| 7051 | 0.55 | 0.395 | 0.46 |
| 7052 | 0.48 | 0.581 | 0.43 |
| 7053 | 0.53 | 0.445 | 1.29 |
| 7054 | 0.51 | 0.339 | 0.54 |
| 7055 | 0.48 | 0.534 | 0.63 |
| 7056 | 0.62 | 0.635 | 0.45 |
| 7057 | 0.56 | 0.531 | 0.49 |
| 7058 | 0.45 | 0.363 | 0.43 |
| 7059 | 0.52 | 0.435 | 0.90 |
| 7060 | 0.37 | 0.504 | 0.53 |
| Mean | 0.507 | 0.4762 | 0.615 |
| SD | 0.068 | 0.0967 | 0.276 |
| N | 10 | 10 | 10 |

Individual Animal Terminal Body and Organ Weights

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female  Day(s) Relative to Start Date

| 1536 mg/kg/day Group 4 | Terminal BW (g) | Adrenal Glands Wt (g) | Brain Wt (g) | Heart Wt (g) | Kidneys Wt (g) | Liver Wt (g) | Ovaries with Oviducts Wt (g) |
|---|---|---|---|---|---|---|---|
| | - | - | - | - | - | - | - |
| 7071 | 235 | 0.065 | 2.03 | 0.81 | 1.77 | 8.18 | 0.144 |
| 7072 | 232 | 0.074 | 2.02 | 0.85 | 1.87 | 7.67 | 0.142 |
| 7073 | 244 | 0.073 | 1.94 | 0.91 | 1.72 | 7.76 | 0.140 |
| 7074 | 221 | 0.064 | 2.08 | 0.78 | 1.90 | 7.15 | 0.105 |
| 7075 | 225 | 0.077 | 2.05 | 0.81 | 1.80 | 8.84 | 0.145 |
| 7076 | 234 | 0.080 | 2.02 | 0.82 | 2.02 | 8.32 | 0.145 |
| 7077 | 255 | 0.064 | 2.05 | 0.89 | 1.87 | 7.75 | 0.126 |
| 7078 | 222 | 0.082 | 1.93 | 0.83 | 1.79 | 7.09 | 0.129 |
| 7079 | 248 | 0.092 | 2.04 | 0.99 | 1.70 | 7.39 | 0.160 |
| 7080 | 222 | 0.066 | 2.05 | 0.79 | 1.71 | 7.48 | 0.128 |
| Mean | 233.8 | 0.0737 | 2.021 | 0.848 | 1.815 | 7.763 | 0.1364 |
| SD | 11.9 | 0.0093 | 0.049 | 0.065 | 0.101 | 0.548 | 0.0150 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

Individual Animal Terminal Body and Organ Weights

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

| 1536 mg/kg/day Group 4 | Spleen Wt (g) | Thymus Wt (g) | Uterus Wt (g) |
|---|---|---|---|
| 7071 | 0.60 | 0.643 | 0.46 |
| 7072 | 0.54 | 0.459 | 0.52 |
| 7073 | 0.51 | 0.379 | 0.52 |
| 7074 | 0.39 | 0.379 | 0.52 |
| 7075 | 0.48 | 0.440 | 0.50 |
| 7076 | 0.53 | 0.665 | 0.49 |
| 7077 | 0.54 | 0.616 | 0.38 |
| 7078 | 0.49 | 0.584 | 0.41 |
| 7079 | 0.58 | 0.440 | 0.56 |
| 7080 | 0.47 | 0.613 | 0.54 |
| Mean | 0.513 | 0.5218 | 0.490 |
| SD | 0.060 | 0.1127 | 0.057 |
| N | 10 | 10 | 10 |

# APPENDIX R: INDIVIDUAL ANIMAL ORGAN-TO-BODY WEIGHT RATIOS[1]

## PRODUCT IDENTIFICATION

Soy Leghemoglobin Preparation

[1] Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.
Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient.
Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

Individual Animal Organ-to-Body Weight Ratios

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

| 0 mg/kg/day Group 1 | Adrenal /TBW (Ratio) | Brain /TBW (Ratio) | Epididymides /TBW (Ratio) | Heart /TBW (Ratio) | Kidneys /TBW (Ratio) | Liver /TBW (Ratio) | Spleen /TBW (Ratio) |
|---|---|---|---|---|---|---|---|
| | - | - | - | - | - | - | - |
| 7001 | 0.183 | 5.49 | 2.857 | 3.28 | 7.99 | 27.77 | 2.16 |
| 7002 | 0.198 | 6.02 | 2.618 | 3.15 | 7.83 | 39.16 | 2.17 |
| 7003 | 0.189 | 5.72 | 2.500 | 3.16 | 7.07 | 33.32 | 2.26 |
| 7004 | 0.166 | 5.88 | 2.433 | 3.15 | 6.71 | 32.64 | 2.14 |
| 7005 | 0.191 | 6.38 | 3.161 | 3.25 | 6.69 | 25.65 | 2.31 |
| 7006 | 0.165 | 5.49 | 2.993 | 3.24 | 6.33 | 29.68 | 2.44 |
| 7007 | 0.172 | 5.39 | 2.962 | 3.42 | 7.16 | 29.57 | 2.66 |
| 7008 | 0.200 | 6.23 | 2.930 | 3.32 | 7.30 | 26.59 | 2.56 |
| 7009 | 0.168 | 5.41 | 2.514 | 3.00 | 6.68 | 26.38 | 2.08 |
| 7010 | 0.150 | 6.47 | 3.107 | 3.53 | 8.08 | 34.72 | 1.78 |
| Mean | 0.1781 | 5.846 | 2.8075 | 3.251 | 7.184 | 30.549 | 2.256 |
| SD | 0.0165 | 0.411 | 0.2682 | 0.151 | 0.610 | 4.348 | 0.255 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

Individual Animal Organ-to-Body Weight Ratios

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

| 0 mg/kg/day Group 1 | Testes /TBW (Ratio) | Thymus /TBW (Ratio) |
|---|---|---|
| 7001 | 9.15 | 2.118 |
| 7002 | 6.07 | 1.624 |
| 7003 | 8.70 | 1.316 |
| 7004 | 7.21 | 1.142 |
| 7005 | 8.84 | 1.924 |
| 7006 | 7.78 | 0.990 |
| 7007 | 10.03 | 1.668 |
| 7008 | 9.41 | 1.166 |
| 7009 | 8.73 | 1.281 |
| 7010 | 9.58 | 0.904 |
| Mean | 8.549 | 1.4134 |
| SD | 1.201 | 0.4037 |
| N | 10 | 10 |

Individual Animal Organ-to-Body Weight Ratios

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

| 512 mg/kg/day Group 2 | Adrenal /TBW (Ratio) | Brain /TBW (Ratio) | Epididymides /TBW (Ratio) | Heart /TBW (Ratio) | Kidneys /TBW (Ratio) | Liver /TBW (Ratio) | Spleen /TBW (Ratio) |
|---|---|---|---|---|---|---|---|
| | - | - | - | - | - | - | - |
| 7021 | 0.209 | 5.40 | 3.223 | 3.14 | 7.38 | 30.44 | 2.20 |
| 7022 | 0.198 | 5.91 | 2.941 | 3.42 | 8.05 | 30.86 | 2.25 |
| 7023 | 0.140 | 5.75 | 3.083 | 3.34 | 6.40 | 27.98 | 2.02 |
| 7024 | 0.179 | 6.18 | 2.888 | 3.42 | 6.87 | 28.72 | 1.95 |
| 7025 | 0.191 | 5.77 | 2.901 | 3.09 | 6.69 | 29.70 | 2.38 |
| 7026 | 0.140 | 5.74 | 3.095 | 3.33 | 7.57 | 32.41 | 2.43 |
| 7027 | 0.238 | 5.87 | 2.760 | 3.50 | 7.24 | 28.88 | 1.86 |
| 7028 | 0.173 | 6.37 | 3.155 | 3.36 | 7.95 | 31.79 | 3.10 |
| 7029 | 0.145 | 5.16 | 2.150 | 3.60 | 7.03 | 29.25 | 1.68 |
| 7030 | 0.154 | 5.50 | 3.156 | 3.41 | 6.82 | 30.50 | 2.12 |
| Mean | 0.1766 | 5.766 | 2.9351 | 3.362 | 7.199 | 30.052 | 2.199 |
| SD | 0.0328 | 0.355 | 0.3125 | 0.151 | 0.541 | 1.405 | 0.391 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

Individual Animal Organ-to-Body Weight Ratios

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

| 512 mg/kg/day Group 2 | Testes /TBW (Ratio) | Thymus /TBW (Ratio) |
|---|---|---|
| | - | - |
| 7021 | 9.34 | 0.989 |
| 7022 | 8.26 | 1.666 |
| 7023 | 7.64 | 1.350 |
| 7024 | 9.06 | 1.709 |
| 7025 | 8.73 | 1.122 |
| 7026 | 10.48 | 1.714 |
| 7027 | 9.34 | 1.954 |
| 7028 | 10.80 | 1.827 |
| 7029 | 8.32 | 1.502 |
| 7030 | 9.11 | 1.377 |
| Mean | 9.108 | 1.5209 |
| SD | 0.971 | 0.3105 |
| N | 10 | 10 |

Individual Animal Organ-to-Body Weight Ratios

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

| 1024 mg/kg/day Group 3 | Adrenal /TBW (Ratio) | Brain /TBW (Ratio) | Epididymides /TBW (Ratio) | Heart /TBW (Ratio) | Kidneys /TBW (Ratio) | Liver /TBW (Ratio) | Spleen /TBW (Ratio) |
|---|---|---|---|---|---|---|---|
| | - | - | - | - | - | - | - |
| 7041 | 0.181 | 5.87 | 3.040 | 3.07 | 7.71 | 35.92 | 2.19 |
| 7042 | 0.176 | 5.44 | 2.542 | 3.28 | 6.91 | 31.38 | 1.85 |
| 7043 | 0.158 | 6.03 | 2.620 | 3.41 | 7.04 | 29.35 | 2.17 |
| 7044 | 0.165 | 5.74 | 3.325 | 3.35 | 7.29 | 33.94 | 1.85 |
| 7045 | 0.170 | 5.97 | 2.493 | 3.37 | 6.50 | 31.51 | 1.80 |
| 7046 | 0.144 | 5.43 | 2.297 | 3.49 | 7.44 | 31.67 | 1.96 |
| 7047 | 0.114 | 4.63 | 2.426 | 3.22 | 6.91 | 31.04 | 2.05 |
| 7048 | 0.160 | 5.59 | 2.567 | 3.20 | 7.51 | 36.44 | 1.89 |
| 7049 | 0.107 | 6.46 | 2.835 | 3.45 | 7.65 | 29.24 | 2.38 |
| 7050 | 0.166 | 6.06 | 2.886 | 3.32 | 7.78 | 29.13 | 1.98 |
| Mean | 0.1540 | 5.722 | 2.7030 | 3.315 | 7.274 | 31.962 | 2.012 |
| SD | 0.0253 | 0.497 | 0.3143 | 0.128 | 0.421 | 2.654 | 0.184 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

Individual Animal Organ-to-Body Weight Ratios

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

| 1024 mg/kg/day Group 3 | Testes /TBW (Ratio) | Thymus /TBW (Ratio) |
|---|---|---|
| | - | - |
| 7041 | 9.52 | 1.368 |
| 7042 | 7.10 | 1.268 |
| 7043 | 9.66 | 1.242 |
| 7044 | 9.26 | 1.236 |
| 7045 | 8.75 | 1.483 |
| 7046 | 7.54 | 2.012 |
| 7047 | 7.72 | 1.366 |
| 7048 | 7.70 | 1.482 |
| 7049 | 9.63 | 1.247 |
| 7050 | 8.75 | 1.466 |
| Mean | 8.564 | 1.4171 |
| SD | 0.970 | 0.2319 |
| N | 10 | 10 |

Individual Animal Organ-to-Body Weight Ratios

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

| 1536 mg/kg/day Group 4 | Adrenal /TBW (Ratio) | Brain /TBW (Ratio) | Epididymides /TBW (Ratio) | Heart /TBW (Ratio) | Kidneys /TBW (Ratio) | Liver /TBW (Ratio) | Spleen /TBW (Ratio) |
|---|---|---|---|---|---|---|---|
| | - | - | - | - | - | - | - |
| 7061 | 0.168 | 5.49 | 2.730 | 3.20 | 6.85 | 28.66 | 2.15 |
| 7062 | 0.153 | 5.65 | 2.322 | 3.32 | 7.47 | 28.73 | 2.03 |
| 7063 | 0.178 | 5.64 | 3.201 | 3.06 | 7.88 | 35.13 | 2.46 |
| 7064 | 0.155 | 5.50 | 2.107 | 3.12 | 7.38 | 30.19 | 2.08 |
| 7065 | 0.185 | 5.53 | 2.247 | 3.36 | 7.93 | 33.36 | 2.02 |
| 7066 | 0.175 | 5.46 | 2.792 | 3.27 | 7.03 | 36.12 | 1.90 |
| 7067 | 0.188 | 5.40 | 2.699 | 2.90 | 6.38 | 28.79 | 1.88 |
| 7068 | 0.233 | 6.15 | 3.102 | 3.32 | 7.67 | 35.65 | 2.80 |
| 7069 | 0.140 | 5.77 | 2.686 | 3.20 | 7.09 | 26.94 | 1.74 |
| 7070 | 0.198 | 6.25 | 2.826 | 3.37 | 8.21 | 35.35 | 2.31 |
| Mean | 0.1773 | 5.682 | 2.6712 | 3.214 | 7.387 | 31.893 | 2.139 |
| SD | 0.0264 | 0.294 | 0.3544 | 0.149 | 0.560 | 3.559 | 0.312 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

Individual Animal Organ-to-Body Weight Ratios

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

| 1536 mg/kg/day Group 4 | Testes /TBW (Ratio) | Thymus /TBW (Ratio) |
|---|---|---|
| | - | - |
| 7061 | 8.45 | 1.249 |
| 7062 | 7.92 | 0.966 |
| 7063 | 9.21 | 1.445 |
| 7064 | 8.86 | 1.058 |
| 7065 | 8.02 | 1.765 |
| 7066 | 7.61 | 1.391 |
| 7067 | 7.69 | 1.411 |
| 7068 | 9.86 | 1.945 |
| 7069 | 10.14 | 1.317 |
| 7070 | 8.80 | 1.391 |
| Mean | 8.657 | 1.3939 |
| SD | 0.885 | 0.2919 |
| N | 10 | 10 |

Individual Animal Organ-to-Body Weight Ratios

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

| 0 mg/kg/day Group 1 | Adrenal /TBW (Ratio) | Brain /TBW (Ratio) | Heart /TBW (Ratio) | Kidneys /TBW (Ratio) | Liver /TBW (Ratio) | Ovaries with oviducts/TBW (Ratio) | Spleen /TBW (Ratio) |
|---|---|---|---|---|---|---|---|
| | - | - | - | - | - | - | - |
| 7011 | 0.314 | 9.43 | 3.76 | 8.20 | 34.07 | 0.639 | 2.01 |
| 7012 | 0.364 | 9.42 | 3.59 | 8.16 | 30.10 | 0.621 | 2.04 |
| 7013 | 0.316 | 8.05 | 3.76 | 7.78 | 29.44 | 0.571 | 2.26 |
| 7014 | 0.335 | 9.21 | 3.96 | 8.06 | 29.91 | 0.639 | 2.16 |
| 7015 | 0.292 | 8.81 | 3.81 | 6.99 | 31.02 | 0.589 | 1.78 |
| 7016 | 0.300 | 8.55 | 3.66 | 7.40 | 36.08 | 0.546 | 2.47 |
| 7017 | 0.327 | 9.46 | 3.46 | 7.32 | 29.51 | 0.507 | 2.29 |
| 7018 | 0.290 | 8.38 | 3.78 | 7.68 | 30.00 | 0.647 | 2.20 |
| 7019 | 0.329 | 8.54 | 3.54 | 7.75 | 32.25 | 0.450 | 2.75 |
| 7020 | 0.272 | 8.16 | 3.32 | 7.24 | 30.40 | 0.516 | 1.76 |
| Mean | 0.3139 | 8.801 | 3.665 | 7.657 | 31.278 | 0.5727 | 2.171 |
| SD | 0.0265 | 0.545 | 0.189 | 0.412 | 2.212 | 0.0669 | 0.300 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

Individual Animal Organ-to-Body Weight Ratios

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

| 0 mg/kg/day Group 1 | Thymus /TBW (Ratio) | Uterus /TBW (Ratio) |
|---|---|---|
| | - | - |
| 7011 | 1.902 | 2.94 |
| 7012 | 1.252 | 2.91 |
| 7013 | 1.805 | 3.61 |
| 7014 | 2.026 | 2.86 |
| 7015 | 2.081 | 2.37 |
| 7016 | 2.119 | 2.11 |
| 7017 | 1.878 | 4.24 |
| 7018 | 1.548 | 4.02 |
| 7019 | 1.721 | 1.83 |
| 7020 | 2.532 | 4.68 |
| Mean | 1.8863 | 3.159 |
| SD | 0.3463 | 0.949 |
| N | 10 | 10 |

Individual Animal Organ-to-Body Weight Ratios

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

| 512 mg/kg/day Group 2 | Adrenal /TBW (Ratio) | Brain /TBW (Ratio) | Heart /TBW (Ratio) | Kidneys /TBW (Ratio) | Liver /TBW (Ratio) | Ovaries with oviducts/TBW (Ratio) | Spleen /TBW (Ratio) |
|---|---|---|---|---|---|---|---|
| | - | - | - | - | - | - | - |
| 7031 | 0.308 | 8.63 | 3.76 | 8.03 | 33.63 | 0.504 | 2.61 |
| 7032 | 0.343 | 9.49 | 3.70 | 8.84 | 34.35 | 0.551 | 1.99 |
| 7033 | 0.392 | 9.26 | 3.64 | 8.99 | 34.75 | 0.650 | 2.49 |
| 7034 | 0.307 | 9.65 | 3.77 | 8.09 | 31.86 | 0.568 | 1.96 |
| 7035 | 0.292 | 8.24 | 3.65 | 6.91 | 32.75 | 0.609 | 1.85 |
| 7036 | 0.276 | 8.16 | 3.60 | 7.72 | 38.73 | 0.566 | 2.63 |
| 7037 | 0.324 | 10.33 | 4.12 | 8.63 | 32.58 | 0.527 | 2.14 |
| 7038 | 0.336 | 7.61 | 3.52 | 7.41 | 28.54 | 0.538 | 1.78 |
| 7039 | 0.288 | 8.89 | 3.58 | 8.23 | 35.47 | 0.510 | 2.51 |
| 7040 | 0.304 | 8.02 | 3.58 | 8.09 | 35.53 | 0.611 | 2.88 |
| Mean | 0.3168 | 8.828 | 3.692 | 8.094 | 33.819 | 0.5635 | 2.284 |
| SD | 0.0336 | 0.852 | 0.171 | 0.639 | 2.693 | 0.0474 | 0.384 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

Individual Animal Organ-to-Body Weight Ratios

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

| 512 mg/kg/day Group 2 | Thymus /TBW (Ratio) | Uterus /TBW (Ratio) |
|---|---|---|
| 7031 | 2.021 | 1.97 |
| 7032 | 2.065 | 2.50 |
| 7033 | 2.452 | 2.49 |
| 7034 | 2.472 | 2.06 |
| 7035 | 1.764 | 1.63 |
| 7036 | 2.105 | 1.89 |
| 7037 | 2.033 | 2.97 |
| 7038 | 2.530 | 1.82 |
| 7039 | 1.630 | 1.69 |
| 7040 | 1.669 | 1.60 |
| Mean | 2.0742 | 2.060 |
| SD | 0.3287 | 0.452 |
| N | 10 | 10 |

Individual Animal Organ-to-Body Weight Ratios

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

| 1024 mg/kg/day Group 3 | Adrenal /TBW (Ratio) | Brain /TBW (Ratio) | Heart /TBW (Ratio) | Kidneys /TBW (Ratio) | Liver /TBW (Ratio) | Ovaries with oviducts/TBW (Ratio) | Spleen /TBW (Ratio) |
|---|---|---|---|---|---|---|---|
| | - | - | - | - | - | - | - |
| 7051 | 0.258 | 9.86 | 3.78 | 7.88 | 32.49 | 0.618 | 2.53 |
| 7052 | 0.295 | 8.55 | 3.66 | 7.97 | 36.74 | 0.476 | 2.11 |
| 7053 | 0.247 | 8.38 | 3.44 | 6.56 | 30.53 | 0.470 | 2.15 |
| 7054 | 0.313 | 8.17 | 3.50 | 6.18 | 28.90 | 0.496 | 2.07 |
| 7055 | 0.253 | 7.90 | 3.58 | 7.70 | 30.54 | 0.545 | 1.87 |
| 7056 | 0.264 | 8.44 | 3.24 | 7.24 | 28.96 | 0.428 | 2.48 |
| 7057 | 0.230 | 8.87 | 3.69 | 7.88 | 32.93 | 0.604 | 2.52 |
| 7058 | 0.290 | 9.24 | 3.84 | 7.59 | 30.45 | 0.469 | 2.01 |
| 7059 | 0.310 | 7.90 | 3.59 | 7.82 | 26.49 | 0.581 | 2.10 |
| 7060 | 0.351 | 9.60 | 3.73 | 8.22 | 33.56 | 0.538 | 1.64 |
| Mean | 0.2812 | 8.692 | 3.605 | 7.505 | 31.158 | 0.5222 | 2.149 |
| SD | 0.0372 | 0.686 | 0.178 | 0.657 | 2.883 | 0.0643 | 0.291 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

Individual Animal Organ-to-Body Weight Ratios

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

| 1024 mg/kg/day Group 3 | Thymus /TBW (Ratio) | Uterus /TBW (Ratio) |
|---|---|---|
| | - | - |
| 7051 | 1.820 | 2.12 |
| 7052 | 2.559 | 1.89 |
| 7053 | 1.802 | 5.22 |
| 7054 | 1.378 | 2.20 |
| 7055 | 2.078 | 2.45 |
| 7056 | 2.540 | 1.80 |
| 7057 | 2.392 | 2.21 |
| 7058 | 1.621 | 1.92 |
| 7059 | 1.754 | 3.63 |
| 7060 | 2.240 | 2.36 |
| Mean | 2.0184 | 2.579 |
| SD | 0.4057 | 1.063 |
| N | 10 | 10 |

Individual Animal Organ-to-Body Weight Ratios

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

| 1536 mg/kg/day Group 4 | Adrenal /TBW (Ratio) | Brain /TBW (Ratio) | Heart /TBW (Ratio) | Kidneys /TBW (Ratio) | Liver /TBW (Ratio) | Ovaries with oviducts/TBW (Ratio) | Spleen /TBW (Ratio) |
|---|---|---|---|---|---|---|---|
| | - | - | - | - | - | - | - |
| 7071 | 0.277 | 8.64 | 3.45 | 7.53 | 34.81 | 0.613 | 2.55 |
| 7072 | 0.319 | 8.71 | 3.66 | 8.06 | 33.06 | 0.612 | 2.33 |
| 7073 | 0.299 | 7.95 | 3.73 | 7.05 | 31.80 | 0.574 | 2.09 |
| 7074 | 0.290 | 9.41 | 3.53 | 8.60 | 32.35 | 0.475 | 1.76 |
| 7075 | 0.342 | 9.11 | 3.60 | 8.00 | 39.29 | 0.644 | 2.13 |
| 7076 | 0.342 | 8.63 | 3.50 | 8.63 | 35.56 | 0.620 | 2.26 |
| 7077 | 0.251 | 8.04 | 3.49 | 7.33 | 30.39 | 0.494 | 2.12 |
| 7078 | 0.369 | 8.69 | 3.74 | 8.06 | 31.94 | 0.581 | 2.21 |
| 7079 | 0.371 | 8.23 | 3.99 | 6.85 | 29.80 | 0.645 | 2.34 |
| 7080 | 0.297 | 9.23 | 3.56 | 7.70 | 33.69 | 0.577 | 2.12 |
| Mean | 0.3157 | 8.664 | 3.625 | 7.783 | 33.269 | 0.5835 | 2.191 |
| SD | 0.0399 | 0.492 | 0.163 | 0.602 | 2.772 | 0.0581 | 0.206 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

Individual Animal Organ-to-Body Weight Ratios

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

| 1536 mg/kg/day Group 4 | Thymus /TBW (Ratio) | Uterus /TBW (Ratio) |
|---|---|---|
| | - | - |
| 7071 | 2.736 | 1.96 |
| 7072 | 1.978 | 2.24 |
| 7073 | 1.553 | 2.13 |
| 7074 | 1.715 | 2.35 |
| 7075 | 1.956 | 2.22 |
| 7076 | 2.842 | 2.09 |
| 7077 | 2.416 | 1.49 |
| 7078 | 2.631 | 1.85 |
| 7079 | 1.774 | 2.26 |
| 7080 | 2.761 | 2.43 |
| Mean | 2.2362 | 2.103 |
| SD | 0.4918 | 0.277 |
| N | 10 | 10 |

# APPENDIX S: INDIVIDUAL ANIMAL ORGAN-TO-BRAIN WEIGHT RATIOS[1,2]

## PRODUCT IDENTIFICATION

Soy Leghemoglobin Preparation

[1] [organ weight/brain weight]

[2] Group 2: 512 mg/kg/day of test substance corresponds to 250 mg/kg/day of the active ingredient.

Group 3: 1024 mg/kg/day of test substance corresponds to 500 mg/kg/day of the active ingredient.

Group 4: 1536 mg/kg/day of test substance corresponds to 750 mg/kg/day of the active ingredient.

Individual Animal Organ-to-Brain Weight Ratios

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

| 0 mg/kg/day Group 1 | Adrenal /BrW (Ratio) | Epididymides /BrW (Ratio) | Heart /BrW (Ratio) | Kidneys /BrW (Ratio) | Liver /BrW (Ratio) | Spleen /BrW (Ratio) | Testes /BrW (Ratio) |
|---|---|---|---|---|---|---|---|
| | - | - | - | - | - | - | - |
| 7001 | 0.033 | 0.521 | 0.60 | 1.46 | 5.06 | 0.39 | 1.67 |
| 7002 | 0.033 | 0.435 | 0.52 | 1.30 | 6.51 | 0.36 | 1.01 |
| 7003 | 0.033 | 0.437 | 0.55 | 1.24 | 5.83 | 0.40 | 1.52 |
| 7004 | 0.028 | 0.414 | 0.54 | 1.14 | 5.56 | 0.36 | 1.23 |
| 7005 | 0.030 | 0.495 | 0.51 | 1.05 | 4.02 | 0.36 | 1.39 |
| 7006 | 0.030 | 0.545 | 0.59 | 1.15 | 5.41 | 0.45 | 1.42 |
| 7007 | 0.032 | 0.549 | 0.63 | 1.33 | 5.48 | 0.49 | 1.86 |
| 7008 | 0.032 | 0.471 | 0.53 | 1.17 | 4.27 | 0.41 | 1.51 |
| 7009 | 0.031 | 0.465 | 0.56 | 1.24 | 4.88 | 0.39 | 1.62 |
| 7010 | 0.023 | 0.480 | 0.55 | 1.25 | 5.37 | 0.28 | 1.48 |
| Mean | 0.0306 | 0.4813 | 0.558 | 1.232 | 5.238 | 0.388 | 1.469 |
| SD | 0.0031 | 0.0465 | 0.038 | 0.114 | 0.727 | 0.057 | 0.235 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

Individual Animal Organ-to-Brain Weight Ratios

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

| 0 mg/kg/day Group 1 | Thymus /BrW (Ratio) |
|---|---|
| | - |
| 7001 | 0.386 |
| 7002 | 0.270 |
| 7003 | 0.230 |
| 7004 | 0.194 |
| 7005 | 0.301 |
| 7006 | 0.180 |
| 7007 | 0.309 |
| 7008 | 0.187 |
| 7009 | 0.237 |
| 7010 | 0.140 |
| Mean | 0.2436 |
| SD | 0.0739 |
| N | 10 |



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Individual Animal Organ-to-Brain Weight Ratios

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

| 512 mg/kg/day Group 2 | Adrenal /BrW (Ratio) | Epididymides /BrW (Ratio) | Heart /BrW (Ratio) | Kidneys /BrW (Ratio) | Liver /BrW (Ratio) | Spleen /BrW (Ratio) | Testes /BrW (Ratio) |
|---|---|---|---|---|---|---|---|
| | - | - | - | - | - | - | - |
| 7021 | 0.039 | 0.597 | 0.58 | 1.37 | 5.64 | 0.41 | 1.73 |
| 7022 | 0.033 | 0.498 | 0.58 | 1.36 | 5.22 | 0.38 | 1.40 |
| 7023 | 0.024 | 0.536 | 0.58 | 1.11 | 4.86 | 0.35 | 1.33 |
| 7024 | 0.029 | 0.468 | 0.55 | 1.11 | 4.65 | 0.32 | 1.47 |
| 7025 | 0.033 | 0.502 | 0.54 | 1.16 | 5.14 | 0.41 | 1.51 |
| 7026 | 0.024 | 0.539 | 0.58 | 1.32 | 5.65 | 0.42 | 1.82 |
| 7027 | 0.040 | 0.470 | 0.60 | 1.23 | 4.92 | 0.32 | 1.59 |
| 7028 | 0.027 | 0.495 | 0.53 | 1.25 | 4.99 | 0.49 | 1.70 |
| 7029 | 0.028 | 0.416 | 0.70 | 1.36 | 5.67 | 0.33 | 1.61 |
| 7030 | 0.028 | 0.574 | 0.62 | 1.24 | 5.54 | 0.39 | 1.65 |
| Mean | 0.0307 | 0.5095 | 0.585 | 1.251 | 5.228 | 0.380 | 1.581 |
| SD | 0.0056 | 0.0535 | 0.048 | 0.100 | 0.374 | 0.055 | 0.155 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

Individual Animal Organ-to-Brain Weight Ratios

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

| 512 mg/kg/day Group 2 | Thymus /BrW (Ratio) |
|---|---|
| | - |
| 7021 | 0.183 |
| 7022 | 0.282 |
| 7023 | 0.235 |
| 7024 | 0.277 |
| 7025 | 0.194 |
| 7026 | 0.299 |
| 7027 | 0.333 |
| 7028 | 0.287 |
| 7029 | 0.291 |
| 7030 | 0.250 |
| Mean | 0.2630 |
| SD | 0.0472 |
| N | 10 |

Individual Animal Organ-to-Brain Weight Ratios

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date -

| 1024 mg/kg/day Group 3 | Adrenal /BrW (Ratio) | Epididymides /BrW (Ratio) | Heart /BrW (Ratio) | Kidneys /BrW (Ratio) | Liver /BrW (Ratio) | Spleen /BrW (Ratio) | Testes /BrW (Ratio) |
|---|---|---|---|---|---|---|---|
| | - | - | - | - | - | - | - |
| 7041 | 0.031 | 0.518 | 0.52 | 1.31 | 6.12 | 0.37 | 1.62 |
| 7042 | 0.032 | 0.467 | 0.60 | 1.27 | 5.77 | 0.34 | 1.31 |
| 7043 | 0.026 | 0.435 | 0.57 | 1.17 | 4.87 | 0.36 | 1.60 |
| 7044 | 0.029 | 0.579 | 0.58 | 1.27 | 5.91 | 0.32 | 1.61 |
| 7045 | 0.028 | 0.418 | 0.56 | 1.09 | 5.28 | 0.30 | 1.47 |
| 7046 | 0.026 | 0.423 | 0.64 | 1.37 | 5.83 | 0.36 | 1.39 |
| 7047 | 0.025 | 0.524 | 0.70 | 1.49 | 6.71 | 0.44 | 1.67 |
| 7048 | 0.029 | 0.459 | 0.57 | 1.34 | 6.52 | 0.34 | 1.38 |
| 7049 | 0.017 | 0.439 | 0.53 | 1.18 | 4.52 | 0.37 | 1.49 |
| 7050 | 0.027 | 0.476 | 0.55 | 1.28 | 4.80 | 0.33 | 1.44 |
| Mean | 0.0270 | 0.4738 | 0.583 | 1.278 | 5.633 | 0.353 | 1.498 |
| SD | 0.0043 | 0.0521 | 0.052 | 0.114 | 0.740 | 0.039 | 0.123 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

Individual Animal Organ-to-Brain Weight Ratios

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male  Day(s) Relative to Start Date

| 1024 mg/kg/day Group 3 | Thymus /BrW (Ratio) |
|---|---|
| 7041 | 0.233 |
| 7042 | 0.233 |
| 7043 | 0.206 |
| 7044 | 0.215 |
| 7045 | 0.248 |
| 7046 | 0.370 |
| 7047 | 0.295 |
| 7048 | 0.265 |
| 7049 | 0.193 |
| 7050 | 0.242 |
| Mean | 0.2502 |
| SD | 0.0514 |
| N | 10 |

Individual Animal Organ-to-Brain Weight Ratios

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

| 1536 mg/kg/day Group 4 | Adrenal /BrW (Ratio) | Epididymides /BrW (Ratio) | Heart /BrW (Ratio) | Kidneys /BrW (Ratio) | Liver /BrW (Ratio) | Spleen /BrW (Ratio) | Testes /BrW (Ratio) |
|---|---|---|---|---|---|---|---|
| | - | - | - | - | - | - | - |
| 7061 | 0.031 | 0.498 | 0.58 | 1.25 | 5.22 | 0.39 | 1.54 |
| 7062 | 0.027 | 0.411 | 0.59 | 1.32 | 5.09 | 0.36 | 1.40 |
| 7063 | 0.032 | 0.568 | 0.54 | 1.40 | 6.23 | 0.44 | 1.63 |
| 7064 | 0.028 | 0.383 | 0.57 | 1.34 | 5.49 | 0.38 | 1.61 |
| 7065 | 0.033 | 0.406 | 0.61 | 1.43 | 6.03 | 0.37 | 1.45 |
| 7066 | 0.032 | 0.512 | 0.60 | 1.29 | 6.62 | 0.35 | 1.40 |
| 7067 | 0.035 | 0.500 | 0.54 | 1.18 | 5.33 | 0.35 | 1.42 |
| 7068 | 0.038 | 0.505 | 0.54 | 1.25 | 5.80 | 0.45 | 1.60 |
| 7069 | 0.024 | 0.465 | 0.55 | 1.23 | 4.67 | 0.30 | 1.76 |
| 7070 | 0.032 | 0.452 | 0.54 | 1.31 | 5.66 | 0.37 | 1.41 |
| Mean | 0.0312 | 0.4700 | 0.566 | 1.300 | 5.614 | 0.376 | 1.523 |
| SD | 0.0039 | 0.0573 | 0.027 | 0.078 | 0.579 | 0.044 | 0.125 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

Individual Animal Organ-to-Brain Weight Ratios

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Male Day(s) Relative to Start Date

| 1536 mg/kg/day Group 4 | Thymus /BrW (Ratio) |
|---|---|
| 7061 | 0.228 |
| 7062 | 0.171 |
| 7063 | 0.256 |
| 7064 | 0.193 |
| 7065 | 0.319 |
| 7066 | 0.255 |
| 7067 | 0.261 |
| 7068 | 0.316 |
| 7069 | 0.228 |
| 7070 | 0.223 |
| Mean | 0.2450 |
| SD | 0.0476 |
| N | 10 |

Individual Animal Organ-to-Brain Weigth Ratios

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

| 0 mg/kg/day Group 1 | Adrenal /BrW (Ratio) | Heart /BrW (Ratio) | Kidneys /BrW (Ratio) | Liver /BrW (Ratio) | Ovaries with oviducts/BrW (Ratio) | Spleen /BrW (Ratio) | Thymus /BrW (Ratio) |
|---|---|---|---|---|---|---|---|
| | - | - | - | - | - | - | - |
| 7011 | 0.033 | 0.40 | 0.87 | 3.61 | 0.068 | 0.21 | 0.202 |
| 7012 | 0.039 | 0.38 | 0.87 | 3.20 | 0.066 | 0.22 | 0.133 |
| 7013 | 0.039 | 0.47 | 0.97 | 3.66 | 0.071 | 0.28 | 0.224 |
| 7014 | 0.036 | 0.43 | 0.88 | 3.25 | 0.069 | 0.23 | 0.220 |
| 7015 | 0.033 | 0.43 | 0.79 | 3.52 | 0.067 | 0.20 | 0.236 |
| 7016 | 0.035 | 0.43 | 0.87 | 4.22 | 0.064 | 0.29 | 0.248 |
| 7017 | 0.035 | 0.37 | 0.77 | 3.12 | 0.054 | 0.24 | 0.198 |
| 7018 | 0.035 | 0.45 | 0.92 | 3.58 | 0.077 | 0.26 | 0.185 |
| 7019 | 0.039 | 0.41 | 0.91 | 3.78 | 0.053 | 0.32 | 0.201 |
| 7020 | 0.033 | 0.41 | 0.89 | 3.73 | 0.063 | 0.22 | 0.310 |
| Mean | 0.0357 | 0.418 | 0.872 | 3.566 | 0.0652 | 0.248 | 0.2158 |
| SD | 0.0024 | 0.031 | 0.056 | 0.325 | 0.0075 | 0.039 | 0.0459 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

Individual Animal Organ-to-Brain Weigth Ratios

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

| 0 mg/kg/day Group 1 | Uterus /BrW (Ratio) |
|---|---|
| 7011 | 0.31 |
| 7012 | 0.31 |
| 7013 | 0.45 |
| 7014 | 0.31 |
| 7015 | 0.27 |
| 7016 | 0.25 |
| 7017 | 0.45 |
| 7018 | 0.48 |
| 7019 | 0.21 |
| 7020 | 0.57 |
| Mean | 0.361 |
| SD | 0.118 |
| N | 10 |



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U.S. Patent No. 11,013,250

Individual Animal Organ-to-Brain Weigth Ratios

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

| 512 mg/kg/day Group 2 | Adrenal /BrW (Ratio) | Heart /BrW (Ratio) | Kidneys /BrW (Ratio) | Liver /BrW (Ratio) | Ovaries with oviducts/BrW (Ratio) | Spleen /BrW (Ratio) | Thymus /BrW (Ratio) |
|---|---|---|---|---|---|---|---|
| | - | - | - | - | - | - | - |
| 7031 | 0.036 | 0.44 | 0.93 | 3.90 | 0.058 | 0.30 | 0.234 |
| 7032 | 0.036 | 0.39 | 0.93 | 3.62 | 0.058 | 0.21 | 0.218 |
| 7033 | 0.042 | 0.39 | 0.97 | 3.75 | 0.070 | 0.27 | 0.265 |
| 7034 | 0.032 | 0.39 | 0.84 | 3.30 | 0.059 | 0.20 | 0.256 |
| 7035 | 0.035 | 0.44 | 0.84 | 3.97 | 0.074 | 0.22 | 0.214 |
| 7036 | 0.034 | 0.44 | 0.95 | 4.75 | 0.069 | 0.32 | 0.258 |
| 7037 | 0.031 | 0.40 | 0.84 | 3.15 | 0.051 | 0.21 | 0.197 |
| 7038 | 0.044 | 0.46 | 0.97 | 3.75 | 0.071 | 0.23 | 0.332 |
| 7039 | 0.032 | 0.40 | 0.93 | 3.99 | 0.057 | 0.28 | 0.183 |
| 7040 | 0.038 | 0.45 | 1.01 | 4.43 | 0.076 | 0.36 | 0.208 |
| Mean | 0.0361 | 0.420 | 0.920 | 3.862 | 0.0644 | 0.261 | 0.2366 |
| SD | 0.0043 | 0.028 | 0.062 | 0.476 | 0.0086 | 0.054 | 0.0434 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

Individual Animal Organ-to-Brain Weigth Ratios

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

| 512 mg/kg/day Group 2 | Uterus /BrW (Ratio) |
|---|---|
| 7031 | 0.23 |
| 7032 | 0.26 |
| 7033 | 0.27 |
| 7034 | 0.21 |
| 7035 | 0.20 |
| 7036 | 0.23 |
| 7037 | 0.29 |
| 7038 | 0.24 |
| 7039 | 0.19 |
| 7040 | 0.20 |
| Mean | 0.232 |
| SD | 0.033 |
| N | 10 |



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Individual Animal Organ-to-Brain Weigth Ratios

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

| 1024 mg/kg/day Group 3 | Adrenal /BrW (Ratio) | Heart /BrW (Ratio) | Kidneys /BrW (Ratio) | Liver /BrW (Ratio) | Ovaries with oviducts/BrW (Ratio) | Spleen /BrW (Ratio) | Thymus /BrW (Ratio) |
|---|---|---|---|---|---|---|---|
| | - | - | - | - | - | - | - |
| 7051 | 0.026 | 0.38 | 0.80 | 3.29 | 0.063 | 0.26 | 0.185 |
| 7052 | 0.035 | 0.43 | 0.93 | 4.30 | 0.056 | 0.25 | 0.299 |
| 7053 | 0.029 | 0.41 | 0.78 | 3.64 | 0.056 | 0.26 | 0.215 |
| 7054 | 0.038 | 0.43 | 0.76 | 3.54 | 0.061 | 0.25 | 0.169 |
| 7055 | 0.032 | 0.45 | 0.98 | 3.87 | 0.069 | 0.24 | 0.263 |
| 7056 | 0.031 | 0.38 | 0.86 | 3.43 | 0.051 | 0.29 | 0.301 |
| 7057 | 0.026 | 0.42 | 0.89 | 3.71 | 0.068 | 0.28 | 0.270 |
| 7058 | 0.031 | 0.42 | 0.82 | 3.29 | 0.051 | 0.22 | 0.175 |
| 7059 | 0.039 | 0.45 | 0.99 | 3.35 | 0.073 | 0.27 | 0.222 |
| 7060 | 0.037 | 0.39 | 0.86 | 3.50 | 0.056 | 0.17 | 0.233 |
| Mean | 0.0325 | 0.416 | 0.866 | 3.592 | 0.0603 | 0.248 | 0.2332 |
| SD | 0.0047 | 0.026 | 0.080 | 0.310 | 0.0079 | 0.035 | 0.0489 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

Individual Animal Organ-to-Brain Weigth Ratios

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

| 1024 mg/kg/day Group 3 | Uterus /BrW (Ratio) |
|---|---|
| 7051 | 0.21 |
| 7052 | 0.22 |
| 7053 | 0.62 |
| 7054 | 0.27 |
| 7055 | 0.31 |
| 7056 | 0.21 |
| 7057 | 0.25 |
| 7058 | 0.21 |
| 7059 | 0.46 |
| 7060 | 0.25 |
| Mean | 0.301 |
| SD | 0.136 |
| N | 10 |



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Individual Animal Organ-to-Brain Weigth Ratios

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

| 1536 mg/kg/day Group 4 | Adrenal /BrW (Ratio) | Heart /BrW (Ratio) | Kidneys /BrW (Ratio) | Liver /BrW (Ratio) | Ovaries with oviducts/BrW (Ratio) | Spleen /BrW (Ratio) | Thymus /BrW (Ratio) |
|---|---|---|---|---|---|---|---|
| | - | - | - | - | - | - | - |
| 7071 | 0.032 | 0.40 | 0.87 | 4.03 | 0.071 | 0.30 | 0.317 |
| 7072 | 0.037 | 0.42 | 0.93 | 3.80 | 0.070 | 0.27 | 0.227 |
| 7073 | 0.038 | 0.47 | 0.89 | 4.00 | 0.072 | 0.26 | 0.195 |
| 7074 | 0.031 | 0.38 | 0.91 | 3.44 | 0.050 | 0.19 | 0.182 |
| 7075 | 0.038 | 0.40 | 0.88 | 4.31 | 0.071 | 0.23 | 0.215 |
| 7076 | 0.040 | 0.41 | 1.00 | 4.12 | 0.072 | 0.26 | 0.329 |
| 7077 | 0.031 | 0.43 | 0.91 | 3.78 | 0.061 | 0.26 | 0.300 |
| 7078 | 0.042 | 0.43 | 0.93 | 3.67 | 0.067 | 0.25 | 0.303 |
| 7079 | 0.045 | 0.49 | 0.83 | 3.62 | 0.078 | 0.28 | 0.216 |
| 7080 | 0.032 | 0.39 | 0.83 | 3.65 | 0.062 | 0.23 | 0.299 |
| Mean | 0.0365 | 0.420 | 0.898 | 3.842 | 0.0676 | 0.254 | 0.2583 |
| SD | 0.0050 | 0.036 | 0.049 | 0.267 | 0.0078 | 0.031 | 0.0561 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

Individual Animal Organ-to-Brain Weigth Ratios

PSL Study Number 43166
A 28-Day Dietary Study in Rats

Sex: Female Day(s) Relative to Start Date

| 1536 mg/kg/day Group 4 | Uterus /BrW (Ratio) |
|---|---|
| 7071 | 0.23 |
| 7072 | 0.26 |
| 7073 | 0.27 |
| 7074 | 0.25 |
| 7075 | 0.24 |
| 7076 | 0.24 |
| 7077 | 0.19 |
| 7078 | 0.21 |
| 7079 | 0.27 |
| 7080 | 0.26 |
| Mean | 0.242 |
| SD | 0.028 |
| N | 10 |



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