Guidance on Assessment Factors to Derive a DNEL

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European Centre for Ecotoxicology and Toxicology of Chemicals
4 Avenue E. Van Nieuwenhuyse (Bte 6), B-1160 Brussels, Belgium.

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EXECUTIVE SUMMARY

The European Regulation on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) requires from chemical manufacturers and importers detailed registration dossiers including chemical safety assessments (CSA) for all chemicals produced or imported in amounts of $\geq$ 10 tons/year. The CSA includes exposure scenarios (ES) and assessments of exposure for all supported uses and requires these to be justified against derived no-effect levels (DNEL) which are in turn based upon hazard assessments. The DNEL developed must address acute or repeated exposure, different exposure routes (such as inhalation or skin contact), differentiate between systemic and local effects, and between workplace and general population exposure as appropriate for the intended use pattern. Thus, in theory, up to 15 DNEL may be defined for each compound although in practice fewer will normally be required. The DNEL that the registrant derives will depend upon the points of departure (POD) selected and the assessment factors (AF) subsequently applied.

Since the publication of Chapter R.8 of the 'Guidance on information requirements and chemical safety assessment' (REACH TGD) chemical companies have been preparing and submitting registrations under REACH. Thereby, valuable experience has been gained on deriving DNEL using the R.8 guidance and on balancing these with the exposure predictions using the ECETOC targeted risk assessment (TRA) tools and other models. It is becoming clear that even for relatively data-rich chemicals submitted in the first tier of registrations (by December 2010) the multiplication of AF result in DNEL that are relatively low. These DNEL are extremely difficult to balance with the conservative exposure predictions, derived using screening tools such as the ECETOC TRA, under the risk characterisation ratio (RCR) recommended under the REACH TGD. Furthermore, it is anticipated that for the chemicals comprising the subsequent tiers of registrations (2013 and 2018) the compounding of more individual AF to account for data limitations will make balancing of the RCR more difficult, if not impossible. While it is recognised that REACH is a precautionary regulation and the guidance anticipates that if the RCR cannot be balanced the exposure prediction should be refined, the extra burden that this will impose on the registrants may not be justified. This may especially be the case, if the compounding of individual AF leads to unnecessary conservatism that can justifiably be avoided.

ECETOC and the R.8 guidance recognise that the use of 'informed' AF is preferred over 'default' AF wherever possible, whether supported by substance-specific data or, for example, by read-across to other chemicals or mechanisms of action. The use of informed AF for hazard and risk assessment is well-established and has been used for many years by organisations such as the Scientific Committee on Occupational Exposure Limits (SCOEL) and national competent authorities to set occupational exposure limits.

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In reviewing the individual default AF recommended in the R.8 guidance, ECETOC referred to its previous publication on AF, Technical Report 86, and supplemented this with an updated review of the literature published on this topic during the intervening years. This review revealed that the available scientific data, while supporting several of the AF being recommended in the R.8 guidance, did not support all of them (see table below). Specifically, no AF for exposure duration are necessary for local effects, and lower AF for intraspecies adjustment for workers and general population are indicated versus the ones proposed by the REACH TGD. In addition, the scientific justification for the additional interspecies AF of 2.5 for 'remaining differences' is questionable as it involves aspects of 'science policy'. Consequently, it is recommended that this factor should be further investigated with data that will become available from the first tier chemicals. As some of the R.8 guidance default AF appear to be unjustified by the current state of scientific knowledge it is recommended that, in the absence of substance-specific data, the ECETOC AF are used preferentially.

Although for most chemicals DNEL will solely be based upon animal data, for some health effects data derived in humans will be an additional and important source of information on effects. In this regard, the ECETOC Technical Report 104 provides a guide for an integrative framework for human and animal data that assesses the quality of each data set with respect to a given chemical or exposure scenario. This report supplements the newly issued REACH technical guidance on 'Characterisation of dose[concentration]-response for human health, DNEL/DMEL derivation from human data' and provides further guidance on the selection of appropriate AF for human data.

In contrast to data generated on experimental animals, data on human exposure and effects are less controlled and therefore require greater expert interpretation. The AF recommended are typical maximum values that may be considered appropriate on a case-by-case basis to account for study deficiencies and are not intended to be arbitrarily multiplied together.

The guidance in this report is illustrated by a number of case studies drawn from SCOEL documentation in which the outcome of assessments based on default (REACH TGD, Chapter R.8) versus ECETOC recommended AF has been compared.

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Default assessment factors from animal data

Assessment factors – accounting for differences in: (page numbers in brackets refer to the REACH TGD)		**Systemic effects**		**Local effects (inhalation)**	
		REACH TGD	**ECETOC**	**REACH TGD**	**ECETOC**
Route-to-route extrapolation (p. 24-28)	Oral to inhalation	2	(no proposal)		
	Inhalation to oral	1			
	Oral to dermal	1			
	Dermal to inhalation Inhalation to dermal	case-by-case			
Interspecies (p. 29-33)	Correction for differences in metabolic rate (allometric factor)	Rat → humans 4 Mice → humans 7	4 7	1	1
	'Remaining differences'	2.5	in total allometry	2.5	1
Intraspecies (p. 33-34)	Worker	5	3	5	3
	General population	10	5	10	5
Exposure duration (p. 34-35)	Sub-acute to sub-chronic*	3	3	3	1
	Sub-chronic to chronic	2	2	2	1
	Sub-acute to chronic	6	6	6	1
Dose-response (p. 35-36)	Reliability of dose-response, LOAEL/NAEL extrapolation and severity of effect	≥1 3 (in majority of cases) → 10 (in exceptional cases)	3	≥1	
Quality of whole database (p. 36-37)	Completeness and consistency of available data	≥1		≥1	
	Reliability of alternative data (e.g. read-across)	≥1		≥1	

* These factors are implied

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Typical assessment factors applied to human data

		Nature of assessment factor	AF* applied to account for deficiency
Intraspecies	-	worker to worker	1
	-	worker to general population	2
	-	general population to general population	1
Duration of exposure	-	sub/semi-chronic to chronic	2
	-	chronic to lifetime	1
Dose-response	-	LOAEL / NOAEL extrapolation	2**
(issues related to reliability of dose-	-	steep dose-response curve	2
Quality of whole database	-	issues related to completeness of available data	***
	-	issues related to consistency of available data	****
	-	issues related to reliability of available data	2
	-	study substantially influenced by healthy worker effect	2
	-	small study size	3

* AF is typical factor applied rather than default for all situations
** Typically a value of 2 is sufficient, but if information on the dose-response curve is available a more appropriate AF should be used.
*** No general AF can be recommended; expert judgement is required on a case-by-case basis.
**** No general AF can be recommended; if the human data are inconsistent, refer to animal data.

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1. INTRODUCTION / SCOPE

In the context of the European Regulation on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) (EU, 2006a), the European Chemicals Agency (ECHA) has issued guidance on setting derived no-effect levels (DNEL). Specifically, Chapter R.8 of the 'Guidance on information requirements and chemical safety assessment'[a] proposes a tiered and systematic approach for the delineation of DNEL and DMEL (derived minimal-effect levels) (ECHA, 2008):

Step 1: Gather typical dose descriptors and/or other information on potency
Step 2: Decide on mode of action (threshold or non-threshold) and which next step(s) to choose
Step 3-1: Derive DNEL(s) for threshold endpoints
Step 3-2: If possible, derive DMEL(s) for non-threshold endpoints
Step 3-3: Follow a more qualitative approach when no dose descriptor is available for an endpoint
Step 4: Select the leading health effect(s)

A tiered and systematic approach for the delineation of DNEL as described in the REACH technical guidance document (TGD) is scientifically justified and supported by ECETOC.

While DNEL are defined as safe exposure levels for threshold effects, such safe levels cannot be defined for non-threshold effects, e.g. effects of genotoxic carcinogens or mutagenic effects. In this case, one should calculate a DMEL which is an exposure level considered to be of 'very low concern'. Derivation of DMEL will not be addressed in this document.

The biological starting points for DNEL are dose descriptors such as the no observed adverse effect levels (NOAEL)[b] or benchmark doses (BMD) that are expected to be mostly obtained from animal experiments. The dose descriptors are adapted to human exposure periods and life time (in relation to the experimental setting), and extrapolated to human populations by means of physiological scaling factors and a number of assumptions which are condensed into a system of standardised assessment factors (AF).

Both the REACH TGD and ECETOC recognise that when substance- or category-specific information is available there may be a scientific justification for deviating from default guidance. ECETOC has introduced the term 'informed' AF to address these alternative AF. Wherever possible, informed AF should be used as this provides the greatest confidence in predicting effects in humans. There are many examples of the use of informed AF documented in

[a] Throughout this report referred to as 'REACH TGD'.
[b] N(O)(A)EC [No (observed) (adverse) effect concentration] and N(O)(A)EL [No (observed) (adverse) effect level] are used synonymously in this report, i.e. 'concentration' refers to inhalation studies and 'level' refers to oral studies.

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the files of various national occupational exposure limit setting committees and the Scientific Committee on Occupational Exposure Limits (SCOEL).

The term ‘default’ AF, in contrast, is conceived for those cases where little else other than the experimental dose descriptor is known about a compound (or category) and other aspects of the toxicological profile, mode of action (MOA), toxicokinetics and species variability are unknown.

The default AF given in the REACH TGD were taken from publications and reports by a number of research groups and regulatory bodies including ECETOC TR 86, as summarised in the REACH TGD, Appendix R.8-3. As no justification is provided for the individual factors, ECETOC reviewed the REACH TGD against the AF identified in ECETOC TR 86 as these were based upon an extensive and documented scientific review of the available literature at that time (ECETOC, 2003). For the present report this was further supplemented by an update review consisting of literature published, or made available, in the intervening period.

The review revealed that the ECETOC TR 86 AF are broadly consistent with those recommended by the REACH TGD, but with a few significant differences. The ECETOC Task Force preparing this report has used the comparison of REACH TGD AF and the ECETOC TR 86 AF as the starting point, and where differences were identified has verified which AF are justified by the current state of knowledge. It is recognised that this state of knowledge is continually changing. Therefore it is proposed that all default AF should be periodically reconsidered utilising a review process whenever new information becomes available, e.g. by post-REACH evaluations. For the examples given in this report to illustrate the basis for the proposed AF and their use in deriving DNEL, evaluations published to date from SCOEL, the German Maximale Arbeitsplatzkonzentration (MAK) Commission and the US National Toxicology Program (NTP) were utilised.

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2. GENERAL CONSIDERATIONS

2.1 DNEL derivation from published OEL

For workplace exposure, existing occupational exposure limits (OEL) and/or the underlying information used for setting them can be used to derive DNEL values under circumstances described in the REACH TGD, Appendix R.8-13. Three situations are addressed:

- Where an EU indicative occupational exposure limit value (IOELV) has been set, this may be taken as a $DNEL_{worker}$. This requires that the exposure route and duration for the DNEL is the same as that for the IOELV and no new scientific information is available that would lead to a different value being set.
- Where an EU binding occupational exposure limit value (BOELV) has been set by taking into account socio-economic factors and technical feasibility, this cannot be used in place of a DNEL. However, the toxicological evaluation of the health effects described in the assessment may be used and taken into account for setting a DNEL.
- Where a health-based national OEL has been set, the toxicological information used must be evaluated and any differences to the REACH TGD DNEL calculation method must be taken into account.

Under these conditions, it would not be necessary to use the REACH TGD approach and AF for defining $DNEL_{worker}$.

2.2 DNEL versus DMEL

In developing a risk assessment, the risk assessor needs to first decide on the MOA, namely whether the critical effect observed (or to be assumed) is threshold-based or not. For stochastic types of processes, especially mutagenicity and genotoxic carcinogenicity, the default assumption is that there is no threshold and the dose-response relation is based, in principle, on linear extrapolation to a dose of ‘very low concern’. Therefore, no classical DNEL can be established and this case will not be considered further in this report. If the MOA is threshold-based, the dose descriptors are converted into points of departure (POD) and then extrapolated via AF as described in Chapter 3 of this report.

2.3 Consideration of point of departure

The REACH TGD was principally developed for risk assessment to humans based on animal data. For many high-production volume chemicals with widespread use, there is human experience including, in some situations, evidence of adverse health effects in humans. Commonly this is in the form of epidemiology studies that can be used for risk assessment

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purposes. A decision has to be made if and how these data are to be used in REACH registrations. In this respect, ECETOC TR 104 (2009a) provides a guide for an integrative framework for human and animal data that assesses the quality of each database with respect to a given chemical or exposure scenario. A scheme is presented to score human data quality and categorise animal data to help with the decision to base the risk assessment on information available for humans or animals or on a combination of both of them. The AF which are recommended to be used with human data are in many cases different from those used with animal data, and are described in Chapter 5 of this report.

While the adjustment of the POD in its strictest sense is not related to the choice of AF, this has a major implication on the numerical value of the DNEL finally derived. This report will not address the scientific issues surrounding derivation and adjustment of POD, as this is well described in the REACH TGD.

A POD can be based upon studies in animals or in humans. In terms of deriving a final POD from animal studies, a number of factors, including exposure duration per day or frequency of exposure per week, are considered in order to extrapolate to the real human exposure situation. For example, according to the REACH TGD the exposure duration in animal experiments by inhalation is generally 6 hours/day. This needs to be extrapolated to the exposure duration with respect to workers (8 hours/day), for humans exposed via the environment (24 hours/day) and for consumers (1-24 hours/day, depending on the exposure scenario). Therefore, for workers, the REACH TGD proposes a correction factor of 0.75 (6 hours/day / 8 hours/day) for the workplace, and factors of 0.25 (6 hours/day / 24 hours/day) and 0.71 (5 days/week / 7 days/week), if appropriate, for general population exposures via the environment. Furthermore, animals are at rest during experimental exposure whilst for the worker light physical activity with an increased ventilation rate has to be taken into account during the 8 hours working shift. This is addressed through the use of a factor of 0.67 (respiratory volume during 8 hours at rest: 6.7 m^3/person; under light activity: 10 m^3/person). The factor of 0.67 does not apply to local effects driven by concentration (e.g. irritation of the respiratory tract), or to the 24 hours/day exposure duration of the general population that will be at rest for nearly the total time span. Additional consideration should be given to specific experimental designs; e.g. nose-only vs. whole-body exposure; bolus application by gavage vs. feeding; ‘window dosing’ over a limited time span in developmental toxicity experiments. For human studies, the differences in exposure duration between workers and the general population has to be taken into account by factors of 8/24 and 5/7 assuming an 8 hours shift/day, 5 days of work/week and 48 weeks of work/year.

For local effects, the REACH TGD states (p.25) that such “*time-scaling is not appropriate when the toxic effect is mainly driven by the exposure concentration (as for irritation)*”. This also applies to controlled chamber studies on human volunteers in which the exposure duration is generally in the range of 1-4 hours. Here the no observed adverse effect concentration (NOAEC)

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can generally be taken as the final POD as is shown in Section 3.3.2 on exposure duration extrapolation; local effects. The final POD, whether adjusted or not, is the basis for applying AF.

2.4 General considerations for deviating from default AF

For the majority of substances being registered, only data in animals are available. However, in a few cases, particularly high-volume substances, there are also data in humans. The derivation of DNEL from human data is described in Chapter 5. The remainder of this chapter, as well as Chapters 3 and 4, refer principally to animal data.

Deviating from default AF is generally only possible for chemicals with sufficient data, or if read-across to a similar chemical with a solid database can scientifically be justified. This means that epidemiological and/or toxicological information as well as physico-chemical data are of sufficient quality and reliability to allow identification of valid dose descriptors such as NOAEL which may be converted into robust POD for subsequent extrapolation steps (IPCS, 2005). In cases where the database is insufficient, no relevant regulatory values are available and no meaningful read-across is possible the DNEL development may require the full set of default AF.

There are two types of AF that can be applied to the POD, i.e. default or informed. With increasing strength of the database on mechanism or the substance, informed AF may be substituted for one or more of the default AF.

- Default AF: the REACH TGD values are principally derived from historically used defaults; ECETOC TR 86 AF were derived by evaluating the literature to come to a scientifically-based conclusion. In the event that an AF could not be justified by scientific evidence, an alternative was not proposed.
- Substance-specific ‘informed’ AF: these values are derived from an evaluation of the complete database for a chemical. They are not defaults, but rather more realistic adjustment factors which take into account the quality of the information available. These ‘informed’ AF will often be smaller than the corresponding default AF, but it should be noted that they could also be larger if the data necessitate.

Regardless of the type of AF (REACH TGD or ECETOC factors) the following parameters must be reviewed and evaluated:

1. interspecies extrapolation including allometric differences in metabolic rates between humans and laboratory animals; the standard assumption is that humans are 4-fold more susceptible than rats, especially if the parent compound is the toxic entity and is detoxified by metabolic processes; possible exemptions from this basic principle are given by the REACH TGD in Section 8.4.3;
2. duration of experimental exposure in relation to duration of human exposure (e.g. sub-chronic to chronic);

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3. intraspecies variation with possible higher sensitivities among subpopulations / risk groups (if exposed) than the population studied;
4. nature and severity of the effect;
5. quality of the database.

There are several basic principles allowing for substituting default AF by informed AF (e.g. Dourson *et al*, 1996; Kalberlah and Schneider, 1998; Lewis *et al*, 1990; Meek *et al*, 2002; IPCS, 2005; Vermeire *et al*, 1999). These include toxicokinetic and toxicodynamic factors for inter- and intraspecies variability, the severity of effects, the number of species investigated, and the species being the basis for the POD.

Toxicokinetics
If the MOA is established and if the toxic entity is known (parent chemical or metabolite) this should be taken into account as much as possible for risk assessment. Considerations should be based on the concentration of the toxic entity at the target tissue. This would lead to better (or more precise) informed AF related to inter- and intraspecies differences in toxicokinetics.

Toxicodynamics
Regarding inter- and intraspecies differences in toxicodynamics, similarities and differences in the MOA, the target tissue and the concentrations at which effects occur should be taken into consideration. For an informed AF, the relevance of the MOA for humans and the variability of the responses between species and within a species (e.g. differences in binding to an enzyme, receptor or DNA as well as differences on the secretion of mediator substances and in the effect on the cells or the organ) should be carefully evaluated.

Severity of effects
The effects observed in animals or humans must be interpreted with respect to adversity. For example, a slight but statistically significant reduction in body weight, which could plausibly be related to unpleasant taste in feeding or smell in inhalation studies, would not justify applying the full set of AF. This is particularly the case when a higher DNEL provides adequate protection against any toxicologically relevant effects.

Number of animal species investigated
The number of species showing similar effects at the same or different dose levels (after allometric adjustment) should influence the AF for inter- and intraspecies differences. Similarities in the dose-response of different species might indicate that the overall variability is less than assumed by the default approach. On the other hand, if there is a large difference, taking the most sensitive species for defining the POD would mean that this approach would be largely on the conservative side without an appropriate modification of the default AF. In such cases, relevance to humans needs to be considered by taking human data into account or by using information from the most appropriate animal species studied.

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Price *et al* (2008) analysed the impact of the current practice to always apply the same AF for interspecies variability, i.e. irrespective of how many animal species the database contained to define the NOAEL. In this investigation, the authors compared the maximum tolerated dose (MTD) from humans and different animal species. It was found that the human to animal ratio of the MTD was clearly reduced when the lowest MTD of the most sensitive species was used as compared to the MTD of a single species. This analysis clearly indicated that a lower interspecies AF would be appropriate for compounds with toxicity data from multiple species as would be indicated by the human to animal ratio from a single species.

A DNEL is not an absolute value, i.e. different assessors may derive somewhat different DNEL for the same substance within certain limits. The balance between protective DNEL and those which lead to excessive risk management measures is often difficult to delineate. Expert judgement and default assumptions may vary to some extent and from case to case; however, in each case an overall agreement on scientific grounds should be possible.

In summary, the considerations of DNEL derivation consisting of:

1. Decision on non-threshold (DMEL) or threshold (DNEL) effect;
2. Identification of dose descriptor and adjustment to POD;
3. Dividing the POD by AF to derive DNEL;

are scientifically well-supported and have been used successfully by many regulatory bodies to establish exposure limits.

The following points should be considered for whatever AF are used:

- interspecies extrapolation including allometry;
- duration of exposure;
- intraspecies variability;
- nature and severity of effect;
- quality of the database.

Several aspects that might help to decide on informed AF include:

- Toxicokinetics;
- Toxicodynamics;
- severity of effects;
- number of species investigated;
- extrapolation from experimental animals or observations in humans.

The major cause for controversy is the selection of appropriate numerical values for the AF and deviations from default AF as they are, for example, proposed by the REACH TGD.

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3. ASSESSMENT FACTORS (REPEATED-DOSE TOXICITY IN ANIMALS)

The REACH TGD gives guidance on the characterisation of the dose[concentration]-response for human health risk assessment. Following an overview on aspects that need to be considered for the derivation of DNEL/DMEL, criteria for the identification of dose descriptors and POD, the approach to derive DNEL/DMEL and criteria for the selection of leading health effects are presented. Section R.8.4.3 in the REACH TGD specifically relates to the application of AF.

Considerations for route-to-route extrapolation (Section R.8.4.2 in the REACH TGD) refer rather to the identification of the POD but not to AF. But as major uncertainties may be involved in route-to-route extrapolation, the default approach that is proposed by the REACH TGD will be discussed in this document.

Comparison of default AF of REACH TGD and ECETOC

The default AF of the REACH TGD (Table R.8-6) are summarised in Table 1 which includes the default assumptions for route-to-route extrapolation (the related pages in the REACH TGD are given in brackets in the first column). For comparison, the AF of ECETOC TR 86 (2003) are also shown. The single AF are multiplied to derive a total AF which is then applied to the dose descriptor (or POD) in order to determine the value of the final DNEL. These TR 86 AF are broadly consistent with those recommended by the REACH TGD, but there are some major differences as can be seen in Table 1.

The scientific and empirical basis of the default factors where available are critically discussed in the following.

Consequences of multiplication of assessment factors

The difficulties associated with the use of AF for setting occupational exposure standards was already discussed by Fairhurst (1995) based on the experience of the UK WATCH panel from 1990-1993. He indicated *"that it is difficult (for AFs) to set, from fundamental principles, a simple and workable framework"* and further that *"the size for the values proposed to account for each unknown element and the <u>multiplication</u> of individual elements …. would produce, in many cases, an (overall) uncertainty factor so large that a standard so derived would be in an unrealistically low exposure region."*

One should be well aware of these early warnings of Fairhurst (1995) when using the proposed default AF of the REACH TGD and their multiplicative combination. The problem of possible over-conservatism is clearly shown when comparing the IOELV derived by SCOEL with the DNEL according to the REACH TGD approach (see Appendix A). There are often large differences between the occupational exposure limits derived by SCOEL, which are intended to provide a practical measure of safety, and the DNEL obtained by simply applying the full range of default AF given in the REACH TGD. SCOEL did not discuss individual AF that have to be

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multiplied to derive an overall AF. Their documentation in many cases does not enable the identification of the applied individual factors because they use an overall weight of evidence approach taking into account all data obtained for humans and experimental animals.

The principle of AF multiplication is a default assumption on its own. In any case, the desired conservatism or the acceptable uncertainty must be balanced against the severity of effect, against which the factor should protect, i.e. against a severe, irreversible effect or a mild local nuisance/irritation.

It should be noted that the AF in the REACH TGD are composite factors, which account for both uncertainty and variability. There is however a fundamental difference between these two aspects because variability is inherent to the target population, whereas uncertainty may be reduced by gathering more specific data. For instance, the default AF of 10 which is proposed in the REACH TGD to account for interspecies differences (i.e. rat and man) is a typical uncertainty factor. In the EU risk characterisation for repeated-dose toxicity of 2-butoxyethanol, the informed AF applied for interspecies differences was composed of a factor to account for differences in toxicodynamics of only 0.1, based on the available toxicological data in rats and humans (EU, 2008). These data allowed reducing the uncertainty and thereby the overall AF by a factor of 25 compared to the default. In addition the factor to account for differences in toxicokinetics between rodents and humans was based on the available physiologically based toxicokinetic models instead of the standard allometric scaling factors. Variability, for example due to genetic polymorphisms, is well recognised and can in itself not be reduced by gathering more data. But more data would allow getting a more reliable value for variability (by reducing the associated uncertainty).

That the multiplicative use of all default AF proposed by the REACH TGD may lead to highly conservative DNEL is exemplified by a hypothetical example given below.

In this example, a DNEL is derived for a hypothetical compound of low toxicity, i.e. with a NOAEL of 1000 mg/kg in a sub-acute oral study in rats. Applying standard values for workers' body weight (70 kg) and respiratory volume per shift (10 m^3) yield a starting point of 7000 mg/m^3. The following AF default values would apply: route-to route: 2 (default absorption oral route 50%; inhalation 100%), allometric scaling 4 (rats to humans), additional uncertainty: 2.5, intraspecies (worker): 5, exposure duration (sub-acute to chronic): 6, dose-response: 1, quality of data: 1. The resulting overall AF would be 600 and the corresponding $DNEL_{long\text{-}term\ worker}$ 12 mg/m^3.

This DNEL will, in the majority of cases, lead to excessive and unjustified risk management measures being applied as it is lower than the OEL proposed by scientific organisations for defining exposure limits for chemicals. For example, if one benchmarks this DNEL value for a

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hypothetical compound of low toxicity (unclassified) with an IOELV published by SCOEL and included in the 3rd list of IOELV (EU, 2009b), it becomes evident that the derived DNEL for this hypothetical compound of low toxicity is highly conservative because only 8 out of 15 compounds published in this list have IOELV above 12 mg/m^3. Indeed, only in the cases of mercury (0.02 mg/m^3), sulphuric acid (0.02 mg/m^3), hydrogen sulphide (7 mg/m^3), phenol and 2-ethoxy ethanol (both 8 mg/m^3), bisphenol A (10 mg/m^3) and 2-ethoxyethanol acetate (11 mg/m^3) was the IOELV below the derived DNEL for a non-hazardous compound. All of these chemicals are characterised by a specific toxicological profile of considerable concern and cannot be considered as of low toxicity.

This hypothetical example of a compound with a NOAEL ≥ 1000 mg/kg/day points to another general issue not discussed in the REACH TGD. Modern guidelines for repeated-dose toxicity testing in animals (e.g. OECD TG) define 1000 mg/kg/day as the limit dose and no further testing at higher doses is allowed. The underlying assumption of limit tests is that substances that produce no effects at limit doses are not hazardous. There is currently no answer to the question whether it is appropriate to use data from limit tests as a basis for setting DNEL. But this is not within the scope of this report.

For extrapolation from the NOAEL in animal experiments to an acceptable exposure level of workers and the general population the following AF are of major importance:

1. An AF for extrapolation from relatively short exposure times to life time exposure duration; this mostly applies to animal experiments.
2. An AF for species differences between the experimental animal and man.
3. An intraspecies AF considering the heterogeneity of sensitivity in the human population. This intraspecies variability of humans is generally assumed to be larger as compared to that of experimental animals.

Generally, as also required by the REACH TGD, the single AF are multiplied with each other. This procedure is based on the underlying assumption that the AF are independent of each other. This is actually not the case because the time-extrapolation based on animal experiments, interspecies extrapolation and intraspecies variability depends on the experimentally observed distribution curves. As the interdependency of these three AF is not taken into consideration by their multiplicative connection, this will automatically add an implicit conservative element to this approach. Therefore, ECETOC recommends using the geometric mean of the AF for duration and interspecies variability and the 5th percentile of the human distribution of intraspecies variability in sensitivity. By applying the 5th percentile of only one AF in estimating the overall AF, the statistical noise is only accounted for one time.

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Further, in order to remain conservative, the NOAEL is taken as a POD and no transformation to the corresponding GM value is performed during the calculation of the animal intraspecies variability.

Comments on the statistics of the variability of AF (Ten Berge, personal communication)

In the derivation of AF, many NOAEL of different substances are compared at different exposure duration and in different species. The ratio of the NOAEL, considering variation of exposure duration for many substances in the same species, forms a geometric distribution with a geometric mean (GM-duration) and a geometric standard deviation (GSD-duration). The ratio of the NOAEL between species for many substances forms also a geometric distribution with its own GM-interspecies and GSD-interspecies.

The intraspecies variability in sensitivity of the experimental animal and human population for a specific toxic compound is represented by the slope of the dose response, which is inversely related to the GSD of intraspecies variability of sensitivity. The GSD of intraspecies variability of sensitivity has its own geometric distribution within a species, if taken for many substances in the same species and the same duration of study.

One of the problems is to which extent the magnitude of the GSD is affected by statistical variation or better statistical noise. The magnitude of the GSD is not only controlled by real small differences, but also by the study design like dose spacing, toxicological endpoint and the number of exposed animals per group. The GSD-duration is largely controlled by the GSD-noise by study design, the GSD interspecies is also largely controlled by the GSD-noise by study design and the GSD-intraspecies equally too by the GSD-noise by study design. Taking into account the full GSD-duration, the full GSD-interspecies variability and the full GSD-intraspecies variability for estimating the lower 95% confidence limit (5th percentile), containing each the GSD-noise by study design, assumes that the GSD of duration, interspecies variability and intraspecies variability are fully independent. These GSD, however, are not fully independent, because the magnitude of the GSD of duration, of interspecies variability and of intraspecies variability are each largely controlled by the GSD-noise of study design. The 5th percentile of a distribution is estimated by dividing the geometric mean by the GSD raised to the power of 1.645. If the geometric means (duration, interspecies, intraspecies distribution of assessment factors) are multiplied and divided by the full GSD of duration, interspecies variability and intraspecies variability raised to the power of 1.645 for estimating the 5th percentile, the GSD-noise by study design for each of the three GSD is taken into account. This means, that (GSD-noise-duration*GSD-noise-interspecies*GSD-noise-intraspecies) is part of the overall AF. The GSD-duration, the GSD-interspecies and the GSD-intraspecies are not independent, because the magnitude of the GSD of each of these three GSD is controlled by a GSD-noise by study design, originating from mostly the same package of animal studies.

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On the basis of the arguments above, ECETOC proposes the following AF:

1. In extrapolating the difference of exposure duration, only the geometric mean of the ratios between short and longer exposure duration will be considered (GM duration).
2. In extrapolating the difference between species, only allometric scaling will be considered. This has been shown as sufficient for extrapolation of LD_{10} in mouse or rats to a human MTD in case of cytostatic medicines (GM interspecies allometric scaling). This AF is inherently conservative because a) the animal LD_{10} is compared to the human MTD and b) healthy animals are compared to severely ill cancer patients.
3. For intraspecies extrapolation only, the full human GSD of susceptibility is taken into account. The GSD susceptibility of the human population is 2 for workers and 3 for the general population. In order to estimate the 1st , 5th or 10th percentile of response for a certain effect in the human population, the human intraspecies factor for the general population becomes $3^{2.326}$, $3^{1.645}$ or $3^{1.282}$ (13, 6 or 4), respectively. In the case of workers these figures are $2^{2.326}$, $2^{1.645}$ or $2^{1.282}$ (5, 3 or 2.4), respectively. This clearly indicates that the default AF of 10 for the general population as proposed in the REACH TGD is too high, and the AF of 5 as proposed in ECETOC TR 86 is more reasonable. Furthermore, the AF of 3 for workers as proposed by ECETOC (in contrast to the AF of 5 in the REACH TGD) is clearly supported. As an exhaustive analysis of the published literature was not in the scope of this report, an in-depth analysis is recommended in the future to more precisely define this AF.

The REACH TGD, Appendix R.8-3, states: *"It is to be realised that this multiplication is in general very conservative: when each individual assessment factor by itself is regarded as conservative, multiplication will lead to a piling up of conservatism. Hence, the more extrapolation steps are taken into account, the higher the level of conservatism.*

Although not widely used up to now, a more recent development in risk assessment is the use of probability distributions and Monte Carlo simulation to obtain the overall assessment factor. By acknowledging that each assessment factor is uncertain …. propagation of the uncertainty can be evaluated by Monte Carlo simulation. …. This offers the possibility for a quantitative estimate of the probability that an adverse effect will occur in a certain population at the estimated exposure level. Moreover, the distribution of the overall assessment factor can be probabilistically combined with the distribution of the Benchmark dose, as also the effect parameter is uncertain..."

Although the Monte Carlo simulation to obtain an overall AF is mentioned in the REACH TGD, no further guidance is given. Furthermore, a probabilistic combination of the distributions of the AF and of the benchmark dose cannot be applied to many chemicals under REACH because it requires extensive data. However, a qualitatively similar result is accomplished through the use of scientific judgement and weight of evidence approaches

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which have been taken by SCOEL and by other recognised EU national authorities (e.g. German Maximale Arbeitsplatzkonzentration-MAK Commission, UK Health and Safety Executive-HSE, Nordic Expert Group-NEG and Dutch Expert Committee on Occupational Standards-DECOS).

Table 1: Default assessment factors from animal data
(REACH TGD values are cited in ECHA, 2008, Table R.8-6; ECETOC values are cited in ECETOC, 2003)

Assessment factors – accounting for differences in: (page numbers in brackets refer to the REACH TGD)		**Systemic effects**		**Local effects (inhalation)**	
		REACH TGD	**ECETOC**	**REACH TGD**	**ECETOC**
Route-to-route extrapolation (p. 24-28)	Oral to inhalation	2	(no proposal)		
	Inhalation to oral	1			
	Oral to dermal	1			
	Dermal to inhalation Inhalation to dermal	case-by-case			
Interspecies (p. 29-33)	Correction for differences in metabolic rate (allometric factor)	Rat → humans 4 Mice → humans 7	4 7	1	1
	'Remaining differences'	2.5	in total allometry	2.5	1
Intraspecies (p. 33-34)	Worker	5	3	5	3
	General population	10	5	10	5
Exposure duration (p. 34-35)	Sub-acute to sub-chronic*	3	3	3	1
	Sub-chronic to chronic	2	2	2	1
	Sub-acute to chronic	6	6	6	1
Dose-response (p. 35-36)	Reliability of dose-response, LOAEL/NAEL extrapolation and severity of effect	≥1 3 (in majority of cases) → 10 (in exceptional cases)	3	≥1	
Quality of whole database (p. 36-37)	Completeness and consistency of available data	≥1		≥1	
	Reliability of alternative data (e.g. read-across)	≥1		≥1	

* These factors are implied.

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In summary, the REACH TGD has proposed default AF to be used with animal data. In many cases, ECETOC agrees with them. However, there are cases, where the REACH TGD recommends AF that are significantly higher than those proposed by ECETOC. As ECETOC has shown the scientific basis for the alternative proposals, it is recommended to use these values instead of the ones in the REACH TGD. It is recognised that the multiplication of default AF, whether from the REACH TGD or from ECETOC, will in most cases lead to conservative DNEL. Multiplication of different AF is based on the underlying assumption that the AF are independent of each other. However, this is not the case. Therefore, this multiplicative connection automatically adds an implicit conservative element. These DNEL are not scientifically justified for studies in which no effects were observed at practical test limits, and they may provide unrealistically low levels for establishing safe use through the multiplication of conservative AF.

There is no generic way to overcome the effects of multiplication of AF. This may in part be alleviated if each individual AF is critically reviewed so as not to be overly conservative. Therefore, a critical scientific assessment of every single AF, including a discussion whether and under what circumstances to deviate from the default values, is mandatory for the derivation of DNEL under REACH.

3.1 Route-to-route extrapolation

According to the REACH TGD and ECETOC TR 86, route-to-route extrapolation is appropriate for systemic effects but not appropriate for substances with a local MOA where tissue damage is more dependent on concentration and local effects than on dose.

ECETOC TR 86 did not provide guidance on chemical-specific differences in toxicokinetics (ECETOC 2003) that may impact route-to-route extrapolation. When coming to a more informed decision on the possibility to deviate from the default position of the REACH TGD, a number of factors need to be considered.

The Technical Guidance Document on Risk Assessment gives a number of physico-chemical properties that normally determine oral, inhalation and dermal absorption (ECB, 2003a). These can be used in developing route-to-route AF. These parameters include molecular weight, log Kow, pKa values and, for inhalation, also particle size distribution, vapour pressure and others. Molecules with a molecular weight <500 and a log Kow between 0 and 4 can assumed to be well absorbed by the oral and inhalation routes. Oral absorption may be reduced for acids and bases depending on their pKa value and their possibility of absorption in the GI tract. More lipophilic substances may be better absorbed in the gastrointestinal tract due to the solubilisation with bile

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acids and thus oral absorption may be higher than inhalation absorption. Physico-chemical parameters should be considered before using default assumptions.

Factors to be taken into consideration for route-to-route extrapolation of chemicals with systemic toxicity have been summarised in ECETOC TR 86 (p.14):

- absorption efficiency is known for both routes, or can be quantified;
- elimination half-life of the chemical is relatively long compared to the absorption half-life;
- first pass metabolism is minimal;
- critical target organ is not the port of entry;
- chemical undergoes no significant metabolism by intestinal microflora or pulmonary macrophages;
- chemical is relatively soluble in body fluids;
- adequate toxicity data are available for the route used as a basis for extrapolation.

Because of the variety of elements that have to be considered, no single defined numerical AF is proposed in ECETOC TR 86 for route-to-route extrapolation.

In addition, bolus versus prolonged application has to be taken into consideration when oral gavage studies (or i.p. or i.v. applications) are extrapolated to inhalation exposures. Here peak concentrations may determine the toxicological profiles rather than the area under the curve (AUC).

For systemic effects, route-to-route extrapolation is considered appropriate in the REACH TGD, Section R.8.4.2, only under certain conditions, e.g. no first pass effects for the exposure routes under consideration. Since differences in metabolism, excretion and distribution are difficult to quantify for different routes, in practice only differences in absorption can be accounted for. The most important case is extrapolation from oral animal data (that are often available) to inhalation exposure of humans (at the workplace or the general public). For this situation, the REACH TGD states in Section R.8.4.2:
"It is proposed, thus, in the absence of route-specific information on the starting route, to include a default factor of 2 (i.e. the absorption percentage for the starting route is half that of the end route) in the case of oral-to-inhalation extrapolation. The inclusion of this factor 2 means for example that 50% (instead of 100%) absorption is assumed for oral absorption, and 100% for inhalation. Note that if data on the starting route (oral) are available these should be used, but for the end route (inhalation), the worst case inhalation absorption should still be assumed (i.e. 100%). Note that this does not apply if there is a first pass effect, if there is non-resorption, or for bolus effects.

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No default factor should be introduced (i.e. factor 1) in case of inhalation-to-oral extrapolation, because a two times higher oral compared to inhalation absorption appears on empirical grounds not justified.
On the assumption that, in general, dermal absorption will not be higher than oral absorption, no default factor (i.e. factor 1) should be introduced when performing oral-to dermal extrapolation."

According to the REACH TGD, as a general rule, it must be assessed whether a substance will be systemically available or not before performing a route-to-route extrapolation.

For the purpose of extrapolating oral data to derive an inhalation DNEL, the REACH TGD stipulates default assumptions of 50% absorption by the oral route and 100% for the inhalation route. Hence, an AF of 2 is recommended. The default assumption for oral absorption can really only be challenged on a case-by-case basis with measured or modelled toxicokinetics data or by (Q)SAR. But the default assumption for absorption by the inhalation route may be challenged on a general basis by consideration of pulmonary physiology and toxicodynamics. For example, the clearance of non-reactive gases and vapours from the human lung rarely increases above 50%, especially for longer term acute exposures (Nomiyama and Nomiyama, 1974; Yu and Weisel, 1996), while inhalation of insoluble solid materials by experimental species largely results in oral not inhalation exposure (US EPA, 1994a). At all size ranges, the fraction of particulate matter and aerosols that reaches the deep lung, and is not transported to the gut or expired, is quite small, i.e. a maximum of only 30% for particles with a mass median aerodynamic diameter of 1µm (US EPA, 1994b). The AF for oral-to-inhalation extrapolation may be adjusted on the basis of these considerations.

The factor of 2 suggested in the REACH TGD for the oral-to-inhalation extrapolation clearly is a default approach without any detailed scientific or toxicological rationale. The general applicability of this extrapolation factor is inconsistent with an evaluation of the published EU risk assessment data[c] as performed by Verband der Chemischen Industrie (VCI) (personal communication, April 2008):
" - All substances with the exception of metals and inorganic chemicals were evaluated (55 substances).
- In 8 cases after inhalation exposure a higher absorption rate was reported than after oral intake (EDTA and Na4EDTA, musk ketone and musk xylene, DINP and DIDP[d], anthracene, bis(pentabromophenyl)ether), but with DINP and DIDP the difference was less than 2.

[c] To be found on the (former) ECB website: http://ecb.jrc.ec.europa.eu/
[d] This might be the case due to experimental conditions rather than true differences. These substances were tested as aerosols and most likely cleared from the lung via mucociliary transport and swallowed. As GI absorption is dose dependent, this afforded a greater opportunity for absorption than the comparable bolus oral dose studies.

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- An analysis carried out by VCI showed that in 3 cases the oral absorption was even higher compared to the inhalation absorption (tetrabromobisphenol A, 1,4-dichlorobenzene, 2-methoxy-2-methylbutane, tert-amyl methylether.

- In the remaining 44 cases, no difference was obvious and this was in part due to insufficient information concerning pulmonary absorption rates and/or oral absorption was available to perform a route-to-route extrapolation."

As ECETOC concluded in TR 86, it is impossible to give a generic factor for all cases. Thus, it is recommended to generate substance-specific factors if necessary.

Similarly, if the critical dermal dose is derived from an oral study, the internal dose is estimated first assuming 50% absorption by the oral route, then correcting for dermal absorption (assumed to be 50%) resulting in an oral to dermal route-to-route factor equal to 1. Of course, these absorption rates are very rough estimates and there are many exemptions including the vast differences that usually exist in absorption kinetics between oral and dermal dosing. Oral dosing, for example, provides a much shorter time to Cmax than dermal dosing, and if Cmax is an important factor in the toxicity then dermal dosing will almost always produce less evidence of toxicity than oral dosing. If a factor of 1 is used for oral to dermal extrapolations, this will be overly conservative in most cases.

In summary, route-to-route extrapolation is characterised by considerable scientific uncertainty. Therefore, ECETOC TR 86 (2003) refrained from giving advice for any general strategy or a default approach. The default AF of 2 of the REACH TGD for oral to inhalation extrapolation does not correspond with the evaluations carried out by the European competent authorities under the previous EU Existing Chemicals Regulation (EC, 1993; EC, 1994). Similarly, the oral to dermal extrapolation AF of 1 will very often lead to an overly conservative estimate of the POD for dermal exposure, while an AF<1 would be appropriate, though not allowed, in the present REACH Regulation (EU, 2006a). Thus, a critical assessment of the default AF is mandatory and will often result in lower AF if all available data are taken into account.

3.2 Inter- and intraspecies variability

3.2.1 General considerations

For many years, the approach to calculate a safe dose for the general population based on animal data has been the application of a total AF of 100 to the NOAEL observed in animal experiments. Often different studies give different NOAEL. Expert judgement is necessary to select the most appropriate one depending on validity of the studies, study duration, endpoints investigated, dose spacing and population under consideration. The total AF of 100 is comprised of a factor of 10 each for inter- and intraspecies variability, respectively. Renwick (1991) proposed to subdivide

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both, inter- and intraspecies AF, by sub-factors for toxicokinetic and toxicodynamic components. He concluded that the total AF of 100 is difficult to justify on theoretical grounds and is rather a pragmatic solution to the interpretation of animal data. But its application (to food additives) should provide a more than adequate safety margin and greater flexibility could be introduced. Renwick and Lazarus (1998) specifically proposed to evenly subdivide the 10-fold AF for intraspecies variability for toxicokinetics and -dynamics.

Calabrese and Gilbert (1993) assessed the fundamental assumption that the uncertainty factors for inter- and intraspecies variability are independent of each other and therefore should be combined through a multiplicative scheme. The interspecies AF of 10 provides an extrapolation from average animal to the average human, assuming that humans may be 10-fold more sensitive. That means about half of the human population would already be covered by the interspecies AF alone. The intraspecies AF of 10 for humans assumes that most human responses will fall within approximately a 10-fold range. The authors discussed that the application of the AF for human intraspecies variability is dependent on the population from which one starts the extrapolation; e.g. ‘average’ human after interspecies extrapolation from experimental animal data will require another intraspecies factor to extrapolate to the general population compared to the extrapolation from healthy worker in human studies. The authors concluded that the use of a 10-fold intraspecies AF as typically applied to animal toxicological studies used in risk assessment represents an important deviation from the original intention of uncertainty factor use and proposed to apply a smaller intraspecies factor (5 instead of 10) when the extrapolation is based on ‘average’ humans after interspecies extrapolation from animal data.

Overall, the authors concluded that interspecies AF and intraspecies AF are interdependent and simple multiplication of interspecies AF and intraspecies AF is not appropriate. Therefore, when starting with inter- and intraspecies AF of 10 each, respectively, the total factor for variability would be 50 instead of 100. This concept is applicable to whatever AF for inter- and intraspecies variability are finally selected.

The following evaluates the scientific basis for the selection of the appropriate AF for inter- and intraspecies AF.

3.2.2 Interspecies extrapolation; systemic effects

For interspecies differences the default factor of 10 as proposed by the REACH TGD is generally subdivided into a factor 4 (specifically for extrapolation from rats to humans) for toxicokinetics and 2.5 mainly for toxicodynamics. As described above, the concept of subdividing the interspecies AF into subcomponents for toxicokinetics and toxicodynamics, as introduced by Renwick (1991), suggests that species differences in toxicokinetics may be of much greater magnitude than differences in sensitivity of the target tissue. Most of the toxicokinetic

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differences can be explained by basal metabolic rate which can be accounted for by allometric scaling. The underlying principle is that due to the faster metabolic rate of small animals, humans would less effectively detoxify and/or excrete xenobiotics than laboratory animals and thus are more vulnerable. This is, in principle, the concept of allometric scaling.

ECETOC supports the inclusion of the factor for allometry, but considers that routine application of the factor of 2.5 is unjustified as a default factor. There is evidence that multiplicative association between inter- and intraspecies AF is overly conservative and that the inclusion of a factor for remaining differences is unnecessary. The REACH TGD proposes a factor of 5 for intraspecies adjustment for workers leading to a total factor of 12.5 (5 x 2.5) for inter- and intraspecies assessment excluding allometry, while ECETOC proposes an AF of 3 in this case.

A number of surveys support this assumption for the interspecies extrapolation of systemic effects (Freireich *et al*, 1966; Schein *et al*, 1979; Travis and White, 1988). However, care must be exercised in the interpretation of the datasets (Price *et al*, 2008; see below). Allometric scaling in order to adjust for physiologically-based species differences is widely accepted for systemic toxicity after oral or dermal administration. However, it does not apply to:

1. direct local effects such as skin or gastrointestinal irritation/corrosion;
2. local or systemic effects after inhalation;
3. doses in oral animal studies expressed as concentrations (e.g. ppm in diet or mg/l in drinking water).

The rationale for 2 and 3 is that in humans, inhalation rate and food and water uptake is 4-fold lower compared to rats according to the slower metabolic rate and thereby the allometric species difference is already implicitly taken into account. This means that allometric scaling should not be applied in these situations.

Table 2: Allometric scaling factors (cited in ECHA, 2008, Table R. 8-3)

Species	**Body weight (kg)**	**Metabolic rate vs. humans***
Rat	0.250	4
Mouse	0.03	7
Hamster	0.11	5
Guinea pig	0.8	3
Rabbit	2	2.4
Monkey	4	2
Dog	18	1.4

* assuming the human body weight is 70kg

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The allometric scaling factors for different species as compared to humans (Table 2) are used for oral and dermal exposure; they are not applicable for the extrapolation of inhalation studies to human inhalation exposure.

Allometric scaling by metabolic rate is widely accepted and appears to be scientifically well defensible on the basis of general biological principles. On the other hand, the analysis of a large database did not support the general applicability of this allometric scaling approach. Rhomberg and Wolff (1998) investigated the patterns in the correspondence of oral LD_{50} values across several mammalian species reported in the Registry of Toxic Effects of Chemical Substances (RTECS). The number of agents with species-specific LD_{50} values ranged from 19371 for mice to 4 for humans. The advantage of LD_{50} values over NOAEL/LOAEL is that the former are numerically much better defined than the latter. The shortcomings of the RTECS data base were clearly recognised, but the large number of LD_{50} values for many of the species under consideration was thought to preclude a bias in a specific direction. The authors found a good correspondence of the oral LD_{50} values across species when the dose levels were expressed in terms of mg/kg body weight. Thus, these findings contrasted to the analyses of anti-neoplastic agents that supported scaling of oral doses by the ¾-power of body mass. The authors suggested that, especially for severe toxicity, single- and repeat-dosing regimes may have different cross-species scaling properties. But nevertheless, it should be kept in mind that this very large database does not support allometric scaling by metabolic rate or body surface.

Two restrictions to the general approach of allometric scaling are given by the REACH TGD, Section R.8.4.3.1, which should be taken into consideration before coming to a conclusion:

1. "*Allometric scaling is an empirical approach for interspecies extrapolation of a significant number of kinetic processes related to toxicity which is generally applicable to substances that are essentially renally excreted, but not to compounds that are highly extracted by the liver and excreted in bile. It appears that species differences in biliary excretion and glucuronidation are independent of caloric demand.*
2. *Allometric scaling according to caloric demand would apply most appropriately to those substances for which the unmetabolised parent or a stable metabolite is the relevant toxic species and clearance is according to first-order processes. Conversely, the applicability of allometric scaling when toxicity is a consequence of exposure to a very reactive parent compound (or metabolite) that is not removed from the site of formation, is less well supported.*"

Several attempts have been made to compare interspecies differences in the response to chemical-induced toxicity by comparing human and animal data for chemotherapeutic agents. These data sets have been summarised and evaluated by Price *et al* (2008)[e], who have compared the doses at

[e] This review included papers by Greishaber and Marsoni (1986), Rozencweig *et al* (1981), Paxton *et al* (1990) and Goldsmith *et al* (1975) that were published prior to ECETOC TR 86 (2003).

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which a defined degree of toxicity occurs in several experimental test species (mouse, rat, dog, and monkey) as well as humans. The 'toxic dose' in humans is in most cases lower than in other species, and has served as the basis for the determination of allometric scaling factors (e.g. Sidhu, 1992). Several limitations to these analyses have been identified (Price *et al*, 2008) including, but not limited to: the endpoints that define toxicity vary between species; the definition of the 'toxic dose' also varies across species; and the compromised health status of the human subjects included in the analyses in comparison to animals.

The endpoint(s) and POD used in order to define an adverse response to treatment vary substantially between species (Price *et al*, 2008):

- *Human*: Data from human subjects have been gathered from clinical trials of cancer chemotherapeutic agents. In such studies, the maximum tolerated dose in humans (MTD_H) is usually defined over 5 days of treatment as *"the dose level at which no more than one of six cancer patients experience dose limiting toxicity with the next higher dose group of six patients having two or more patients experiencing dose limiting toxicity"* (cited in Price *et al*, 2008).
- *Monkey and dog*: Toxicity endpoints in non-rodent experimental species are defined as either the toxic dose low (TDL) or the maximum tolerated dose in animals (MTD_A). The TDL is defined as the lowest dose that causes pathological alterations in haematological, chemical, clinical, or morphological endpoints and doubling of which causes no lethality. The MTD_A is defined as the highest dose in test animals that suppresses body weight by no more than 10% in a 90-days sub-chronic study.
- *Rat and mouse*: The endpoint used to define toxicity in rodents is the LD_{10}, the acute, single dose resulting in the death of 10% of the population within a treatment group.

Thus, it is evident that the comparison of 'toxic doses' across species is actually a comparison between doses that cause 'dose-limiting' toxicity (MTD_H) in a sensitive human subpopulation (health-compromised cancer patients) at one extreme and lethality in 10% of the population of animals otherwise assumed healthy (lethal dose - LD_{10}) at the other. This will overestimate the sensitivity of humans in relation to other species, but to an extent which is (largely) unquantifiable. As a consequence, the further adjustment of interspecies AF beyond allometric scaling to account for the differences noted in such analyses is not scientifically justified.

Falk-Filipsson *et al* (2007) discussed the default AF for interspecies extrapolation referring to the analyses of Kalberlah and Schneider (1998), Schneider *et al* (2004) and Vermeire *et al* (1999, 2001) and interpreted these papers as follows: Vermeire *et al* (1999) compared the NOAEL of 184 substances in mice, rats and dogs taking into account metabolic size. After this adjustment, the remaining variability would include differences in toxicodynamics and in species-specific toxicokinetics. The geometric mean (GM) of the adjusted NOAEL ratios was on average 1, with a geometric standard deviation (GSD) on average of 6. In the absence of human data it was

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suggested that this distribution would also characterise the difference between animals and humans. With an extended database the same GM of 1, but a lower GSD of 4.5 were obtained. Vermeire *et al* (1999) proposed a particular percentile of this probabilistic distribution for defining a default AF accounting for the remaining variability after allometric scaling (mainly toxicodynamics). For example, the 90th percentile would lead to a default value of 7.

Similarly, Schneider *et al* (2004) compared long-term NOAEL of pesticides from mice, rats and dogs, and the MTD, TDL and LD_{10} for anti-neoplastic agents from six species including humans. For 63 anti-neoplastic agents again a GM of 1 with a GSD of 3.2 was found. The 90th percentile would lead to a 'remaining' interspecies AF of 4 not including the allometric factor for caloric demand.

Based on these data, Falk-Filipsson *et al* (2007) concluded that interspecies extrapolation should be based on caloric demand with an AF of e.g. 4 for rats. But the remaining variability should take into account the uncertainty described by the probabilistic distribution. They admit that the selection of the percentile of the distributions is a matter of policy. The 95th percentile would lead to an AF of 7 for the 'remaining' AF for interspecies extrapolation.

In this respect, it has to be taken into consideration that such an AF for possible 'remaining' interspecies differences is not science-based but rather reflects 'science policy' depending on whatever level of conservatism is deemed to be appropriate. Furthermore, this approach is in conflict with that taken in the REACH TGD for exposure duration extrapolation (see Section 3.3), in which the AF is based on the central estimate (50th percentile). If the same approach is taken to account for interspecies differences, this would result in interspecies AF that is only based upon allometric scaling (caloric demand), thereby avoiding the need for an additional AF for remaining differences.

ECETOC (2003) evaluated the data of Freireich *et al* (1966) and Schein *et al* (1979) based on the MTD ratios calculated for each substance by Travis and White (1988): Freireich and co-workers compared the MTD of chemotherapeutic drugs in the mouse, rat, dog monkey and human, and found that for the 18 substances examined, the largest discrepancy in the ratio of predicted to observed MTD for human was 3. The ratios of animal/human toxicity on the basis of body surface for the mouse, hamster, dog and monkey was remarkably close to unity. Analysis of the Freireich *et al* data, augmented with additional data by Watanabe *et al* (1992), likewise revealed a maximum difference of 3. By analysing the data of Freireich and co-workers and Schein and co-workers it was found that the GM of the MTD ratios between animal and man approximated the allometric scaling factor for each species, while the GSD of each series of dose ratios was less than 3, i.e. 2.5-2.6.

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Based on this analysis, ECETOC in TR 86 (2003) concluded that the concept of adjusting animal dose by allometric scaling predicts reasonably well the appropriate dose in humans. However, the GSD of 2.5–2.6 suggests the likelihood of some variability or additional uncertainty around the predicted NOAEL in humans. This analysis is based on a comparison of animal to actual human data that per se includes intraspecies variability in humans. As the human population under investigation comprised cancer patients, this represents a very sensitive subpopulation. Thus, this 'additional' variability represented by the GSD of 2.5-2.6 is probably due to not only potential differences in biological sensitivity between species, but also intraspecies differences. The intraspecies variability in humans is taken into account by the specific AF of 3 (for workers) and of 5 (for the general population) as proposed by ECETOC TR 96. The introduction of the 'remaining' AF of 2.5 for interspecies variability would therefore mean an unjustified compilation of AF. Therefore, although 'residual' interspecies variability may remain following allometric scaling, this is largely accounted for in the default AF proposed for intraspecies variability, i.e. reflecting the interdependency of inter- and intraspecies AF (Calabrese and Gilbert, 1993).

Within the ERASM project[f], studies in rats and mice are being examined to substantiate whether the factors for allometry and 'remaining' differences would be appropriate for these species. Preliminary results suggest that a factor of 2.5 for 'remaining' interspecies differences may be questionable as a standard procedure (Escher and Mangelsdorf, 2009; Batke *et al*, 2010; Bitsch *et al*, 2006).

The comparison of rats and mice indicated an interspecies difference of 1.4 for these two species. This corresponds closely to an interspecies AF solely explained by allometry (7:4 = 1.75) without giving support for an additional factor of 2.5 mainly related to toxicodynamic differences. Such toxicodynamic differences should roughly be the same for all species under consideration. It may be argued that an interspecies difference of 1.4 was reported for geometric means and not, for example, the 90th percentile. But if a 'remaining' factor of 2.5 (mainly for toxicodynamics) was scientifically justified, such a factor should also become apparent when comparing the GM for rats and mice, which was however not the case. If the factor of 2.5 is meant to add sufficient conservatism, this would not be a scientific but rather a 'science-policy' argument.

Whilst the Task Force believes a standard approach of utilising a default residual factor of 2.5 is not appropriate in the majority of cases, there may be substance-specific situations that would lead to a different value. These are indicated by the hazard data that may justify a higher or lower AF reflecting the greater or lesser sensitivity of animals compared to humans. Therefore it is

[f] Within the ERASM project, the Fraunhofer Institute for Toxicology and Experimental Medicine examines time- and interspecies-extrapolation factors by evaluating a broad database of repeated-dose toxicity studies.

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recommended that the hazard data for the substance of interest should be carefully evaluated for alerts to a significant difference in the MOA between humans and the test species for which additional chemical specific toxicokinetic/toxicodynamic informed AF may need to be considered.

Rodent to human dermal absorption factor
In some cases, toxicity data obtained by dermal exposure of animals have to be extrapolated to humans and /or to other routes of exposure. Furthermore, data on dermal absorption obtained from studies with animal skin under *in vivo* or *in vitro* conditions are sometimes used to estimate dermal absorption in humans. In both cases, it is important to appreciate that rodent skin is far more permeable to chemicals than human skin. In general, mouse skin is more permeable than rat skin, which is in turn more permeable than human skin. Van Ravenzwaay and Leibold (2004a,b) have compared the differences in absorption for a large number of chemicals and found that the dermal absorption through rat skin is generally at least 2.3 times greater than through human skin.

In summary, interspecies extrapolation for systemic effects has to consider both toxicokinetic and toxicodynamic aspects. Toxicokinetics are covered by the principle of allometric scaling, with a factor of 4 for rats to humans, as the default approach. Allometry is generally accepted in the scientific community when the parent chemical or a stable metabolite is the toxic entity that is metabolically detoxified and when renal excretion is the predominant route of elimination. The factor 2.5 for remaining differences including toxicodynamics is not justified as shown above. In those cases where toxicity or absorption data are available by dermal exposure, it should be taken into account that rodent skin is more permeable than human skin and appropriate adjustment factors should be used prior to applying an AF.

3.2.3. Interspecies extrapolation; local effects

Local effects under consideration here are mainly related to irritation of the respiratory tract in inhalation studies. Cytotoxic irritation as indicated by tissue damage in animal experiments represents a clear adverse effect (although still a local phenomenon). These should, wherever possible, be distinguished from transient sensory irritation that typically may not be adverse and can only be identified by careful clinical observation.

According to the REACH TGD, Section R.8.4.3.1, allometric scaling should not be applied (allometric scaling factor of 1) since local effects are independent of the basic metabolic rate. *"For the remaining uncertainties in kinetic (at a smaller extent) and in dynamic (at a larger extent) interspecies differences, consideration of the mechanism of toxicity is crucial, e.g. if the effect is a simple destruction of membranes due to the physicochemical properties (e.g. pH) of the chemical concerned as opposed to a mechanism involving local metabolism"*.

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In this respect the REACH TGD, in the same section, gives the following guidance for local effects:
"Given that there could be significant quantitative differences in deposition, airflow patterns, clearance rates and protective mechanisms between humans and animals and when there is no data to inform on this uncertainty, it is prudent to assume that humans would be more sensitive than animals to effects on the respiratory tract. In such a situation, a chemical-specific remaining uncertainties factor or the default factor of 2.5 should be applied, as would be the case for systemic effects."

Extrapolation for local effects after inhalation is discussed in detail by ECETOC (2003). The available data and information from computer-derived models of the respiratory tract in humans and rodents indicate that local effects of water soluble gases and vapours observed in the rat nasal cavity when extrapolated to the human situation are likely to over-estimate the effects in humans by factors of at least 2-4.

Gases with low water solubility will reach the lower respiratory tract. The amount reaching the lower respiratory tract may be lower in rodents than in humans because rodents may extract larger amounts within the nasal cavity and may reduce the respiratory volume. On the other hand, the surface of the lower respiratory tract (alveoli and bronchioli) is linearly related to body mass, while the alveolar ventilation is related to body mass to the power of 0.75. This factor per se means that for irritant vapours and gases with low water solubility the exposure in the human lung, as compared to rodents, is likely to be lower. Thus, a default factor of 1 is considered to be sufficiently conservative. With substance-specific data or if quantitative structure-activity relationship (QSAR) considerations are available an informed AF, of even below 1, may be appropriate.

The response to particles and aerosols is more complex and is discussed further in Section 4.1. In general, the size of the particle and the potential solubility needs to be taken into account when determining the AF that should be applied. Ultrafine particles have the potential to reach the lower respiratory tract and elicit a response not anticipated with larger particles which are not likely to penetrate to the deep lung. General guidance on the AF for local effects from aerosol and particle exposure cannot be provided and the guidance in Section 4.1 should be used.

If the data set for the substance is robust, and an evaluation indicates a higher sensitivity of humans compared to rodents, a substance-specific informed AF>1 is appropriate.

In summary, it is clear for local effects that allometric scaling should not be applied, especially where metabolism is not a driving force for the local effect. For water soluble gases and vapours an overestimation of effects in humans is seen if rodent data are directly extrapolated to humans. For gases and vapours with low water solubility the relatively higher amounts that reach the

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lower respiratory tract in humans, the surface of the lower respiratory tract (alveoli and bronchioli) linearly related to body mass and the alveolar ventilation related to body mass should be taken into account. A default factor of 1 for interspecies extrapolation for local effects is considered to be sufficiently conservative for both groups of substances. With substance-specific data or if QSAR considerations are available, an informed AF of below 1 may be appropriate.

3.2.4 Intraspecies extrapolation; systemic effects

Typically, when deriving an AF for intraspecies variability one solely relies on the distribution curves observed in humans, be it for the total variability or for the subsets on toxicokinetics or toxicodynamics. Therefore, any decision depends on the selection of the percentile of the human population to be covered by such an AF. This is similar to the AF for 'remaining' differences for interspecies extrapolation (see above) and in contrast to the AF for exposure duration and interspecies differences of toxicokinetics. In these latter cases, the AF are derived from different distribution curves (for different exposure durations or for different species) and they are based on central estimates (50th percentile). However, the choice of intraspecies variability for deriving an AF is not a science-based decision but depends on 'science policy' after defining the level of conservatism deemed necessary.

The intraspecies variation in humans is greater than that in the more homogenous experimental animal population. For intraspecies extrapolation, the REACH TGD requires a default AF of 10 for the general population and of 5 for the more homogenous workforce, because the very young and very old are not part of this target population.

According to the REACH TGD, Section R.8.4.3.1, a higher intraspecies AF should be considered for children when the following two criteria are both fulfilled:

- *"…..indications of effects on organ systems and functions that are especially vulnerable under development and maturation in early life….., and*
- *…..deficiencies in the database on such effects in young animals."*

ECETOC (2003) arrived at the AF of 3 (for workers) and of 5 (for the general population by a detailed review of the literature and especially by analysing the data of Renwick and Lazarus (1998) and Hattis *et al* (1987, 1999a) (see below).

It was further concluded that there is little scientific basis for the need of an additional AF for children of 6-12 months on the basis of Renwick (1998) analysing renal function and hepatic metabolism in young children. These processes are immature at birth but mature rapidly over the first months of age. The higher clearance of many xenobiotics by children compared with adults may compensate, at least in part, for increased organ sensitivity during development. Differences between children and adults may occur apart from toxicokinetics also by respiratory uptake

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(especially babies in their first months), and because developmental effects are still possible in young children. Neonatal and young animals show similar patterns of immaturity to those found in humans. Therefore an increased AF would not be required provided there was an adequate developmental study in rats.

Falk-Filipsson *et al* (2007) analysed data on the variations in sensibility available for neonates and young children and interpreted the publications as follows:

- *"A children's pharmacokinetic database … by Hattis et al"* (1999a) *"….indicated that premature and full-time neonates tend to have 3-9 times longer half-lives than adults"* for drug clearance. *"This difference disappears by 2-6 months of age….. As the range of neonate/adult half-life exceeds the default assessment factor of 3.2, this factor may not be adequate in the early postnatal period."* The factor of 3.2 was taken from IPCS (1994; 1999) that suggested subdividing the intraspecies AF of 10 evenly into 3.2 for both toxicokinetics and -dynamics.
- *"In a follow-up article Hattis et al (2003)…"* showed that up to 2 months of age a substantial fraction of children had drug clearance half-lives that exceeded those of adults. But *"….in the 2 months to 18 years age groups children's half-lives did not differ from those in adults."*
- According to Scheuplein *et al* (2002), *"…the most prominent differences in toxicokinetics are found in children of less than one year of age and especially in the first days and weeks of life. By the age of 2 years, most of the biochemical and physiological parameters that affect toxicokinetics have reached maturation…..."*

Therefore, Falk-Filipsson and co-workers suggest an additional intraspecies AF of 1-10 for young children under the conditions also defined by the REACH TGD (see above). This proposal if related to neonates is also supported by ECETOC.

Regarding the default AF for the general population it has to be taken into consideration, that elderly people and persons with existing diseases or other dispositions may be more sensitive and form specific risk groups that need to be covered. Furthermore, due to enzyme / receptor polymorphisms and differences in expression, intraspecies variation may be higher in the human population than in inbred experimental animals. Renwick and Lazarus (1998) analysed the possible impact of polymorphism. They point to the fact that for many compounds alternative or multiple pathways of elimination are operative. Poor metabolisers for one pathway may switch to another one resulting in little or no increase in plasma concentrations of the parent compound compared to normal metabolisers. Thus, polymorphism will not automatically require an increased AF.

At the work place, the exposed population is much more homogeneous because the elderly, chronically ill and children are by definition excluded and the health of the work force is typically

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better controlled compared to the general population (healthy worker effect). Therefore, for occupational DNEL a lower default factor is often appropriate.

Depending on the compound or category, specific lower intraspecies AF may be appropriate if supported by data, for example if there is no influence of metabolic transformation. Moreover, if an exposure is already driven far below the experimental NOAEL by other factors, the influence of e.g. enzyme polymorphisms which are important at saturating concentrations decreases in a disproportionate way.

When analysing datasets for intraspecies variability it has to be taken into consideration that there is a relatively broad basis for the toxicokinetic components of human variability, as these parameters are studied routinely for drugs and chemicals. However, identifying data representing toxicodynamics only is considerably more difficult as these effects are likely to be influenced by many variables including feedback mechanisms and toxicokinetics.

For an assessment of intraspecies variability for humans an important aspect is how to subdivide total intraspecies variability into factors for toxicokinetics and toxicodynamics. Hattis *et al* (1999b) showed that the variability for toxicodynamic parameters was larger than that for toxicokinetic parameters. According to Falk-Filipsson *et al* (2007) the data of Renwick and Lazarus (1998) support this conclusion. Falk-Filipsson and co-workers analysed the literature available for intraspecies variability as follows [summarised from the publication]:

- According to an evaluation of Kalberlah and Schneider (1998), based on the datasets of Hattis *et al* (1987), a factor of 4.5 would achieve a level of statistical safety of about 95% for healthy adults, but only toxicokinetics were taken into account without toxicodynamics. Analysing the datasets of Hattis *et al* (1987) and Renwick (1993), Kalberlah and Schneider (1998) proposed a factor of 8 for toxicokinetics and of 3 for toxicodynamics (total AF for intraspecies variability ~25), but the toxicodynamic data base was limited in relation to that for toxicokinetics.

- Hattis *et al* (1999b) estimated the incidence of effects to be expected by lowering exposure 10-fold from a 5% incidence level (approximately equivalent to the NOAEL level). They concluded that such a reduction would correspond to effect incidences of slightly less than 1 in 10000 for a median chemical or a median response. Incidences of a few per 1000 were to be expected for chemicals and responses having greater intrahuman variability than 19 out of 20 typical chemicals/responses.

- Schneider *et al* (2005) [based in a report by the BAuA] describes the distribution of intraspecies extrapolation factors based on toxicokinetic and -dynamic data from Hattis and co-workers. A factor of 5 would protect 95% of the population against

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50% of the chemicals and a factor of 11 would protect 95% of the population against 75% of the chemicals. In order to achieve a protection of 95% of the population against 95% of the chemicals a factor of 44 was estimated to be necessary. But the uncertainty associated with these extrapolations is large.

- Renwick (1991) analysed toxicokinetic and -dynamic variability separately using seven toxicokinetic and eight toxicodynamic studies. He concluded that a factor of 3-4 was sufficient for toxicokinetics in 99% of the healthy adult population for 80% of the substances. Therefore, the total intraspecies AF of 10 should be subdivided into a toxicokinetic factor of 4 and a toxicodynamic factor of 2.5.

- Renwick and Lazarus (1998) analysed the AF for human variability on the basis of toxicokinetic data for 60 chemicals and toxicodynamic data for 49 chemicals. A standard AF of 3.2 for either toxicokinetics or -dynamics was assumed to cover 95% of the population, but the data were derived from single exposures and most data referred to healthy young adults.

- Finally, Falk-Filipsson *et al* (2007) described the pathway-related approach developed by Renwick and co-workers. This approach can be used when the metabolic pathways of a chemical are known by taking into account the variability of the key enzymes in humans. These studies indicated that a factor of 3.2 would cover =/> 99% of healthy adults for non-polymorphic pathways. But certain subgroups, especially neonates, would require higher factors.

Thus, Falk-Filipsson *et al* (2007) concluded that an AF of 3.2 for intraspecies toxicokinetic variability might not be sufficient and proposed a factor of 4.5 as a minimum. As the data for toxicodynamics are limited, they retained an AF of 3.2 for toxicodynamics arriving at a total AF for intraspecies variability of 15 (4.5 x 3.2). The factor of 3.2 was taken from IPCS (1994; 1999) suggesting to subdivide the intraspecies AF of 10 evenly into 3.2 for both toxicokinetics and -dynamics (as mentioned above). They also suggested that if data were insufficient to evaluate the susceptibility of neonates, an additional AF (1-10) should be considered.

ECETOC (2003) evaluated the intraspecies variability within the human population by examining the distributions of human data for various toxicokinetic and -dynamic parameters (Hattis *et al*, 1987, 1999a; Hattis and Silver, 1994; Renwick and Lazarus, 1998). These datasets included ‘healthy’ adults of both genders, as well as limited data from young and elderly, mixed races and patients with various medical treatments.

In a more recent publication, Hattis and co-workers analysed a larger database than the one previously published (Hattis *et al*, 2002; see comments on the statistical evaluations below). On

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the basis of the Hattis *et al*, and Renwick and Lazarus databases, it can be concluded that the default AF of 10 as proposed in the REACH TGD is too high.

Comments on the statistics of the variability within the human population in the Hattis *et al* and Renwick and Lazarus databases

Most of the datasets examined by Hattis *et al* (1987, 1999a) were characterised by log-normal distributions, while the data of Renwick and Lazarus (1998) were transformed to log-normal distributions by ECETOC (2003). For a log-normal distribution the variability within an individual dataset for both toxicokinetics and -dynamics is represented by the GSD. The GSD of all datasets taken together again form a log-normal distribution which itself has a GM and a GSD. The intraspecies variability may be represented by the product of the overall GSD for toxicokinetics and -dynamics. The 95th percentile of the combined distribution of the toxicokinetic and -dynamic variabilities can then be obtained by multiplying the GM with the GSD raised to the power of 1.645 for each for toxicokinetics and -dynamics, i.e. (GM_{kin} x $GSD_{kin}{}^{1.645}$) x (GM_{dyn} x $GSD_{dyn}{}^{1.645}$). This represents an estimate of the total intraspecies variability for toxicokinetic and -dynamic parameters. This approach is a statistical one based on published toxicological datasets.

The estimates for the upper 95th percentile of the distribution of the variability based on both toxicokinetic and -dynamic parameters were 4.3 for the dataset of Renwick and Lazarus (1998) and 3.8 for Hattis *et al* (1999a). As the data analysed by these authors included both genders, a variety of disease states and ages, ECETOC (2003) considered the use of the 95th percentile sufficiently conservative to account for intraspecies variability in the general population. Therefore, they recommended a default factor of 5 for the general population with a lower factor of 3 for the more homogenous worker population.

Hattis *et al* (2002) analysed a considerably larger database (447 data groups) as compared to that of Hattis *et al* (1999b) (only 218 data groups) but both included children (defined as below the age of 12). In the analysis of the larger database (Hattis *et al*, 2002) the log(GSD) for model uncertainty (statistical noise) over all extrapolation parameters was estimated to be 0.161. The authors applied their findings on extrapolation parameters, related to human variability, to many substances for which the US EPA had derived a reference dose. The geometric mean of the combined log(GSD) for human variability was found to be 0.476. By considering the kinetic variability of adults and adults including children, independently and combined, the difference is marginal (in case of adults only the GSD is 2.91; in case of adults including children the GSD is 2.99). This is equal to a GSD of approximately 3 for the general population with or without including children. On the basis of the database of Hattis *et al* (2002), the 95th or the 90th percentile for the intraspecies AF of the general human population can be estimated as approximately 6 and 4, respectively. This clearly indicates that the default AF of 10 as proposed in the REACH TGD is too high, and the AF of 5 as proposed in ECETOC TR 86 is more reasonable.

Since an exhaustive analysis of the published literature was not in the scope of this report, an in-depth review is recommended in the future to more precisely define this AF.

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In summary, there is a major difference in the AF proposed by the REACH TGD and ECETOC for intraspecies extrapolation of systemic effects if the POD is derived from animal studies (worker: REACH TGD 5, ECETOC 3; general population: REACH TGD 10, ECETOC 5). The proposal of ECETOC is based on an evaluation of the scientific literature while the REACH TGD refers to standard default procedures. Therefore, it is proposed to follow the ECETOC guideline until the scientific basis for using an alternative approach has been established. For children, a higher AF is generally not necessary. But it may be considered for neonates and very young children (2-6 months of age), especially if there are clear indications for effects on the developing organ systems in early life phases or major deficits in the database for young animals.

3.2.5 Intraspecies extrapolation; local effects

The REACH TGD considers the availability of information on intraspecies variation of local effects very sparse and therefore proposes the same default AF as for systemic effects, i.e. 5 for workers and 10 for the general population. But it is noted that relevant substance-specific information should always be used for adjustment.

Similarly, after reviewing data on respiratory irritants in human volunteers, ECETOC (2003) concludes that the database is small. It is therefore recommended to use the same default AF as for the intraspecies variability of systemic effects (deviating from those proposed by the REACH TGD), namely 3 for workers and 5 for the general population.

In summary, the same intraspecies AF for local effects are proposed by the REACH TGD as for systemic effects although those proposed by ECETOC (worker: 3; general population 5) are lower than those proposed by the REACH TGD (worker: 5; general population 10).

3.2.6 Interdependency of inter- and intraspecies variability and the 'remaining' AF of 2.5

Considering that there is no difference in the AF proposed by the REACH TGD and by ECETOC for allometric scaling, it is worthwhile to specifically consider the interspecies AF excluding allometry ('remaining' AF of 2.5 according to REACH TGD) in combination with the intraspecies AF. In this respect, the REACH TGD proposes 2.5 x 5 = 12.5 for workers and 2.5 x 10 = 25 for the general population. In contrast, ECETOC proposed an overall factor of 3 for the workplace and of 5 for the general population. As discussed in Chapter 3, a separate 'remaining' AF for interspecies is unnecessary because inter- and intraspecies variability are not independent variables. ECETOC recommends using allometric scaling (or in other words the difference of the GM of the AF for interspecies variability) and the 5th percentile of the human distribution of intraspecies variability. Consequently, the 'remaining' uncertainty for interspecies variability is already accounted for by the intraspecies AF (Calabrese, 1985; Hattis *et al*, 1987).

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The interdependency of the AF for inter- and intraspecies variability was shown by Calabrese and Gilbert (1993). They demonstrated that a simple multiplication of both (unmodified) AF is inappropriate. Therefore, both AF may be considered in conjunction or even combined.

Some time after publication of the REACH TGD, the German Auschuss für Gefahrstoffe - AGS published its concept of how to account for inter- and intraspecies variability (AGS, 2010a). For the workplace, they apply an overall variability AF of 5 closer to the AF of 3 of ECETOC but clearly lower than the AF of 12.5 as proposed by the REACH TGD. No additional factor for 'remaining' differences is deemed necessary by AGS. The factor for allometry corresponds to that of ECETOC and REACH TGD. AGS points to the limited literature available. A factor of 2 should cover the largest part of the toxicokinetic variability in workers and another factor of 2-3 should be sufficient for toxicodynamic variabilities.

Within the ongoing ERASM project (see Section 3.2.2), studies in rats and mice are being examined to substantiate whether the factors for allometry and 'remaining' differences would be appropriate for these species. Preliminary results indicate that a factor of 2.5 for 'remaining' interspecies differences is not supported as a standard procedure (Escher and Mangelsdorf, 2009; Batke *et al*, 2010).

In Section 3.6, the Task Force compared DNEL derived by default AF as per the REACH TGD with IOELV proposed by SCOEL. Six substances were identified, where the SCOEL IOELV was based upon systemic effects in animals, and a further six substances, where it was based upon local effects in animal studies (see Tables 3 and 4 below). In nearly all cases, in which the IOELV was based upon systemic effects, the overall AF applied by SCOEL was lower than the recommended one by the REACH TGD. In only one of these cases, i.e. pyrethrum, it was higher than the one proposed by ECETOC. In the case of pyrethrum, there was no relevant inhalation study in humans or animals upon which to base the IOELV assessment. SCOEL was, however, able to apply an informed AF based upon substance-specific ADME data showing marked route-to-route differences (further details given in Appendix A). In all six cases, in which the IOELV was based upon local effects in animal studies, the overall AF applied was substantially lower (between 10- to 20-fold) than that of the REACH TGD and lower (1- to 3-fold) than those proposed by ECETOC.

This comparison shows that applying the default AF of the REACH TGD to both local and systemic effects in a standardised manner often leads to a situation where the resulting DNEL would be one order of magnitude lower than the IOELV. Considering that IOELV have been established by an independent scientific expert committee and are meant to be protective of worker health, the REACH TGD approach appears unduly conservative. Although the SCOEL documentation is not always transparent in explaining the individual factors underlying these assessments, there is a strong indication that the differences between IOELV and DNEL are in

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part due to differences in interpretation with respect to how to apply the combined factors of inter- and intraspecies variability. In this regard, the Task Force believes that one possible explanation for differences in the interpretation of health outcomes may be correlated to the residual factor of 2.5 and to the combined inter- and intraspecies AF of 12.5 (excluding allometry) proposed by REACH TGD. It may be argued that the IOELV were derived for data rich chemicals using 'informed' AF. But even for such substances, generally, no robust information is available that would allow omitting such a combined AF of 12.5. This is because as shown above there is no defendable scientific basis for the application of this factor apart from convention. This combined AF cannot be justified on the basis of science, only, but appears to be driven by 'science policy' depending primarily on the level of protection deemed adequate for the different (sub)factors. Overall, the approach of SCOEL argues against the use of this conservative combined AF irrespective of the completeness of the data base.

TABLE 3: Comparison of assessment factors used by SCOEL with the default factors proposed in the REACH TGD and by ECETOC. For further details see APPENDIX A.
Key information discussed by SCOEL to derive IOELV: animal data – systemic effects

Compound	**SCOEL Assessment Factors**	**REACH TGD Assessment Factors Total Factors** (RtR^ax AS^bx RD^cx IS^d xED^ex DR^f)	**ECETOC Assessment Factors Total Factors** (RtR^ax AS^bx RD^cx IS^d xED^ex DR^f)
Cyanamide	**1.4**	**35** $\mathbf{2^a}$ x $\mathbf{1.4^b}$ x $\mathbf{2.5^c}$ x $\mathbf{5^d}$ x 1^e x 1^f	**4.2** 1^a x $\mathbf{1.4^b}$ x 1^c x $\mathbf{3^d}$ x 1^e x 1^f
N,N-Dimethylformamid (DMF)	**1**	**12.5** $(1)^a$ x $(1)^b$ x $\mathbf{2.5^c}$ x $\mathbf{5^d}$ x 1^e x 1^f	**3** $(1)^a$ x 1^b x 1^c x $\mathbf{3^d}$ x 1^e x 1^f
((2-(2-Methoxyethoxy) ethanol) (DEGME)	**5**	**60** $\mathbf{2^a}$ x $\mathbf{2.4^b}$ x $\mathbf{2.5^c}$ x $\mathbf{5^d}$ x 1^e x 1^f	**7.2** 1^a x $\mathbf{2.4^b}$ x 1^c x $\mathbf{3^d}$ x 1^e x 1^f
Mono-chlorobenzene	**10**	**75** $(1)^a$ x $(1)^b$ x $\mathbf{2.5^c}$ x $\mathbf{5^d}$ x $\mathbf{2^e}$ x $\mathbf{3^f}$	**18** $(1)^a$ x $(1)^b$ x 1^c x $\mathbf{3^d}$ x $\mathbf{2^e}$ x $\mathbf{3^f}$
Pentanes	**3**	**12.5** $(1)^a$ x $(1)^b$ x $\mathbf{2.5^c}$ x $\mathbf{5^d}$ x 1^e x 1^f	**3** $(1)^a$ x 1^b x 1^c x $\mathbf{3^d}$ x 1^e x 1^f
Pyrethrum	**50**	**100** $\mathbf{2^a}$ x $\mathbf{4^b}$ x $\mathbf{2.5^c}$ x $\mathbf{5^d}$ x 1^e x 1^f	**12** 1^a x $\mathbf{4^b}$ x 1^c x $\mathbf{3^d}$ x 1^e x 1^f

a Route-to-route extrapolation (RtR)
b Interspecies differences; allometric scaling (AS)
c Interspecies differences; remaining differences (RD)
d Intraspecies differences (IS)
e Exposure duration (ED)
f Dose response ; LOAEL $\geq$ NOAEL (DR)
(1): AF not applicable

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TABLE 4: Comparison of assessment factors used by SCOEL with the default factors proposed in the REACH TGD and by ECETOC. For further details see APPENDIX A.
Key information discussed by SCOEL to derive IOELV: animal data – local effects

Compound	**SCOEL Assessment Factors**	**REACH TGD Assessment Factors Total Factors** (RtR^ax AS^bx RD^cx IS^d xED^ex DR^f)	**ECETOC Assessment Factors Total Factors** (RtR^ax AS^bx RD^cx IS^d xED^ex DR^f)
Bisphenol A	**1**	**25** $(1)^a$ x $(1)^b$ x **2.5**^{c} x **5**^{d} x **2**^{e} x 1^f	**3** $(1)^a$ x $(1)^b$ x 1^c x **3**^{d} x 1^e x 1^f
((2-(2- Butoxyethoxy) ethanol) (DEGBE)	**1**	**25** $(1)^a$ x $(1)^b$ x **2.5**^{c} x **5**^{d} x **2**^{e} x 1^f	**3** $(1)^a$ x $(1)^b$ x 1^c x **3**^{d} x 1^e x 1^f
Ethyl acrylate	**1**	**12.5** $(1)^a$ x $(1)^b$ x **2.5**^{c} x **5**^{d} x 1^e x 1^f	**3** $(1)^a$ x $(1)^b$ x 1^c x **3**^{d} x 1^e x 1^f
Hydrogen sulphide	**2**	**41.3** $(1)^a$x$(1)^b$ x **2.5**^{c} x **5**^{d} **x 3.3**^{e} x 1^f	**3** $(1)^a$ x $(1)^b$ x 1^c x **3**^{d} x 1^e x 1^f
Methyl acrylate	**3**	**37.5** $(1)^a$ x $(1)^b$ x **2.5**^{c} x **5**^{d} x **3**^{e} x 1^f	**9** $(1)^a$ x $(1)^b$ x 1^c x **3**^{d} x 1^e x **3**^{f}
Phenol	**2**	**25** $(1)^a$ x $(1)^b$ x **2.5**^{c} x **5**^{d} x **2**^{e} x 1^f	**3** $(1)^a$ x $(1)^b$ x 1^c x **3**^{d} x 1^e x 1^f

[a] Route-to-route extrapolation (RtR)
[b] Interspecies differences; allometric scaling (AS)
[c] Interspecies differences; remaining differences (RD)
[d] Intraspecies differences (IS)
[e] Exposure duration (ED)
[f] Dose response ; LOAEL $\geq$ NOAEL (DR)
(1): AF not applicable

In summary, the REACH TGD proposes a total AF for inter- and intraspecies variability (excluding allometry) of 12.5 for workers and of 25 for the general population, while ECETOC proposes 3 and 5. The corresponding AF for workers used by AGS is close to the ECETOC proposal but far off the one of the REACH TGD. The ECETOC proposal is based on a detailed evaluation of published data.

The high combined variability AF of the REACH TGD is probably the major cause of the large differences observed when comparing workplace DNEL derived according to the REACH TGD with workplace exposure limits developed by SCOEL.

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3.3. Exposure duration extrapolation

3.3.1 Exposure duration extrapolation; systemic effects

This section covers the AF that should be applied to correct for differences in study duration (acute, sub-acute, sub-chronic and chronic). Differences in length of exposure should be accounted for when modifying the POD. The AF proposed by the REACH TGD and ECETOC (2003) are virtually identical to each other (sub-chronic to chronic: 2; sub-acute to chronic: 6; sub-acute to sub-chronic: 3). According to the REACH TGD (Section R.8.4.3.1) these defaults should be substituted by substance-specific information that may lead to higher or lower AF.

- *"A lower AF may …. be used if there is specific evidence that increasing exposure duration does not increase the incidence or severity of adverse effects……*
- *A higher factor may …. be used if there are indications for potential severe chronic effects which cannot possibly be detected in a short-term study."*

For general guidance, the REACH TGD in the same section recommends:
"A factor allowing for differences in the experimental exposure duration and the duration of exposure for the population and scenario under consideration needs to be considered taking into account that a) in general the experimental NOAEL will decrease with increasing exposure times and b) other and more serious adverse effects may appear with increasing exposure times. Consequently, to end up with the most conservative DNEL for repeated dose toxicity, chronic exposure is the 'worst case'. So, if an adequate chronic toxicity study is available, this is the preferred starting point and no assessment factor for duration extrapolation is needed. If only a sub-acute or sub-chronic toxicity study is available, the following default assessment factors are to be applied, as a standard procedure (Table R.8-5)", given below in Table 5.

Malkiewicz *et al* (2009) analysed the default AF proposed by the REACH TGD. By referring to the principal analyses of Kalberlah and Schneider (1998) and of Vermeire *et al* (1999, 2001) they concluded that these AF are based on the central estimates (50th percentile) of the distributions for the relationships of sub-acute/sub-chronic/chronic NOAEL. Higher AF would be obtained if percentiles higher than the 50th are selected for derivation of the default AF. For example, Falk-Filipsson *et al* (2007) came to a factor of 7 (instead of 2) for sub-chronic to chronic extrapolation based on the 95th percentile of the distribution. But nevertheless it is important to note that the REACH TGD relies on the central estimates, and the selection of any specific percentile of the distribution for defining the AF would rather be a matter of 'policy decision' than of science.

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Table 5: Assessment factors for duration extrapolation (cited in ECHA, 2008, Table R.8-5)

Duration	Default assessment factor
sub-chronic to chronic	2
sub-acute to chronic	6
sub-acute to sub-chronic	3

[a] 'sub-chronic' usually refers to a 90-day study
[c] 'sub-acute' usually refers to a 28-day study
[b] 'chronic' usually refers to a 1.5 - 2-year study (for rodents)

ECETOC (2003) reviewed various publications with rodents and dogs on this issue and came to the conclusion that studies involving 6 months of exposure provide the same NOAEL as those observed after chronic (lifetime) exposures. Thus, a study of 6 months' duration was identified as sufficiently conservative for predicting long-term (non-tumourigenic) effects. The limited impact of studies with a duration >6 months on the NOAEL in dogs is supported by Dellarco *et al* (2010). The authors compared the NOAEL obtained in 13-week dog studies to those of 1-year dog studies. 110 pesticide chemicals with an adequate dataset were analysed. 70/110 had similar critical effects regardless of duration and NOAEL and LOAEL within a difference of 1.5-fold of each other. 31 of the remaining pesticides had lower NOAEL/LOAEL in the 1-year study primarily due to dose selection and spacing. Only for nine pesticides the difference between the 13-week and 1-year NOAEL/LOAEL could not be ascribed to dose selection. The authors concluded that a dog toxicity study beyond 13 weeks does not have a significant impact on the derivation of a chronic reference dose for pesticide risk assessment.

For substances with a short half-life (e.g. <15 hours) ECETOC assumes that extending the exposure duration to more than 28 days is unlikely to have a significant effect on the NOAEL. Other substance properties pointing into the same direction are that the substance does not produce toxic metabolites, is not reactive towards tissue components, and/or does not deplete essential elements.

In the absence of chronic toxicity studies in rodents, studies with sub-acute or sub-chronic duration will in most cases serve to identify any affected target organ(s). Thus, they should identify also any chronic effects (with the exception of carcinogenicity). Often a sub-chronic toxicity study may even be superior to a chronic study and more sensitive for many critical effects. An example is nephrotoxicity which may be less clearly discernible in a chronic study due to the spontaneous nephropathy of aging rats in treatment and control groups.

It is a general assumption that effective dose levels and thresholds for saturation phenomena decrease with increasing exposure time. Intuitively, one would agree that in 'effective dose' ranges, detrimental effects would accumulate upon repeated and/or continuous exposure and even may generate secondary effects. Below effective doses, however, this assumption is less justified

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and there is often no influence of exposure time on the threshold (or the true NOAEL), unless a compound shows genotoxic or cumulative toxic properties or if there is a decreasing resiliency in aging animals (the latter probably being rather linked to the overall variability factor; see Sections 3.1 and 3.2). Similarly, if there are very mild systemic effects, which are not seen in a short-term study, they may be seen in studies of longer duration. Old rats with a large body mass have a slower metabolic rate which could make these rats more sensitive and the allometric difference to humans somewhat smaller. This, again, shows that there may be some overlapping in the biology of the different AF.

Also for systemic effects, the plasma (or target organ) peak concentration may be critical and the impact of time (and even AUC) low. Extrapolation in terms of exposure time and even allometric factors should therefore consider not only the total doses (absorbed and excreted). It is conceivable that under certain circumstances rats may achieve higher tissue concentrations than humans at the same dose and, thus, become more vulnerable. This has been tentatively shown in the case of NTA (Budny and Arnold, 1973), a material that does not undergo biotransformation. On the other hand, humans are more sensitive towards the nephrotoxicant diethylene glycol (MAK, 1998; pg. 73-90); to some extent, this may be related to diuretic effects of the parent compound (Wiener and Richardson, 1989). Furthermore, if peak concentrations are critical, the effects may show up already after the first dosage without a further impact of exposure duration. This has been shown e.g. in the case of butoxyethanol (hemolytic effects through butoxyacetic acid; MAK, 1994; pg. 47-52; Ghanayem *et al*, 1989), also for the nephrotoxic effects of NTA (Anderson *et al*, 1985) or for MetHb-forming agents (e.g. aniline; MAK, 1994; pg. 17-36). Compounds which exert and require enzyme induction may need several days or weeks of exposure until the full pattern appears to be developed.

Many studies have been carried out with the liver enzyme inducers DEHP (Cattley *et al*, 1987) or 1,4-dioxane (Young *et al*, 1978; MAK, 2003; pg. 105-133) and the overall evidence shows that after an initial phase of enzyme induction the critical doses do not vary much depending on length of exposure. Even a compound with strongly accumulating properties, e.g. TCDD, showed remarkably similar NOAEL for different lengths of exposure (Kociba *et al*, 1976; 1978). If two time points are available (e.g. 7 and 28 days, or 28 and 90 days) and the effects are quantitatively similar, this would indicate a low time factor for the chemical and its category. It is also pointed out that certain effects (e.g. neurotoxicity) may not always be fully developed within 28 days. Therefore, 'informed' time extrapolation AF should consider the category of the chemical and also carefully exploit short-term toxicity investigations, toxicokinetics and potential enzyme induction.

Within the ERASM project, time-extrapolation factors were evaluated with the database RepDose[g] that currently contains about 670 substances and 2200 studies on repeated-dose

[g] www.fraunhofer-Repdose.de

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toxicity. It has been shown that as long as the material is soluble, the sub-acute to sub-chronic factor was 1.5, rather than 3 , the sub-acute to chronic factor was 3.4 and the sub-chronic to chronic factor was 1.4 (Batke *et al*, 2010). For this evaluation, only studies were included for the same chemical, same species, same route of administration, comparable dose-spacing and scope of examination. This approach reduces the number of suitable data but the variance of the distributions is reduced and the derived extrapolation factors are toxicologically verified. The results thereby obtained should be taken into consideration to eventually modify the default AF. These result for oral and inhalation studies in smaller time-extrapolation factors than those proposed by the REACH TGD.

To arrive at an informed decision about AF for exposure duration the following aspects should be taken into consideration:

- nature of effect;
- dose spacing in sub-acute and sub-chronic studies to decide whether during the time span of 1 week up to 3 months a decrease of the NOAEL actually occurs;
- half-life of the chemical;
- dependency of the effect on peak concentration or AUC.

In summary, differences in length of exposure should be accounted for when modifying the POD. The differences in duration of exposure are addressed through the use of an AF. It is assumed that effective dose levels and thresholds for saturation phenomena decrease with increasing exposure time. It has been shown that this is not always the case and adding this factor may increase the level of conservatism in the DNEL calculation. In some cases, it may be necessary to derive a substance-specific informed AF and this should be done on a need basis. Studies with an exposure duration of 6 months or longer are sufficient to identify chronic effects. For differences in exposure duration, ECETOC proposes the same AF for exposure duration extrapolation of systemic effects as in the REACH TGD, i.e. for sub-acute to sub-chronic an AF of 3, for sub-chronic to chronic an AF of 2 and for sub-acute to chronic an AF of 6.

3.3.2 Exposure duration extrapolation; local effects

Local irritation and tissue destruction

According to the REACH TGD the same default AF should be used both for systemic effects and, in the case of toxicity testing by inhalation, for local tissue damage in the respiratory tract. A lower factor (minimum 1) may be used for certain local effects in the respiratory tract for which there is no substantial difference in N(L)OAEL following acute and sub-acute exposure by inhalation.

A more detailed rationale is given by ECETOC (2003): local effects (e.g. on the respiratory tract, but also on skin or internal organs) are related to the deposited dose per unit of surface area, i.e.

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concentration rather than the total dose (AUC). Below a certain concentration, the capacity of the epithelial cells to neutralise a substance is not overwhelmed. A crucial point is the definition of the threshold for cytotoxicity, e.g. by histopathology or cell proliferation. It is concluded that no additional AF is needed for substances with a local effect below the threshold of cytotoxicity for exposure duration.

The REACH TGD cites Kalberlah *et al* (2002) as the justification for using default AF for local effects. This publication reports an analysis of 46 technical reports of the US National Toxicology Program (NTP) with sub-acute, sub-chronic and chronic inhalation duration in order to derive time-extrapolation factors for locally acting substances. On the basis of geometric mean values decreases in effect concentrations by factors of 3.2 (sub-acute to sub-chronic), 2.7 (sub-chronic to chronic) and 6.6 (sub-acute to chronic) were found. These extrapolation factors for local respiratory effects were very similar to those proposed for systemic effects in a report of Kalberlah and Schneider (1998). NTP inhalation studies with less than life time exposure (sub-acute, sub-chronic) in many cases showed different locations of respiratory effects as compared to chronic studies. Unfortunately, in this publication the chemicals and studies analysed are not given; therefore an independent substance-by-substance evaluation is not possible. Hence, the ECETOC Task Force carried out a detailed analysis of the NTP data with respect to local effects (see Appendix B).

Contrary to the findings reported in Kalberlah *et al* (2002) and Kalberlah and Schneider (1998) the NTP data set suffers from some severe deficiencies making it inappropriate and inadequate to draw any reliable conclusions regarding AF to account for study duration with respect to local effects. Indeed, in some cases the limited information supports an AF of nearer 1 and in other cases, where additional studies designed to assess local effects have been conducted, an AF of 1 is clearly indicated.

In the time available, the ECETOC Task Force was not able to conduct an exhaustive review. However, the Task Force was able to identify specific examples from SCOEL, AGS and the EU Existing Substances Risk Assessment (ESR) programme that clearly support an AF of 1 for local effects (see Appendix C).

In conclusion, therefore, this limited dataset indicates that an AF>1 for time extrapolation starting from sub-acute or sub-chronic studies is not appropriate.

Sensory irritation

If the POD is defined by transient sensory irritation, which may not be adverse, as derived from clinical signs in experimental animals or from controlled chamber studies with volunteers, an exposure duration extrapolation is not appropriate (AF=1). Since the onset of sensory irritation will occur quickly, neither the extrapolation from experimental exposure times to the total

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working day nor an AF for prolonged periods (days to months or longer) is appropriate. This has been substantiated by an investigation of Shusterman *et al* (2006). The authors analysed whether the time/concentration relationship follows Haber's (c x t) law, meaning that protracted, low-level exposures are equivalent to brief, high-level exposures. They analysed sensory irritation reported by humans that were exposed to defined concentrations of airborne irritants over different periods. The exposure concentration was found to have a proportionally greater effect on sensory irritation than exposure duration. Furthermore, an intensity-time 'plateauing' was observed with time effects disappearing or even reversing after a relatively short period. For example, for ammonia a diminution of the time effect was apparent within the first 10 sec of exposure, and for formaldehyde sensory irritation ratings peaked by 90 min and began to drop off thereafter.

Rapid onset of sensory irritation with subsequent 'plateauing' already after a few seconds was also described by Wise and co-workers. They investigated the threshold of 'true' sensory irritation (not confounded by olfaction) by lateralisation in volunteers. Even after very short exposure periods (up to a few seconds) it was found that the c x t-rule does not apply, and when cutting the concentration in half required more than doubling the exposure concentration to obtain the same subjective level of irritation (Wise *et al*, 2009a). This was shown for carbon dioxide (Wise *et al*, 2004), ammonia (Wise *et al*, 2005) and ethanol (Wise *et al*, 2006). For a series of homologous chemicals it was demonstrated that the deviation from the c x t-rule became smaller as the lipophilicity of homologous alcohols (Wise *et al*, 2007) or propionates (Wise *et al*, 2009b) increased.

In addition, in human volunteer inhalation studies extended over several hours no increase with exposure duration was observed for objective or subjective signs of irritation. Some examples from more recent studies are:

- Lang *et al* (2008) exposed volunteers to different concentrations of formaldehyde ranging from 0 to 0.5 ppm, partly including 4 peak exposures for 15 min of 0.6 and 1 ppm. In addition, co-exposures with ethyl acetate (12-15 ppm) as an odorant were used to enable a differentiation between odour and irritation of formaldehyde. Conjunctival redness and eye blinking frequency as objective signs of eye irritation did not increase from 120 to 195 min after start of exposure.

- The results of Lang *et al* (2008) seem to be in contrast to the findings of Kiesswetter *et al* (2005) who analysed eye blinking rates during exposure to 2-ethylhexanol. The subjects were exposed over 4 hours either to constant concentrations of 1.5 (control), 10 or 20 ppm, or to 4 peak exposures of 20 and 40 ppm superimposed to 1.5 ppm yielding time-weighted average (TWA) concentrations again of 10 and 20 ppm. Eye blinking rates were measured twice, each near start and end of exposure (about 30, 60, 210 and 230 min after start of exposure). For the peak exposure part this

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coincided with the trough and peak concentrations of the first and last peak. For normal subjects there was a small but significant increase in blinking rate from start to end of exposure for both exposure scenarios (constant and peak exposures) but a massive increase when comparing blinking frequencies under trough and peak conditions. In addition, men with self-reported multiple chemical sensitivity (sMCS) were investigated. In comparison to normal subjects, the sMCS group showed higher starting values, but no increase from start to end and only a smaller increase from trough to peak exposure conditions. According to the authors the small increase observed in normal subjects between start and end of exposure very likely represents mainly an asymptotic part of the irritation change. In comparison to Lang *et al* (2008) the first measurement was done within the first hour of exposure when the maximum response was not yet reached, while in the study of Lang and co-workers blinking frequencies were determined at 120 and 195 min, i.e. both on the plateau of the effect.

- Kleinbeck *et al* (2008) investigated sensory effects after exposure to ethyl acetate over 4 hours. When the subjects were exposed to 4 peaks of 800 ppm superimposed to a baseline concentration of 5 ppm the subjective ratings for odour intensity, annoyance, pungent and burning sensations followed the time course of the ethyl acetate concentrations. Thus, the subjective ratings rapidly subsided when the exposure concentration decreased, and there was no indication for an accumulation of subjective symptoms from peak to peak.

- Hey *et al* (2009) exposed volunteers over 4 hours to TWA concentrations of 0.3, 5 and 10 ppm propionic acid. The TWA concentration of 5 ppm consisted of variable concentrations with maximum peaks of 10 ppm. The participants rated the subjective symptoms nine times during exposure. The time course for olfactory and trigeminal sensations were comparable and showed a maximum at the beginning of the exposure followed by a decline across the exposure duration for the 10 and 5 ppm TWA concentrations.

- Van Thriel *et al* (2010) exposed volunteers over 4 hours to concentrations of 0, 0.5, 1 and 2 ppm sulphur dioxide. The participants rated subjective symptoms eight times between the beginning and the end of the exposure. Regarding temporal effects, only perceived odour intensity was significantly affected by exposure duration with a general decline as a function of exposure duration. A time related effect was not described for other sensations that might have been mediated by trigeminal stimulation.

In Section 3.6, the Task Force compared DNEL derived by default AF as per the REACH TGD with IOELV proposed by SCOEL. Six substances were identified where the SCOEL IOELV was

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based upon local effects in animal studies (see Table 4). In all cases, the overall AF applied by SCOEL was lower than those recommended by the TGD supporting the conclusion that there is no evidence that an AF for time extrapolation to account for study duration was considered appropriate.

In summary, the REACH TGD proposes the same default AF for local effects on the respiratory tract as for systemic effects. ECETOC provides a more detailed explanation why for time extrapolation no additional AF is needed for local effects. If the POD is defined by sensory irritation, observed either in animal studies or in humans by epidemiology or in controlled chamber studies, no additional AF is warranted. Therefore, it is proposed to use an AF of 1 for local effects, especially after inhalation exposure.

3.4 Dose-response relationship (LOAEL/NOAEL extrapolation)

According to the REACH TGD, Section R.8.4.3.1, "*the size of an assessment factor* (for LOAEL/NOAEL extrapolation) *should take into account the dose spacing in the experiment (in recent study designs generally spacing of 2-4 fold), the shape and slope of the dose-response curve, and the extent and severity of the effect seen at the LOAEL.*
When the starting point for the DNEL calculation is a LOAEL, it is suggested to use an assessment factor between 3 (as minimum/majority of cases) and 10 (as maximum/exceptional cases). However, the benchmark dose (BMD) approach is, when possible, preferred over the LOAEL-NAEL extrapolation.
A BMD calculated as the lower confidence limit of the dose that produces a response of 5% (BMD5) has on average been proposed to be comparable to a NOAEL (WHO, 2000). If other BMD indicators are used, e.g. BMD10, it should be considered on a case-by-case basis whether an additional dose-response assessment factor is needed."

ECETOC (2003) arrived at a similar conclusion. The maximum value for LOAEL/NOAEL extrapolation generally is 10 but this is considered as overly conservative. Published studies indicate that the LOAEL/NOAEL difference rarely exceeds a factor of 5 to 6 and is typically closer to a value of 3. The NOAEL/LOAEL ratio is highly dependent on the spacing between the doses, and since recent study design generally uses a dose spacing of 2- to 4-fold, it is logical to conclude that the data on this ratio support a value of 3 as default. When applying the BMD approach, generally an incidence level of 5% with the 95% C.I. (confidence interval) is used, but particularly in studies with a small number of animals this may give a value much lower than the experimental NOAEL. Confidence limits are dependent on the size of the dataset and therefore current guideline studies may not be ideal for deriving a BMD (Woutersen *et al*, 2001). Therefore, a better starting point may be the point estimate, especially for continuous data (Murrell *et al*, 1998).

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The severity of effects still observed at the LOAEL is an important criterion for defining the AF; severe effects at the LOAEL will require a larger AF. The REACH TGD, in the same section, proposes that *"when the starting point for the DNEL calculation is a NOAEL, the default assessment factor, as a standard procedure, is 1. However, a larger assessment factor may be applied in specific cases such as:*

- *a shallow dose-response curve….*
- *….serious …. and irreversible effects….*
- *….poor quality of study…."*

In summary, to convert a LOAEL to a NOAEL, the REACH TGD suggests an AF of 3 as a minimum for the majority of cases and going up to a default of 10 for exceptional cases. Higher AF have to be used if severe effects were observed at the LOAEL. ECETOC TR 86 references the published literature showing that for most current well-designed studies a factor of 3 will account for the LOAEL/NOAEL difference. No AF is needed when using a BMD5 with a 95% C.I. (i.e. BMDL5 since this is considered a NOAEL). ECETOC proposes an AF of 3 to account for LOAEL/NOAEL differences. If the dose-response curve provides sufficient information, an informed AF deviating from the suggested default should be applied.

3.5 Quality of 'whole' database

An additional AF in this respect may be applied to compensate for potential remaining uncertainties taking into account whether:

- there are data gaps as compared to the tonnage driven requirements;
- the evaluation is based on alternative approaches (QSAR, read-across);
- the hazard data are reliable and consistent across different studies and endpoints.

The default AF is 1 for a good/standard quality of the database. A larger database AF should, where relevant, be applied and justified on a case-by-case basis.

In summary, for animal and human studies of high quality the AF is 1.
A higher AF may be indicated if:

- there are data gaps;
- the evaluation is based on alternative approaches;
- there are inconsistencies of data across different studies and endpoints.

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3.6 Comparison of DNEL derived by default AF of REACH TGD with IOELV proposed by SCOEL

The Task Force examined a number of the summary documents prepared by SCOEL and compared the IOELV with DNEL derived for systemic and local effects according the REACH TGD (see Tables 3 and 4, and Appendix A).

It is clearly shown that for many substances (irritant chemicals as well as those with systemic effects) the hazard properties are systematically overestimated by the described default factor approach. This leads to DNEL which are on average 10-fold below existing and well accepted SCOEL IOELV, although there is no empirical evidence that these IOELV of SCOEL are not protective of worker health. In most cases, the default AF proposed in this document will also lead to DNEL which are lower than the current IOELV. The discrepancies between DNEL and IOELV are summarised in Appendix A of this report.

Generally, SCOEL used a single uncertainty factor to account for all variation and uncertainties in the database rather than multiplying individual AF. Important studies and uncertainty as well as strength of the whole database were evaluated in the context of all available information to derive a starting point for further evaluation. Although SCOEL documentation is not always explicit in explaining the individual factors underlying these assessments, there is a strong indication that the observed differences between the IOELV and DNEL are the result of differences in interpretation on how to apply the combined factors of inter- and intraspecies variability among other factors as modification of starting point.

Based on this evaluation, the Task Force recommends the application of expert judgement and to refrain from applying the default factors based on a comprehensive analysis and evaluation of the existing data for a specific substance. This is possible within the framework of the REACH TGD. Additionally, Appendix R.8-13 therein allows the use of adopted occupational exposure limits[h] in place of developing a DNEL.

In summary, DNEL obtained by applying the REACH TGD default AF in a standardised manner are often at least one and sometimes several orders of magnitude below the IOELV determined by SCOEL using one overall uncertainty factor. The Task Force believes that the observed differences between the IOELV and DNEL is mainly a result of differences in interpretation on how to account for combined factors of inter- and intraspecies variability. Expert judgement should be applied in determining the overall AF by taking into account the whole database available. In the case of an IOELV or an equivalent robust OEL, this value can be used instead of a DNEL.

[h] EU indicative occupational exposure limit value (IOELV); EU binding occupational exposure limit value (BOELV) ; national occupational exposure limit

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4. ASSESSMENT FACTORS (SPECIFIC ENDPOINTS)

4.1 DNEL for dust / general dust limit

The REACH TGD states in Section R.8.7.1:
"*For exposure to dust, it should be considered whether a derived DNEL for inhalation may have to be lowered. The general dust limits of 10 mg/m^3 for the inhalable airborne fraction and 3 mg/m^3 for the respirable airborne fraction used in setting Occupational Exposure Limits in many countries should be considered in combination with nature of the dust. The following should be considered*:

- *For non-soluble inert dusts if the derived DNEL for inhalation is above these dust limits, the general dust limits should apply for exposure scenarios with exposure to dust*
- *For significantly soluble dusts, if the derived DNEL for inhalation is above* (these dust limits)*, the general dust limit might apply. Where it is not to be used, the rationale for any deviation from the general dust limits should be justified.*

Note that DNELs derived based on substance-specific data can never be adjusted upwards based on the general dust limits and that the dust limits can not be used as a surrogate DNEL when there is no data to set a substance-specific DNEL."

In principle, this approach is supported with some minor specifications. For non-soluble, non-bioavailable inert dusts, general dust limits should be used as long term DNEL for workers if there are no substance-specific data against their use.

For soluble, bioavailable dusts, specific DNEL higher than the general dust limits are possible provided substance-specific data are available. This is in line with common practice of OEL committees.

For example, soluble dusts may be irritating for various reasons such as non-physiological pH, (thermo-) reactivity with water, osmotic effects, electrophilic reactivity with proteins or other reactions leading to cytotoxicity. Hence, the specific irritation threshold of each material should be investigated via the inhalation route or - if scientifically justified - by cross-reading from related materials. Depending on the most relevant MOA, two scenarios are possible:

1. The threshold for local respiratory effects is relatively low, thereby limiting the systemic internal dose such that systemic effects do not develop. In that case, the respiratory toxicity precludes any systemic effects from inhalation, and the derivation of a DNEL for systemic effects by the inhalation route is unnecessary.
2. The threshold for local respiratory effects is high and the DNEL for local effects on the respiratory tract does not preclude systemic effects. The DNEL is to be defined by these systemic effects.

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Thus, depending on the prevalence of systemic or local toxicity, either respiratory effects limit the systemic dose (and preclude a systemic effect from inhalation) or do not necessarily preclude a systemic effect. In the latter case, the systemic DNEL is the limiting value for inhalation exposure.

Size of particles is also an important consideration when evaluating the toxicity of dust/aerosol exposure. Particles <100µm aerodynamic diameter are considered inhalable and those <10µm respirable. Respirable particles are mainly concentrated in the upper respiratory tract for rodents and in the lower respiratory tract for primates including humans. Local effects of direct acting soluble particles will be observed mainly at the site of deposition where they become bioavailable. The complexity of deposition and toxicokinetics of these dusts does not allow a simple AF to be derived and will require detailed substance-specific information to develop an informed AF. However, due to the higher respiratory rate of rodents that leads to a greater respiratory tract burden as compared to humans, the effects observed in rats may overestimate exposure. Therefore, when extrapolating to humans no additional interspecies AF is needed.

In summary, DNEL derivation for dusts / aerosols depends on whether the material is bioavailable (soluble) or not. For non-soluble, inert materials, the general dust limits should apply. For significantly soluble materials, the derived DNEL may be above or below the general dust limits and is defined either by local irritation to the respiratory tract or by systemic toxicity, whichever is the predominant effect.

4.2 DNEL for acute toxicity

4.2.1 REACH TGD for derivation of a $DNEL_{acute}$

General considerations

Section R.8.7.3 of the REACH TGD briefly describes the general considerations for establishing acute DNEL. Regarding the general requirement for a $DNEL_{acute}$, the REACH TGD states that *"… if actual peak exposure levels to toxic substances exceed the long-term DNEL by several-fold, a detailed acute risk assessment clearly has to be made. For systemic, acute effects, two DNELs are normally relevant to compare with peak exposures…*, these being $DNEL_{acute\ inhalation\ worker}$ and $DNEL_{acute\ inhalation\ general\ population}$ (REACH TGD, Table R.8-12): in the case of $DNEL_{acute\ inhalation\ worker}$, this should correspond to the worker inhalation peak exposure, while for $DNEL_{acute\ inhalation\ general\ population}$ this should correspond to occasional inhalation exposure (minutes-hours) of the general population (consumers, humans via the environment).

As regards the route of exposure, the inhalation route is most important for a $DNEL_{acute}$. The REACH TGD, in the same section, specifies that: *"Rarely, and on a case-by-case basis, the other* (oral and dermal) *routes may need to be assessed (potentially constituting three different DNELs).*

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That includes a systemic DNEL acute dermal for workers and the general population, and a systemic DNEL acute oral for the general population, in both cases representing single exposure. However, in a first tier, these exposures should be compared against the corresponding long-term DNELs. For both acute and long-term local effects, …. causing irritation, corrosion and/or sensitisation, ….” acute dermal and acute inhalation $DNEL_{local\ effects}$ may be needed for workers and the general population but an acute oral $DNEL_{local\ effects}$ is not relevant.

Another important aspect in acute DNEL calculations is exposure duration. Presumably because local effects are substance-concentration driven, the REACH TGD specifies in Table R. 8-13 that worker-$DNEL_{acute\ dermal\ local}$ corresponds with worker dermal single exposure and worker-$DNEL_{acute\ inhalation\ local}$ with worker inhalation peak exposure. Specifically for inhalation exposure of workers, REACH TGD states that: “*The $DNEL_{acute}$ is set based on studies involving exposure for very short periods (for inhalation normally 15 minutes' peak exposures)*” and also that: “*The acute toxicity studies are the most relevant studies*”. In addition, “*… human data, such as from case studies, need to be assessed*”.

Adequate data will often not be available for a sound scientific derivation of a $DNEL_{acute}$. Therefore, the REACH TGD proposes that *“…in the absence of experimental data, the acute DNEL can by default be set as 1-5 times the long-term DNEL*”.

Tiered approach of REACH TGD for derivation of a $DNEL_{acute}$

A more detailed guidance for derivation of a $DNEL_{acute}$, specifically for the inhalation route, is given in Appendix R. 8-8 of the REACH TGD. In general, a DNEL for acute toxicity should be established if an acute toxicity hazard has been identified and there is a potential for high peak exposures. However, as the REACH TGD recognises, risks arising from such peak exposures may not be adequately covered by the $DNEL_{long\text{-}term}$ that is derived from repeated-dose toxicity studies. Normally, an assessment of oral or dermal peak exposures is not necessary and no guidance is given here in this respect. As adequate human data are rarely available, $DNEL_{acute}$ should be based, whenever possible, on acute studies in animals.

In theory, a DNEL for acute toxicity is derived in the same way as a DNEL for long-term toxicity. Suitable dose descriptors or POD are the NOAEL/ NOAEC for lethal and sub-lethal effects, local irritation, and CNS depression, if evident from an experimental study. A $DNEL_{acute}$ should not only preclude mortality but also less severe effects. This, however, would require a study adequately addressing the dose-effect relation including non-effective doses (absence of observable clinical or pathological signs). In many studies, however, especially the more recent ones, a smaller number of animals is used and the results are confined to very limited dose descriptors (LD_{50}/LC_{50}, limit dose, LC_o) without information on the dose-effect relationships. The reported outcomes are often limited to mortality, clinical signs, and at best gross pathology. A $DNEL_{acute}$ in such cases could then be based on NOAEL from sub-chronic studies (even range

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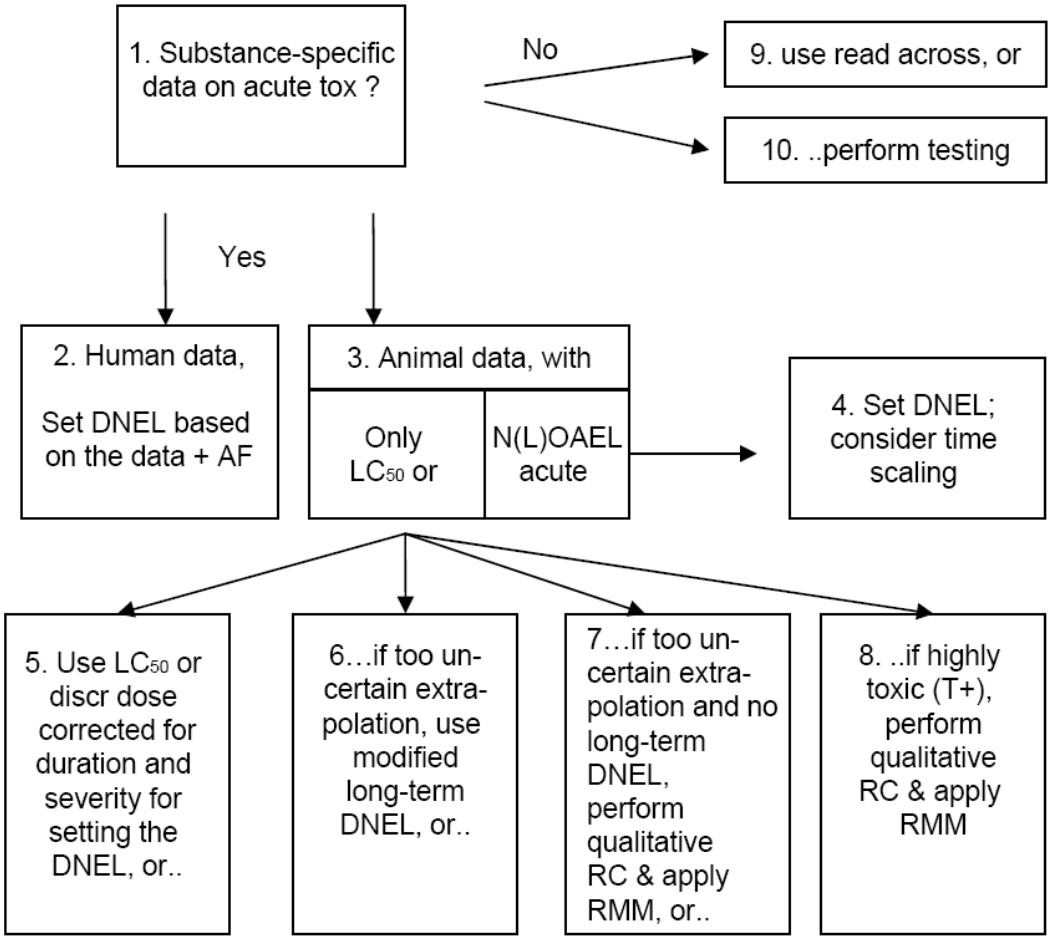
finding experiments), generally used for derivation of the $DNEL_{long\text{-}term}$, or existing OEL. In principle, such OEL should not be exceeded unless for short-term exposure limits (STEL) or ceiling levels with short defined exposure periods.

The basic principles for derivation of a $DNEL_{acute}$ for inhalation as the most important exposure route are outlined by the REACH TGD in a decision tree (Appendix R.8-8, Figure R.8-5; text below adapted from ECHA, 2008).

Figure 1: Decision tree for setting an acute inhalation toxicity DNEL (cited in ECHA, 2008, Figure R.8-5)



- If no acute toxicity data are available (acute oral or inhalation animal data should be present already from the 1 ton/year level) a read-across approach may be used (Box 9). This may require an additional AF for the uncertainties introduced by the read-

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across, apart from those that are generally needed for acute toxicity data (see below). If read-across is not possible, testing is required (Box 1 and 10).

- In some cases, there may be human data (epidemiology, case studies, or reports from poison centres). But the exposure durations are often unclear. The dose descriptors may need to be time scaled and an AF for intraspecies variation may often be needed, depending on the size of the investigated population (Box 2).

- If acute inhalation toxicity data from experimental animals are available, studies with N(L)OAEL for sublethal effects are most valuable. For the worker, the 4 hours exposure duration has first to be corrected to 15 min (exposure duration proposed by the REACH TGD for the worker $DNEL_{acute}$) by the modified Haber rule and for differences in respiratory volume (animals at rest vs. working humans). For the general population, as noted below, the appropriate time should be application specific, and a 1-hour default is recommended as most exposures will be longer than 15 minutes duration. In addition, appropriate AF for inter- and intraspecies variation and for LOAEL to NOAEL extrapolation have to be used. A further AF for inherent deficiencies of the acute study may be necessary, if only a limited number of endpoints were examined. If only an oral (or dermal) study is available, the oral (dermal) N(L)OAEL should be modified by route-to-route extrapolation to the inhalation N(L)OAEL. But thereby major additional uncertainties are introduced in relation to the inhalation time frame and the protracted oral or dermal absorption. Therefore, the REACH TGD discourages this approach (box 3 and 4).

- If only lethality data or the LC_{50} are available (as is most often the case), according to the REACH TGD, there is no scientific basis for extrapolation to relevant sublethal effects. A default AF of 100 is suggested as starting point, when deriving a $DNEL_{acute}$ from either the lethality data or the LC_{50} but modifications may be possible if justifiable. In addition, AF for inter- and intraspecies variation may be needed. It has been shown (Rusch *et al*, 2009) that taking 1/3 of the LC_{50} will define a non-lethal level. Furthermore, taking 1/3 of the non-lethal level in an acute study will generally define the non-toxic level. Finally, application of an interspecies adjustment factor of 3 and an intraspecies adjustment factor of 3, will define a protective $DNEL_{acute}$ (Calabrese, 1985; Hattis *et al*, 1987), although the REACH TGD indicates that some caution is required when taking this approach. If only lethality data are available for an LD_{50} after oral application, this would add considerably to the uncertainties and the $DNEL_{acute}$ obtained by route-to-route extrapolation would be questionable for risk assessment (Box 5).

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- If the $DNEL_{acute}$ based on lethality data is considered to introduce too much uncertainty, the $DNEL_{acute}$ can be based on the $DNEL_{long\text{-}term\ inhalation}$. The latter shall be modified by multiplying with a factor of 1-5 depending on the potency and the dose-response curve of the chemical. But this approach is not recommended if long term data are only available for another route than that for the $DNEL_{acute}$ (Box 6).

- If the derived inhalation $DNEL_{acute}$ is highly uncertain (e.g. in cases of route-to-route extrapolation from an oral LD_{50} value) and a $DNEL_{long\text{-}term}$ is not available the REACH TGD proposes that a qualitative risk assessment shall be considered to define risk management measures. Preferably, risk management should ensure that peak concentrations exceeding the $DNEL_{long\text{-}term}$ will not occur (Box 7). This proposal of the REACH TGD is a contradiction in itself as the same approach is proposed for acutely very toxic (T+) substances (Box 8).

In summary:

- Acute DNEL are most relevant for workers and the general population for an exposure by inhalation and in specific cases also for the dermal route.
- A decision tree for an acute DNEL for inhalation is given with emphasis on acute inhalation studies. AF that may be necessary for specific data constellations are identified.
- Nevertheless, important questions and shortcomings remain for routine implementation of this scheme. The most important ones are:
  - exposure duration for the $DNEL_{acute\ general\ population}$;
  - selection of POD; extrapolation from lethality to sublethal effects and NOAEC;
  - time extrapolation, e.g. from typically 4 hours experimental exposure to 15 min peaks at the workplace or 1 hour for the general population;
  - assessment of local and systemic effects.

4.2.2 ECETOC proposal for a derivation of a $DNEL_{acute}$

The systematic, tiered approach of the REACH TGD has two major implications that need to be taken into consideration:

- even for a reliable database (reliable human data or acute inhalation studies defining sublethal effects) a decision on appropriate AF is necessary. ECETOC proposes to use the same AF that were discussed in the preceding chapters for derivation of $DNEL_{long\text{-}term}$;
- in many instances, sufficiently reliable human or animal data will not be available. ECETOC proposes to apply approaches, whenever possible, used by scientific organisations (ACGIH, AIHA, SCOEL, MAK Commission) that have experience in setting OEL values for decades.

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Exposure duration

The REACH TGD gives clear guidance that the $DNEL_{acute}$ should refer to peak exposures at the workplace generally under 15 min. In contrast, no such guidance is given for the general population, but a scenario of only occasional 15 min peak exposures is quite unrealistic. If mixing and application of paints is taken as a typical example, longer acute exposures of e.g. 0.5-4 hours (typically 1 hour) are more relevant. This will avoid or minimise time extrapolation from 4 hours acute exposure in animal experiments to the acute exposure duration of the general population.

Selection of POD

Short exposure peaks at the workplace, as accounted for by the $DNEL_{acute\ worker}$ occur in addition to the $DNEL_{long\text{-}term\ worker}$. While the REACH TGD does not specify whether it is acceptable that the $DNEL_{long\text{-}term}$ on an 8-hour TWA basis is exceeded by peak exposures, organisations such as SCOEL, MAK and ACGIH require that the overall $DNEL_{long\text{-}term}$ (calculated as an 8-hour TWA) should not be exceeded. An acute, infrequent, exposure should generally be tolerated as well as or better than a chronic exposure. Therefore, the $DNEL_{acute}$ should generally be higher than the $DNEL_{long\text{-}term}$, especially for systemic effects.

In most cases the $DNEL_{acute}$ has to be based on animal studies. As stated above experimental acute inhalation studies covering a broad exposure range from NOAEL over sublethal effects up to mortality are in many cases not available. Acute studies carried out according to modern guidelines will generally not provide the data necessary for a scientifically defensible $DNEL_{acute}$. Further, clinical data are often not available. In these cases the highest non-lethal exposure must be chosen as the POD for the study time interval. If an acute inhalation study is deemed to be of high quality and the MOA is believed to be similar in the test species and in humans, an AF of 3 should be applied for intraspecies variability and no further AF for 'remaining' interspecies variability should be applied according to ECETOC (2003). Thus, if the 4-hour LC_{50} is 150 ppm and the highest level not causing lethality is 100 ppm, then taking the 100 ppm as the POD for the risk assessment and dividing this by 3 as an AF for sensitive members of the population, the result is 33 ppm as the estimated non-lethal level for humans for the same time interval (4 hours). This is rounded to 30 ppm. For studies where only the LC_{50} is given, it has been shown that application of a factor of 3 to the LC_{50} will often result in a non-lethal level that can be the basis for the POD for the DNEL derivation. In the example described above, the concentration not leading to lethality for humans would be based on 1/3 of the LC_{50} of 150 ppm or 50 ppm (Rusch *et al*, 2009). An AF of 3 for intraspecies variation would yield 17 ppm, a value more conservative than the 30 ppm derived above. The $DNEL_{acute}$ should not only protect from lethal effects but from all possible adverse effects. This should be taken into account and the POD has to be modified accordingly.

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If, starting with an LC_{50}, one applied an adjustment factor of 3 to estimate the non-lethal level in animals and a second factor of 3 to estimate the non-lethal level for humans, this would yield an AF of 10. For substances with a steep dose-response curve, application of an additional adjustment factor of 3 to the non-lethal value would yield the non-toxic level for humans. This would result in a total adjustment factor of 30 (from the LC_{50} to estimate a non-toxic level for humans). For substances with a shallow or unknown dose-response curve, the adjustment factor to go from non-lethal to non-toxic should be increased to 10. In this case, the LC_{50} would be divided by 100. Finally, for materials with a very weak database, an additional modifying factor of 3 might be applied. This would equate to the REACH TGD default of 100 for estimation of an $DNEL_{acute}$ for substances with a poor database. The stepwise approach is to first divide the LC_{50} by 3 to estimate a non-lethal level. This becomes the POD for risk assessment. This value is divided by two adjustment factors of 3 each (where 3 x 3 = 10) and one of 10: 3 from animals to man; 10 from a toxic to a non-toxic level; 3 for a poor database. In the example above, the LC_{50} = 150 ppm. The estimated non-lethal level would be 50 ppm. The estimated non-lethal level for man would be 17 ppm. The estimated non-toxic level would be 0.5 ppm (50 / 3 * 10 * 3).

In other cases, the determination of sublethal endpoints can often be accomplished by looking at clinical observations and body weight gains in acute studies or even looking at these endpoints during the first week(s) of exposure in repeated-dose studies. If repeated-dose studies are used for defining the POD for $DNEL_{acute}$, the study with the shortest exposure duration should be selected.

Time extrapolation

The exposure duration in acute inhalation studies generally is 4 hours, and these studies rarely are designed to allow an understanding of the interrelation of concentration (C) with time (T) for extrapolations to exposures of shorter durations as relevant for $DNEL_{acute}$. Indeed, only in skin corrosion studies directed towards classification for transportation (3 min, 1 hour and 4 hours exposure) shorter exposures than 4-hour duration are used.

The original Haber rule, C x T = K was applicable for the class of compounds that would penetrate to the lung and cause irreversible damage. In the 1980s and 1990s, ten Berge, Zwart and Appelman extended the range of the relationship by including a more diverse group of chemicals (ten Berge *et al*, 1986). The relationship that they derived was C^n x T = K. This can also be expressed as C x $T^{n(t)}$ = K. Following their studies of several compounds, it appeared that the values for n ranged from 0.8 to 3.2. Since $DNEL_{acute}$ are developed for time intervals of 15 min (workers) or e.g. 1 hour (general population), when possible the data should fit to this curve to derive a value for n. When the data are insufficient to derive a substance-specific value of n, a default approach, i.e. setting n=3 in extrapolating to shorter time periods and n=1 for extrapolations to longer time points, is proposed. These are approximations for the extremes of the values published by ten Berge *et al* (1986). The ERP committee (Emergence Response

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Planning Committee of the American Industrial Hygiene Association) developed their procedure before the widespread acceptance of this approach and used for their extrapolations a value of n = 2. Again, in going to the shorter time points, this was a more conservative approach than applying C x T = K. This procedure for time extrapolation should be used for systemic effects and for lung toxicants.

In contrast, local irritation of the respiratory tract is strictly a concentration-related response, and a factor of 1 for time extrapolation should be used for exposure durations between 15 min and 4 hours.

If a repeated-dose study has to be used for defining the POD (see above), the study with the shortest exposure duration should be selected. A lower AF (as compared to that used for acute studies) would be appropriate to account for the short exposure duration of the $DNEL_{acute}$ on a case-by-case basis.

Assessment of local versus systemic effects

Any consideration about the AF for derivation of a $DNEL_{acute}$ must be based on an analysis of the POD. Questions that should be considered are:

- Is it based on systemic effects or on local effects of the respiratory tract?
- Is the effect irreversible or reversible and of minor toxicological relevance?
- Will the effect occur after a short or only after a prolonged exposure?

Local effects: Very often the POD is based on local irritation of the (upper) respiratory tract, observed either in humans or animal studies. It has to be determined whether local irritation was defined by cytotoxic effects (tissue destruction, increased cell proliferation) or by sensory irritation due to stimulation of the trigeminal nerve, as these outcomes differ in severity and should be treated differently for DNEL derivation purposes. Generally, cytotoxic irritation will require higher AF while for purely sensory irritation a small AF (generally 1) is appropriate for workers. Specific considerations for effects in humans will be discussed in Chapter 5.

If there are clinical observations indicative of sensory respiratory irritation during exposure in animal studies, these observations may directly be used for defining the $DNEL_{acute}$ but they are more related to comfort than to adverse health effects, and, accordingly, smaller AF may be justified than would be used for actual toxicity. A combined AF of 1 for inter- and intraspecies variability will generally be appropriate to derive the worker $DNEL_{acute}$. For the general population an AF>1 may be required to account for the increased sensitivity of the general population and any influence of the healthy worker effect.

If the $DNEL_{acute}$ is to be based on histopathological effects in the respiratory tract, it should be derived from the NOAEC/LOAEC of the (repeated-dose) study. AF for inter- and intraspecies

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variability should be used as for $DNEL_{long\text{-}term}$. Because of the very short exposure duration the $DNEL_{acute}$ should be increased beyond the $DNEL_{long\text{-}term}$ by a factor of 2-5 using the higher end of a range of possible factors, especially if there is evidence for increasing severity of histopathological effects with increasing exposure duration.

Systemic effects: If the $DNEL_{acute}$ is to be based on systemic effects after repeated exposure, the following factors should be taken into consideration:

- NOAEL/LOAEL of a sub-acute study (or even a study of shorter duration) should be the starting point. AF for inter- and intraspecies variability and route-to-route extrapolation should be used as for $DNEL_{long\text{-}term}$. Then the $DNEL_{acute}$ should be increased beyond the $DNEL_{long\text{-}term}$ based on Haber's Law by an appropriate factor to take account of the short exposure duration. A decision should be made on a case-by-case basis taking into account the severity of the effect and the time course for its manifestation. It has to be taken into consideration whether the effects
    - are of questionable health implications (e.g. slight liver weight increase without histopathological findings) and/or
    - are occurring only after prolonged exposure (e.g. effects on body weight).
- Especially for substances with a long biological half-life a high $DNEL_{acute}$ relative to the NOAEL is justified, e.g. by a factor of 5 higher than the $DNEL_{long\text{-}term}$. For such substances, any short-term exposure exceeding of the $DNEL_{long\text{-}term}$ (or the OEL) will not lead to health effects as long as the overall daily DNEL or TWA is not exceeded.

Approaches used by regulatory organisations for setting short-term exposure limits

Derivation of $DNEL_{acute}$ closely resembles the approach of scientific organisations like ACGIH, SCOEL, MAK or AGS for setting short-term exposure limits above the OEL/TWA. Taking into account all the considerations for defining a $DNEL_{acute}$ by the procedures outlined above, in the majority of cases a $DNEL_{acute}$ must be based on the $DNEL_{long\text{-}term}$. In such a situation, the REACH TGD proposes to apply a default multiplicative factor of 1-5 to the $DNEL_{long\text{-}term}$ similar to the ACGIH approach. Although it is not possible to give clear guidance to substantiate a specific numerical value within the range of 1-5, there are some generic principles that will help to decide whether for a chemical with a specific toxicological profile this factor should be at the upper or the lower end of this range.

The principles applied by the above mentioned committees to limit short-term exposure peaks (generally for durations of 15 min similar to the definition of the worker $DNEL_{acute}$) are as follows:

- ACGIH defines STEL values on a substance-specific basis limiting excursions above the threshold limit value time-weighted average (TLV-TWA) for a maximum of 15 min (4 times a day, at least 1 hour apart). Such STEL values or their excursion

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factors can be used as a guide for a $DNEL_{acute}$ of a substance with a similar toxicological profile (ACGIH, 2008).
If a STEL value is not defined, ACGIH proposes as a default that "*excursions in worker exposure levels may exceed 3 times the TLV-TWA for no more than a total of 30 minutes during a workday, and under no circumstances they should exceed 5 times the TLV-TWA, provided that the TLV-TWA is not exceeded.*" This maximum recommended excursion is derived from the variability generally observed for actual industrial processes **(**ACGIH, 2008**).** This approach of ACGIH may be taken as a default for the derivation of a $DNEL_{acute}$ if specific data are not available by which a data-based $DNEL_{acute}$ can be justified.

- The MAK Commission has defined a default approach for 15 min excursions above the MAK value, 4 per shift at an interval of 1 hour each. MAK defines an excursion factor of 1 for "*substances for which local irritant effects determine the MAK value, also for respiratory allergens*" and an excursion factor of 2 for "*substances with systemic effects*" and indicates that based on substance-specific information excursions factors of up to 8 are permitted. In many cases, there are data-based deviations from these defaults. It is proposed that these substance-specific excursion factors of the MAK Commission can serve as a guide for derivation of a $DNEL_{acute}$ based on similarities of the toxicological profile.

- A similar approach is given by the AGS (2010b). For an 8 hour-shift 4 excursions each of 15 min duration are allowed with intervals of about 1 hour. By such short-term excursions the workplace exposure limit (TWA) must not be exceeded. Two categories are defined:
    - Cat I: substances for which local effects or respiratory sensitisation are relevant for derivation of a workplace exposure limit. For such substances the default excursion factor is 1, but it may be increased up to 8 on a case-by-case basis.
    - Cat II: substances for which systemic effects are relevant for derivation of a workplace exposure limit. For such substances the default excursion factor is 2, but (again) it may be increased up to 8 on a case-by-case basis. The duration of an excursion may exceed 15 min as long as the product of excursion factor x excursion duration is not exceeded (for example: if the excursion factor is 8, a duration of 30 min is allowed for a 4-fold excursion).

- SCOEL has not yet defined a generic approach to derive such excursion factors. Nevertheless, for many IOELV of SCOEL short-term exposure limits have been established. Again, it is proposed that these substance-specific excursion factors of

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SCOEL can serve as a guide for derivation of a $DNEL_{acute}$ based on similarities of the toxicological profile.

- When setting an OEL, the Dutch Expert Committee on Occupational Standards (DECOS) routinely checks whether a proposed 8-hour time-weighted OEL will also protect against acute effects, such as irritation or neurotoxicity. If so, a limit value for a shorter time duration (usually a 15 min TWA value) may be set, especially when there are indications that the dose-response curve is steep.

In summary:
Acute DNEL are generally calculated for exposure times of 15 min for workers and from 0.5 to 4 hours for the general population. The selection of the POD is dependent upon the data set(s) available. The use of human data will be discussed in Chapter 5. When animal data is available for calculating a $DNEL_{acute}$ it is proposed to use the NOAEC from sub-lethal effects and apply an AF of 3. For lethality, the factor would include an adjustment from the lethal concentration (AF=3) and the AF to account for intraspecies variation of 3 for a combined AF of 9.

When calculating the $DNEL_{acute}$, it is often necessary to extrapolate from a 4 hours study to a shorter exposure time for workers. For systemic effects and lung toxicants, a modified Haber's Law can be used (C^n x T = K) where n =1 for local irritancy and for insufficient data sets the default value is n =3. In addition to time extrapolation, consideration must be given to determining if the effects are seen locally or systemically.

For local effects, animal studies that exhibit clinical irritation can utilise an AF for interspecies variation of 1, while the intraspecies factor for workers is 1 and for the general population 3. When histopathological effects in the respiratory tract of repeated-dose animal studies are observed, it is recommended to take the NOAEC as the POD and use the AF for inter- and intraspecies variability as for $DNEL_{long\text{-}term}$ and subsequently increase the $DNEL_{acute}$ by a factor of 2-5 to take account of the short exposure duration.

For systemic effects observed in repeated-dose animal studies, the POD should be the NOAEL and AF for inter- and intraspecies variability and route-to-route extrapolation as for $DNEL_{long\text{-}term}$ should be applied. To take account of the short exposure duration the value would then be increased by an appropriate factor to derive the $DNEL_{acute}$.

If suitable experimental studies in animals or observational studies in humans are not available, as is often the case, the $DNEL_{acute}$ should be based on the $DNEL_{long\text{-}term}$ and a factor should be used (e.g. 1-5 as proposed by the REACH TGD). Within this range the excursion factors used by ACGIH, AIHA, SCOEL, or the MAK Commission for chemicals with a similar toxicological profile may help to come to a final decision.

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4.3 DNEL for reproductive toxicity

Separate DNEL for fertility and for developmental toxicity should be established from appropriately designed studies, as well as human data if available. Developmental effects may occur after a single high exposure, therefore the DNEL should also protect against such a possibility. Reproductive toxicants are generally accepted to act via mechanisms that imply a threshold of exposure below which adverse effects will not be induced. But for those that are also genotoxicants it is prudent to assume a non-threshold mechanism for reproductive effects, unless there are no indications for a genotoxic MOA. In such cases, a DMEL should be derived instead of a DNEL. The derivation of DMEL is outside the scope of this report.

Since different study types, used as basis for the calculation of reproductive toxicity DNEL, provide different levels of confidence in detecting different endpoints, a range of AF is to be discussed.

Different study designs of varying complexity are available to assess reproductive toxicity. Their strengths and weaknesses for the assessment of effects upon reproduction have been extensively discussed elsewhere (REACH TGD, Section R.7.6 and Appendix R.8-12; ECETOC 2002 and 2008) and, consequently, the discussion herein will be limited to the impact of study design on AF selection. For each of these studies different considerations might apply for the derivation of a DNEL, including the selection of appropriate AF and POD. The studies may be grouped into three categories that will be discussed below: studies specifically designed for identification of reproductive toxicity; reproductive toxicity screening studies; and repeated-dose toxicity (RDT) studies.

When considering generic AF to be used for the derivation of DNEL for fertility and developmental toxicity, the same considerations used for the extrapolation steps in Chapter 3 (repeated-dose toxicity) apply.

- Route-to-route;
- interspecies;
- intraspecies;
- dose-response;
- quality of the whole database.

Well after publication of the REACH TGD, the AGS (2010a) published its concept of how to assess reproductive effects and proposed AF for interspecies and exposure duration extrapolation. For male fertility the following AF were selected:

- for interspecies extrapolation first scaling according to caloric demand and an AF of 1;
- for (combined) inter- and intraspecies variability an AF of 5 according to the general approach of AGS for systemic toxicity;

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- for exposure duration extrapolation from sub-chronic to chronic an AF of 1 provided that a detailed investigation of the reproductive organs was carried out in the course of the sub-chronic study. This takes into account the duration of spermatogenesis. Substances with a long biological half-life need to be evaluated on a case-by-case basis. An AF of 2 should be applied for sub-acute to sub-chronic extrapolation provided sufficiently detailed investigations of the reproductive organs in the sub-acute study.

For developmental toxicity no AF were proposed to specifically establish an occupational exposure limit. Factors were selected to indicate at what exposure levels a risk to the unborn child might be expected:

- after allometric scaling for caloric demand a factor of generally 10 is proposed for the NOAEL obtained by prenatal toxicity studies, but a lower factor may be justified taking into account the severity of the developmental effects and the number of species investigated should be taken into consideration
- an AF for exposure duration is not necessary provided that the experimental exposure adequately covered the pregnancy of the species under investigation. Substances with long biological half-lives should be assessed case by case.

4.3.1 Studies specifically designed for identification of reproductive toxicity

The requirements of the REACH TGD for a two-generation study (OECD TG 416) in the light of fertility data from other study types may be challenged. It is stated
(1) in the REACH TGD, Appendix R.8-12: *"Consequently, in cases where there are indications of adverse effects on the reproductive organs of adult animals* (added for clarification: in repeated dose toxicity studies) *a two-generation study (OECD TG 416) may be triggered."*
(2) in the REACH TGD, Section R.7.6.4.1: *"The two-generation study has conventionally been preferred to the one-generation study (OECD TG 415, EU B.34) in the testing of chemicals because the latter does not test for potential effects on all phases of the reproductive cycle. Post weaning development, maturation and the reproductive capacity of the offspring are not assessed. Consequently some adverse effects, for example oestrogenic or antiandrogenic-mediated alterations in testicular development, may not be detected."*

The relevant guideline protocols potentially relevant to this endpoint are:

- OECD TG 414 (prenatal developmental toxicity study)
- OECD TG 415 (one-generation reproductive toxicity study)
- Extended one-generation reproductive toxicity study (under development at OECD)
- OECD TG 416 (two-generation reproductive toxicity study)
- OECD TG 426 (developmental neurotoxicity study)

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Only two of these study types, the two-generation and extended one-generation reproductive toxicity studies, include the complete reproductive cycle (REACH TGD, Section R.7.6; ECETOC, 2008). However, no additional AF is proposed by the REACH TGD for the reduced duration of the other study designs (REACH TGD, Appendix R.8-12). For example, OECD TG 414, while offering a robust assessment of prenatal developmental toxicity, does not allow for any assessment of postnatal development, which may be identified as a data gap in the derivation of $DNEL_{development}$. Additional information may be available from other studies to close this data gap, or developed through the conduct of further studies or by read-across within a suitably-justified category. An AF for exposure duration generally is not to be used ('informed' AF of 1).

4.3.2 Reproductive toxicity screening studies

The relevant guideline protocols for this endpoint are:

- OECD TG 421 (reproduction/developmental toxicity screening test)
- OECD TG 422 (combined repeated-dose toxicity study with the reproduction/developmental toxicity screening test)

The REACH TGD states in Appendix R.8-12:
"A positive result in OECD TG 421/422 may be considered sufficient for the calculation of a $DNEL_{fertility}$ and/or a $DNEL_{development}$; however, an additional assessment factor of 2 to 5, decided on a case-by-case basis, should generally be used to take account of the lower sensitivity of the study, unless there is evidence to support that the lower sensitivity is not relevant for the effect mechanism of the substance (e.g. specific teratogenic effects that are the result of a known mechanism of action).

A negative result in OECD 421/422 test may lower the concerns for reproductive toxicity, but can not provide reassurance of the absence of this hazardous property. However, it can provide the basis for deriving a $DNEL_{fertility}$ and/or $DNEL_{development}$ from the highest dose level tested and by application of an additional assessment factor of 2 to 5, decided on a case-by-case basis that should account for the limitations of this study…. Such a DNEL would be relevant only at the Annex VIII level (10 – 100 tons/year) and below."

As stated by OECD, the reproductive screening studies (OECD TG 421 and 422) provide initial information on male and female reproductive performance such as gonadal function; mating behaviour; conception; development of the conceptus; and parturition. They offer only limited means of detecting post-natal effects. The methods do not provide evidence for definitive claims of no effects and negative data do not indicate absolute safety. But the information obtained may provide some reassurance if actual exposures are less than the dose (mostly NOAEL) used as basis for the DNEL calculation.

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Current guidance states that results from a reproductive toxicity screening study may be sufficient to derive a $DNEL_{fertility}$ or $DNEL_{development}$, but an additional AF of 2 to 5, decided on a case-by-case basis, should generally be applied to take into account the lower sensitivity of these study designs (REACH TGD, Appendix R.8-12). The lower sensitivity of the screening studies is attributed, at least in part, to smaller group sizes in comparison to the more robust designs such as the two-generation reproductive toxicity study (OECD TG 416). In the absence of the REACH TGD defining as to what criteria should be taken into account in determining the exact value of AF to use in specific cases, the Task Force has developed its own guidance based on the influences of group sizes on the dose descriptor.

Difference in group sizes

The guidelines for OECD TG 421 and OECD TG 422 call for group sizes of at least 10 males and 10 females, with the expectation that this will result in at least 8 pregnant females per dose group. Some laboratories may increase the group sizes, for example to 12 of each gender, to increase the likelihood of 10 successful pairings per dose group, and therefore greater sensitivity of the test.

The guideline for OECD TG 416 calls for sufficient animals to *"yield preferably not less than 20 pregnant females at or near parturition"*. Laboratories may use group sizes of 22-25 males and females, with the expectation that this will result in at least 20 pregnancies per group. Group sizes of 25 males and females typically yield 22 or 23 pregnancies, in the absence of treatment-related effects.

This means that group sizes in the screening and full studies conducted in strict adherence to the appropriate test guidelines may differ by an order of between approximately 2-fold ($\frac{20}{10}$) and 2.5-fold ($\frac{20}{8}$).

Impact of group size on dose descriptor

The larger group size of the OECD TG 416 study design affords a greater probability of detecting adverse effects when the effect of treatment is determined by a group-wise analysis of response. The probability of identifying an effect of treatment is related to a number of factors that influence the 'power' of a study: including sample size, variance, and the significance level. Power increases in relation to the square root of group size.

A NOAEL value is determined by analysis of variance (ANOVA), in which the variances both within and between groups are used to determine the statistical significance of differences between the treatment and control.

In such cases, the statistical significance attributed to an ANOVA will depend on the square root of the group size. Consequently, the larger group sizes of the OECD TG 416 study design afford a probability of detecting a statistically significant difference, and therefore a NOAEL, that is between $\sqrt{2}$ and $\sqrt{2.5}$ lower (1.41- to 1.58-fold) than that of OECD TG 421 and OECD TG 422.

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A DNEL derived from a NOAEL in a screening study must therefore be adjusted to take into account the reduced sensitivity of the study design, by a factor commensurate with its reduced power. This adjustment is in addition to the AF applied as discussed above.

Another factor that influences the NOAEL identified in a study is dose selection. A NOAEL can only be identified as the highest selected dose level for which there is no statistically identified difference with the control group. In contrast to ANOVA, BMD analysis uses data from all groups to interpolate an estimate for the (unknown) true NAEL. As such, the point estimate from BMD analysis is independent of group size, although group size does influence the confidence limits around the point estimate. If the lower bound of the confidence interval (BMDL) is used as the dose descriptor, then this already takes into account the difference in group sizes between full and screening study designs and no further AF is needed in addition to those discussed previously. If the point estimate itself is used, then a further AF of √2-√2.5, according to group size, is warranted (Table 6).

Table 6: AF proposed for reduced group sizes used in reproductive toxicity screening studies

Dose descriptor	Additional AF	Comment
NOAEL	√2 or √2.5 (1.4 or 1.6)	Lower value may be warranted if n=10 pregnant females per group
BMD	1, √2 or √2.5	No AF if the lower CL (BMDL) is used, otherwise √2 if the point estimate (BMD) is used and n=10 pregnant females per group, otherwise √2.5

Impact of study duration on dose descriptor

Fertility: OECD TG 421 and 422 comprise the most of the sensitive phases under consideration for fertility, i.e. sperm maturation, oestrous cycle, mating, egg fertilization and implantation. The duration of these study designs does not allow the detection of effects upon early spermatogenesis or upon mating behaviour arising from prepubertal exposure. Although a $DNEL_{fertility}$ may be derived from such screening studies, these deficiencies cannot be accommodated rationally by the introduction of an additional AF and may be recognised as a data gap or filled by data from other available studies. Therefore, an AF for exposure duration generally is not to be used ('informed' AF of 1).

Developmental effects: OECD TG 421 and 422 include exposure to the test chemical throughout the post-fertilisation pre-implantation phase, the entire period of gestation (including both organogenesis and foetal growth phases), parturition, and the first four days of postnatal life. Therefore, an AF for exposure duration generally is not to be used ('informed' AF of 1). Assessment of development is limited to litter size, pup growth, postnatal survival, and gross

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pathological examination for external abnormalities, although more detailed examination may be conducted on a case-by-case basis. This limited assessment complies with the basic assumption of the Chernoff-Kavlock assay that developmental toxicity may be noted during postnatal assessment as reduced viability and/or growth of the offspring (ECETOC, 1992). However, these study types are not wholly suited for a thorough assessment of prenatal developmental toxicity since malformations occurring at low incidences may not be detected due to cannibalisation of the affected offspring and natural variation in litter sizes, for example. Furthermore, the duration of exposure and time of evaluation (i.e. termination of the F1 generation at lactation day 4) preclude the identification of effects on later developmental landmarks (e.g. many markers of endocrine disruption). Although a $DNEL_{development}$ may be derived from such screening studies, these deficiencies cannot be rationally accommodated by the introduction of an additional AF and may be recognised as a data gap or filled by data from other available studies.

The REACH TGD states that screening studies may be used to derive DNEL values, but that additional AF should be applied (REACH TGD, Appendix R.8-12) and guidance is given herein for AF to account for the smaller group sizes of these study designs. Furthermore, the TGD states that while negative findings may lower the concern for reproductive hazard they cannot provide assurance of the absence of such hazard, exemplified by the fact that some life stages are not evaluated as discussed above. Commission Regulation 134/2009, amending Annex XI to the REACH Regulation (EU, 2009a), stipulates that DNEL values derived from reproductive toxicity screening studies cannot be considered appropriate to omit the conduct of higher-tier tests when other considerations (e.g. production volume, use and exposure patterns) dictate their need. The requirement for further testing should, therefore, be considered within the scope of the intelligent testing strategy and information requirements for REACH, including read-across within a suitable-justified category.

4.3.3. Repeated-dose toxicity (RDT) studies

The relevant guideline protocols for this endpoint are as follows:

- OECD TG 407, TG 410, TG 412 (repeated 28 day-studies);
- OECD TG 408, TG 409, TG 411, TG 413 (repeated 90 day-studies);
- OECD TG 452, TG 453 (chronic studies);
- OECD TG 424 (neurotoxicity study in rodents).

The REACH TGD states in the Appendix R.8-12:
"To account for the lower sensitivity of the RDT studies for detecting effects on reproductive organs due to few animals in the exposure groups and a possible increased sensitivity in the developing foetuses and young animals an additional assessment factor of 2 to 5 should be considered on a case by case basis (e.g. where there are substantiated indications for adverse effects on the reproductive organs of adult animals).

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A RDT study showing no adverse effects on reproductive organs is not considered to provide sufficient information for a DNEL calculation for fertility or other reproductive effects."

Such studies can only be used as indications for the impact upon the fertility status of males and females as it pertains to effects on, and function of, the reproductive tract organs if extensive histopathology assessment is undertaken. These studies are not suitable for the assessment of effects upon mating behaviour or development, including effects upon the development of the reproductive tract organs. This may be recognised as a data gap for the derivation of $DNEL_{fertility}$ or addressed by evaluation of the database as a whole.

Histopathological examinations in repeated-dose toxicity studies are of value for the evaluation of reproductive toxicity in males (Mangelsdorf *et al*, 2003; Ulbrich and Palmer, 1995; Janer *et al*, 2007; Dent 2007) and females (Sanbuissho *et al*, 2009), although the sensitivity of such studies may be reduced in comparison to that of the OECD TG 416 because of the smaller group sizes used (see discussion below on the impact of group size on the dose descriptor). Therefore, at least for fertility assessment, a RDT study showing no adverse effects should be taken into account, and the inclusion of an additional AF to account for group sizes might be considered based on expert judgement. Furthermore, histopathological changes on the reproductive organs in repeated-dose toxicity studies (sub-acute or longer exposure; see e.g. Ulbrich and Palmer, 1995; Mangelsdorf *et al*, 2003) are indicative of effects on fertility. Therefore, RDT studies should be considered to provide sufficient and sensitive information for a DNEL calculation for fertility if histological examination of the reproductive organs is covered by the RDT studies and the MOA of the test substance does not give evidence for a specific toxicity (as would e.g. sex hormone receptor binding activity).

With regards to AF, the generic considerations described above apply. In addition, consideration should be given to additional AF to account for group sizes and study duration.

Impact of group size on dose descriptor

In different retrospective analyses of two-generation reproductive toxicity studies versus sub-chronic toxicity studies (Mangelsdorf *et al*, 2003; Ulbrich and Palmer, 1995; Janer *et al*, 2007; Dent 2007, Sanbuissho *et al*, 2009) histopathology of the reproductive organs was identified as a parameter with higher sensitivity than fertility parameters. The group size of guideline sub-chronic studies (10 animals per gender and dose) is lower than the group size in guideline generation studies (not less than 20 pregnant females) and the RDT studies are accordingly less sensitive. For example, in a comparison to the NOAEL/LOAEL values for fertility effects obtained from guideline 90-day and two-generation reproductive toxicity studies, Janer *et al* (2007) concluded that the NOAEL/LOAEL for the critical effect derived from a sub-chronic study was, on average, between 1.3- and 1.9-fold higher than that from the breeding study. The authors went on to note that "*NOAELs…depend on the study design (e.g. the selection of doses*

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and the sample sizes), as well as statistical error (scatter) in the observed responses". Consequently, similar considerations regarding group size to those given above might be applied to $DNEL_{fertility}$ derived from repeated-dose toxicity studies. The sensitivity of a study design is related to the group sizes, among other factors, and may be appropriately accounted for by the application of a suitable AF (e.g. in the event of a NOAEL being identified as dose descriptor) or no AF (e.g. in the event of the BMDL). Example AF values are presented in Table 7. It is assumed that group sizes meet the minimum requirements laid down in the appropriate test guideline, i.e. the ratio of group sizes compared to a two-generation reproduction study is approximately 1:4 and 1:2 for a 28-day and 90-day repeated-dose study, respectively (Table 7).

Table 7: AF proposed for reduced group sizes used in repeated-dose toxicity studies

Study type	Group size	Dose descriptor	AF	Comment
28-day (e.g. OECD 407)	5	NOAEL	2	
		BMD	1 or 2	Lower value if BMDL
90-day (e.g. OECD 408)	10	NOAEL	1.4	

Impact of study duration on dose descriptor

Studies with durations of more than 70 days will cover all stages of spermatogenesis as well as the full oestrus cycle in rats. Although shorter than the duration of the full spermatogenic cycle, studies of 28 days duration will detect effects upon the early stages of spermatogenesis if suitable histopathology evaluation of the reproductive tract organs is undertaken. None of these studies are suitable for the assessment of mating behaviour or performance. However, these shortcomings cannot be rationally accommodated by an additional AF and may be identified as a data gap to be addressed as appropriate within the intelligent testing strategy, by read-across within a suitably-justified category, or with data from a reproductive toxicity screening study. For exposure duration an AF of 1 is appropriate.

In summary, effects upon reproduction may be evaluated using data from appropriately designed studies that evaluate the full reproductive cycle, or specific parts of the cycle in depth; from screening studies; and from other repeated-dose studies. The data obtained may be used to derive DNEL for effects upon fertility and/or development.

All of the study types discussed herein may be used to derive values for $DNEL_{fertility}$ and/or $DNEL_{development}$. However, some study types (e.g. reproductive screening, repeated-dose toxicity) may not evaluate all life stages appropriate to the derivation of a robust DNEL, for example due to limitations in exposure duration or endpoint evaluation. It is not appropriate to apply

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additional AF to account for these deficiencies, although they should be evaluated in context with the entire database for a substance. In such cases, a DNEL may be derived and any limitations should be recognised and addressed, as appropriate, under the terms of the legislation through application of the intelligent testing strategy or by read-across within a suitably justified category.

Additional AF may be appropriate to account for smaller group sizes used in lower-tier studies. The AF will depend upon the group sizes used and the POD. Guidance is given on the selection of an appropriate AF based on these criteria.

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5. ASSESSMENT FACTORS FOR DNEL DERIVATION FROM HUMAN DATA

Introduction

As previously explained the REACH TGD, Chapter R.8, focuses on the use of animal data for risk assessment to humans. ECETOC TR 104 provides an integrative framework for human and animal data that assesses the quality of each data set with respect to a given chemical or exposure scenario (ECETOC, 2009a). In November 2007, a workshop was organised by ECETOC and TNO to address the use of AF when the POD consists of human data. The report of this workshop (ECETOC, 2009b) formed the basis of the newly issued REACH TGD draft R.8 'Guidance on DNEL/DMEL derivation from human data' (ECHA, 2010).

The most significant difference between the REACH TGD and the guidance in this document is the AF proposed for intraspecies variability in humans. The justification for the intraspecies AF proposed in the REACH TGD is based on the wide range of susceptibility in humans in the general population. ECETOC recognises this large variability but believes that if the study is sufficiently representative of the target population than this variability is already taken into account. Therefore, no further AF is justified.

ECETOC TR 104 recognises that human studies have to meet certain design and quality criteria (as described in TR 104) in order to be suitable as a POD and that it is inappropriate to take poorly conducted studies, and to account for these deficiencies by applying additional AF. In these cases, ECETOC believes it is more appropriate to use robust animal data as the POD.

Use of human data

Epidemiological studies differ principally from animal studies, as they are nearly always of non-experimental nature and are conducted on heterogeneous populations without strict control over exposure or exposure to other factors. It is recognised that the suitability for use of any human data for DNEL and DMEL derivation should be subject to expert review, and the selection of appropriate AF subject to expert judgement.

Although the numerous text books on epidemiological research provide general guidelines for the design and conduct of studies, many of them are, by necessity, designed to meet the specific study objectives and circumstances under which they are conducted. If the epidemiological study is of adequate design and sufficient power, adequately measures the target condition in the appropriate population and appropriately addresses all relevant confounding factors, then it will be representative of that condition/population and no AF needs to be applied. In most cases, however, there will be some recognisable weaknesses in the design, exposure assessment, and ascertainment of effect data or power of the study that will need to be accounted for by one or more AF.

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AF for interspecies extrapolation

The most obvious difference between the use of human data and animal data is that an AF for interspecies extrapolation is redundant if the POD is based on human data, irrespective of whether the study has been conducted in workers and/or the general population.

AF for intraspecies extrapolation

Animal strains used for toxicological studies have been intentionally selected over many generations to reduce genetic variation between individual animals in order to optimise consistency of response. In contrast, human populations generally comprise heterogenic subjects. Hence, most well-designed epidemiology studies, of sufficient sample size, will be representative of the genetic make-up of the larger population from which the study population is selected. If the sample size is adequate, it is unlikely that the sample will contain substantially fewer or substantially more susceptible individuals. Consequently, the study results reflect the presence of susceptible individuals and an additional AF for intraspecies variation is not necessary. Although differences in the distribution of polymorphisms are known to exist within Europe, it is questionable whether these differences would have an effect on the NOAEL in these different populations. Even in the case of a smaller percentage of susceptible individuals in the population studied, the NOAEL will apply to a population with a higher percentage of susceptible individuals, since they will not be affected if the concentration is below the NOAEL. A difference in percentage of susceptible subjects is likely to affect the percentage of responders, but not likely to shift the NOAEL.

Thus, as an adequately sized sample is automatically representative of the target population, and because the NOAEL remains the same between populations with a difference in the distribution of polymorphisms, the introduction of an AF for intraspecies variation is not required.

Where human data have been identified as the POD for DNEL derivation the following AF have to be considered:

- intraspecies differences;
- differences in duration of exposure;
- issues related to dose-response;
- quality of available human data.

Within ‘quality of available human data’ the following 5 elements need to be considered:

- completeness;
- consistency;
- reliability;
- healthy worker effect;
- study size.

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5.1 Intraspecies differences

As indicated previously, humans differ in sensitivity to toxic insult due to a multitude of factors such as environmental influences and/or genetic polymorphisms affecting e.g. toxicokinetics/metabolism, age, gender, health status and nutritional status. These intraspecies differences intrinsically form a part of the human population being targeted (underlying general or worker populations). Provided that the studied population is representative, the sample size of the study group is sufficiently large to guarantee adequate statistical power and that the study data adequately address such considerations, there is no need to apply uncertainty factors. As with animal data, where the lead health effect is a direct one, e.g. respiratory irritation, an AF for intraspecies differences to reflect differences in pharmacokinetics is not required.

In the case of epidemiological studies of sufficient size, which typically use random samples or stratified sampling to obtain an adequate representation of the underlying population base, sensitive individuals are included in the study population. The same is the case when worker studies are used for the occupational scenario, as long as the study population is representative in terms of work tasks, exposure, gender, age, length of service, etc. In these situations when the study population is the same as, or adequately representative of the population being targeted, i.e. worker to worker or general population to general population, an AF of 1 is appropriate.

In instances where the population being targeted is different from the one for which a DNEL is derived, an intraspecies AF is warranted. An example of such a situation is when worker data form the basis of a DNEL for the general population. This is confirmed by the analysis performed by ECETOC in TR 86 indicating that an AF of 3 is appropriate.

In Section 3.6, the Task Force compared DNEL derived by default AF as per the REACH TGD with IOELV proposed by SCOEL. Five substances were selected where the SCOEL IOELV was based upon local effects in humans (see Table 8 below). In four of the five cases the overall AF applied by SCOEL was less than the 5 that would have been applied according to the REACH TGD. In the case of diethylamine the overall AF used by SCOEL was 5 but this accounted not only for intraspecies variability but also for study du ration (see Appendix A). Hence, it may be concluded that these examples support the lower intraspecies AF of 3 being proposed by ECETOC for the workplace rather than the value of 5 specified in the REACH TGD.

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TABLE 8: Comparison of assessment factors used by the Scientific Committee for occupational exposure (SCOEL) with the default factors proposed in the REACH TGD and by ECETOC. For further details see APPENDIX A.
Key information discussed by SCOEL to derive IOELV: human data – local effects

Compound	**SCOEL Assessment Factors**	**REACH TGD Assessment Factors Total Factors** (RtR^ax AS^bx RD^cx IS^d xED^ex DR^f)	**ECETOC Assessment Factors Total Factors** (RtR^ax AS^bx RD^cx IS^d xED^ex DR^f)	**Remark**
Diethylamine	**5**	**5** $(1)^a$ x $(1)^b$x $(1)^c$x $\mathbf{5^d}$ x1^ex 1^f	Strengths and weaknesses of human studies have to be judged by expert evaluation and the whole database has to be taken into account to define AF and to derive a DNEL.	Short term study (15 min) discussed by SCOEL as key information; see Appendix for more.
Formaldehyde	**2.5**	**5** $(1)^a$ x $(1)^b$x $(1)^c$x $\mathbf{5^d}$ x1^ex 1^f		A smaller AF for workers is supported.
Hydrogen peroxide	**1**	**5** $(1)^a$ x $(1)^b$x $(1)^c$x $\mathbf{5^d}$ x1^ex 1^f		A smaller AF for workers is supported.
Methyl methacrylate	**1**	**5** $(1)^a$ x $(1)^b$x $(1)^c$x $\mathbf{5^d}$ x1^ex 1^f		A smaller AF for workers is supported.
Vinyl acetate	**2**	**5** $(1)^a$ x $(1)^b$x $(1)^c$x $\mathbf{5^d}$ x1^ex 1^f		A smaller AF for workers is supported.

a Route-to-route extrapolation (RtR)
b Interspecies differences; allometric scaling (AS)
c Interspecies differences; remaining differences (RD)
d Intraspecies differences (IS)
e Exposure duration (ED)
f Dose response ; LOAEL $\geq$ NOAEL (DR)
(1): AF not applicable

In the case of SCOEL assessments based upon systemic effects in humans, five cases can be identified (Table 9). In these cases, SCOEL applied an overall AF of between 3.5 and 1 reflecting a range between 6.7 and 80% of the REACH TGD values.

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TABLE 9: Comparison of assessment factors used by the Scientific Committee for occupational exposure (SCOEL) with the default factors proposed in the REACH TGD and by ECETOC. For further details see APPENDIX A.

Key information discussed by SCOEL to derive IOELV: human data – systemic effects

Compound	**SCOEL Assessment Factors**	**REACH TGD Assessment Factors Total Factors** (RtR[a]x AS[b]x RD[c]x IS[d] xED[e]x DR[f])	**ECETOC VALUES Assessment Factors Total Factors** (RtR[a]x AS[b]x RD[c]xIS[d] xED[e]x DR[f])	**Remark**
Carbon disulphide	**2**	**5** (1)[a] x (1)[b]x (1)[c]x **5[d]** x1[e]x 1[f]	Strengths and weaknesses of human studies have to be judged by expert evaluation and the whole database has to be taken into account to define AF and to derive a DNEL.	A smaller AF for workers is supported.
2-Ethoxyethanol	**1**	**15** (1)[a] x (1)[b]x (1)[c]x **5[d]** x1[e]x **3[f]**		A smaller AF for workers is supported.
n-Hexane	**3.5**	**15** (1)[a] x (1)[b]x (1)[c]x **5[d]** x1[e]x **3[f]**		A smaller AF for workers is supported.
2-Methoxyethanol	**4**	**5** (1)[a] x (1)[b]x (1)[c]x **5[d]** x1[e]x 1[f]		A smaller AF for workers is supported.
Toluene	**1**	**5** (1)[a] x (1)[b]x (1)[c]x **5[d]** x1[e]x 1[f]		A smaller AF for workers is supported.

a Route-to-route extrapolation (RtR)
b Interspecies differences; allometric scaling (AS)
c Interspecies differences; remaining differences (RD)
d Intraspecies differences (IS)
e Exposure duration (ED)
f Dose response ; LOAEL -> NOAEL (DR)
(1): AF not applicable

5.2 Duration of exposure

Provided human studies are conducted over a sufficient timescale or the population under investigation has been exposed over a sufficiently long period, there is generally no need to introduce a factor to account for differences in the duration of exposure for the population and scenario under consideration, unless there is evidence that cumulative exposure is the more relevant exposure metric than exposure concentration. Examples might include substances that have a relatively long biological half-life and accumulate to toxic levels following repeated and prolonged exposure. Alerts to such situations might be taken from the known latency of the effect taken for the POD, or from repeated-dose toxicity studies in animals where there is a

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significant difference between sub-acute/sub-chronic and chronic repeated-dose NOAEL. Provided human studies are properly conducted over a sufficient timescale (in the same order of magnitude as the exposure actually occurs), the nature of human observational studies accounts for whether the NOAEL for the effect of interest may decrease with increasing exposure times and whether other more serious adverse effects might appear over increasing exposure times.

If a reliable $NOAEL_{human}$ for a chronic endpoint is available, this is the preferred starting point for a $DNEL_{long\text{-}term}$ and no AF for duration extrapolation is required regardless of whether the information is applied to workers or consumers. This is because the chronic $NOAEL_{human}$ is not expected to be lower in the case of extended exposure and the need to account for intraspecies differences is addressed elsewhere. Exceptions to this would be where sub-/semi-chronic effects are observed such as depression of blood counts or transitional chromosomal aberrations following days/weeks of exposure, i.e. they are observable effects of possible pre-clinical significance and serve as a surrogate measure for frank effects, and where a $DNEL_{long\text{-}term}$ must be derived.

As is current practice, an AF of 2 should be applied to the $NOAEL_{human}$ in these cases. A NOAEL for an acute endpoint ($NOAEL_{human}$ following short-term exposure only) should not be used as the basis for the derivation of a $DNEL_{long\text{-}term}$ unless it can be clearly demonstrated that the study design is sufficient to adequately address any latency of the observed effect and the acute effect is protective of long-term exposure.

5.3 Dose-response relationship

Many human studies provide information on the shape of the dose-response curve for the endpoint of interest. Unlike experimental animal data however, response frequencies are not displayed at discrete exposure concentrations, but in the form of population responses within exposure ranges. This affects how LOAEL or NOAEL can be determined from epidemiological studies. It must be kept in mind that in cases where the dose-response is presented by means of exposure ranges, the LOAEL will be located within the lowest exposure range in which an adverse effect (in the form of a higher disease incidence above background) is observed. In the absence of a high prevalence of responders in this exposure category, the lower limit is likely to reflect the no-effect level.

The size of any AF should take into account the shape and slope of the dose-response curve (assuming this be can derived from the data source) and the extent and severity of the effect seen at the LOAEL. An AF of 2 as a default is considered appropriate to account for the uncertainties that may be associated in determining the 'true' NOAEL where this is determined by extrapolation from the LOAEL.

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When the DNEL is derived from a NOAEL, a default AF of 1 should be used. It should be noted, however, that in human studies the NOAEL is not observed per se, but is rather determined from the highest exposure range in which no effect is observed. When the DNEL is derived from a LOAEL (as opposed to the NOAEL) an AF of 2 should be used as default value (see Fairhurst, 1995). It should be noted that a higher AF will be necessary if the study design is considered insufficient to identify the lowest LOAEL for a given effect, provided this weakness has not already been taken into account in an AF for the 'weakness of the study'.

A larger AF should also be considered in situations where substance-specific data indicate that a steep dose-response curve exists, thereby accounting for the greater consequence of any error in estimating the LOAEL/NOAEL.

5.4 Quality of the database

The starting assumption should be that only good quality human data will be used for the determination of DNEL. Further guidance on how such data should be evaluated can be found in ECETOC TR 104 (2009a). Only human data of sufficient quality can be used as POD.

Concerning quality of the database one needs to consider several elements. These include completeness of the database, consistency between the available studies, reliability of the individual studies, influence of any healthy worker effect and study size. It is not possible to give precise guidance on the AF to be applied for each element and its respective weighting. But if the overall quality of the human database is considered insufficient, it is recommended that the data are not used for DNEL derivation. Alternatively, a higher integrated AF is applied. When the overall quality of the human database is considered sufficient, an AF of 1 is appropriate.

Completeness

The evaluation should include an assessment whether the available human information is sufficient to address the range of endpoints consistent with the toxicological data requirements for the respective tonnage band, or whether the knowledge provided by the human information still presents significant data 'gaps' (when compared to the expected breadth of understanding as implied by Annexes VII - X of the REACH regulation). Where no significant gaps are present (e.g. the human data adequately addresses chronic and/or acute effects), then a default AF of 1 should be used.

When the human data are generally considered sufficient, but there are some deficiencies in the human studies considered crucial to provide reliable information for establishing the dose descriptor, caution should be applied to address this uncertainty in deriving the DNEL. In this regard, the assessor should consider the nature of the effect occurring in particular organ systems,

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as well as at different life stages. In such cases, expert judgement should be used establish a larger AF.

When the human data set is incomplete, and does not include the relevant endpoints reported from animal studies, the latter should be used.

Consistency

In the case of large volume and extensively used chemicals for which early, positive findings have necessitated further, in-depth investigation, the available human data may appear internally inconsistent. Comprehensive analysis of the data may, on a weight-of-evidence basis, resolve this situation.

Where human data are truly inconsistent and the overall conclusion is equivocal, e.g. one positive study and one null finding of equal weighting, the data should not be used for DNEL derivation, although even in such cases, the severity of the observed effect may indicate that the findings in humans are accounted for. If, on a weight-of-evidence basis, the data are 'consistent', a default AF of 1 should be used.

Reliability

The hazard data need to be assessed for their reliability by taking into account the quality of the study protocol/methodology, size and power of the study design, biological plausibility, dose-response relationships and statistical association (adequacy of the database).

When the human data are robust and of good quality, a default AF of 1 should be used. However, where the human data set is incomplete, e.g. if other (animal or human data) indicate the effect may occur at significantly lower exposure levels, then either a DNEL should be established based upon other data sources and/or a larger AF (e.g. 2) may be justified.

Healthy worker effect

In some studies, the healthy worker effect (HWE) may lead to an underestimation of the true relative risk. In particular, this applies to cross-sectional studies in which employees that have developed symptoms in the past and may have left their job, resulting in the current sample being under-representative of susceptible subjects. In such cases it should be considered whether or not such bias (in the form of the HWE) may have resulted in an overestimation of the NOAEL. However, its impact should not be exaggerated. The HWE in cohort studies for cancer endpoints is minimal. It should be noted that the HWE bias is widely recognised by epidemiologists and studies are usually designed to minimise this effect. Furthermore, case control and cohort studies with long observation periods are generally not affected by the HWE unless the HWE is particularly relevant to the disease of interest. A default AF for dealing with the HWE is difficult to determine and should be assessed on a case-by-case basis recognising that the impact of the

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HWE will have an important impact on the determination of the NOAEL, but not on the relative risk. If there is good reason to assume bias as a result of the HWE, an AF of 2 seems appropriate.

Study size

Study size is not an intraspecies consideration but relates to residual uncertainty and, hence, is a consideration for the quality of the database. While study size, in part, determines the power of a study (and hence the confidence which can be invested in its findings), there is no reliable, simple approach for applying AF for this aspect. The issue of study size must be addressed on a case-by-case basis and the study quality evaluated accordingly. For studies of adequate size a default AF of 1 should be used. In those situations, however, where a (small) study represents the best dataset on which to establish a DNEL, it is suggested that an AF of 3 is considered. A practical example of this is the Dutch Health Council's recommendation of a STEL for sulphur dioxide based on two human volunteer studies of the limited sample size indicating a NOAEL of 2 mg/m^3 for early effects of respiratory irritation and an AF of 3 (Health Council, 2003).

Statistics

A non-statistical effect in a certain dose-group may still be biologically relevant and should therefore not be disregarded. As such a non-statistical finding or effect, where it is consistent with a known mechanism of action, recognised health effect or pronounced effect in a higher exposure group, should be regarded as biologically significant. On the other hand, a statistical finding, lacking any biological plausibility should preferably not be taken as POD.

5.5 Acute and local effects in humans

The POD in humans is often based on local irritation of the (upper) respiratory tract. As in the case with studies in animals, it is important to determine whether local irritation was defined by cytotoxic effects (tissue destruction, increased cell proliferation) or by sensory irritation due to stimulation of the trigeminal nerve, as these outcomes differ in severity and should be treated differently for DNEL derivation purposes. Generally, cytotoxic irritation will require higher AF while for purely sensory irritation a small AF (generally 1) is appropriate. For effects observed in humans the following factors need to be taken into consideration.

Observational studies in workers

Typically, just an exposure range is known for the workplace situation. If only slight or at most moderate sensory irritation was reported, the upper range of the exposure may be used as the starting point for deriving the worker $DNEL_{acute}$. This is based on the fact that sensory irritation occurs at lower concentrations than cytotoxic irritation, that reporting of irritation will relate to past episodes of high exposure, and that the study population is the relevant one for a worker $DNEL_{acute}$. Under these conditions the worker $DNEL_{acute}$ should be defined by the upper range of

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exposure (or may even be slightly higher if only very mild effects were reported) and an additional AF of 2 would be appropriate for the general population.

If only a mean exposure concentration was reported, a higher worker $DNEL_{acute}$ is appropriate, i.e. by a factor of 3 according to the arguments given by ACGIH (see below), or higher if other data justify it. The $DNEL_{acute}$ for the general population should be reduced by an AF of 2, taking into account the higher variability of the general population.

Chamber inhalation studies

If data from chamber inhalation studies with volunteers are available (exposure duration generally 1-4 hours) it has to be determined whether only subjective or objective signs of irritation (e.g. redness of conjunctivae, increased eye blinking rate) were reported.

Objective signs for sensory irritation (e.g. slight hyperaemia of the conjunctival mucosa or increase of eye blinking rate) starts at exposure levels at which the exposed persons report subjective sensations of irritation on a scale very slight to slight. In the absence of any scientific investigation into variability for this effect, ECETOC recommends that the NOEL of such objective signs should be used as POD without application of an additional AF for workers and an AF of 3 for the general population. Very slight to slight discomfort due to subjective irritation will generally be in the range of the NOEL for local effects.

If the only information available is indicative of subjective effects, there are several important factors that need to be considered before these findings can be interpreted as true adverse health effects (Dalton *et al*, 1997; Dalton, 2002; Arts *et al*, 2006a):

- exposure history: workers in comparison to naïve volunteers;
- expectations and beliefs: prior information obtained for the chemical;
- bias from odour perception: problems in differentiation between irritation and odour;
- social factors: influence by behaviour of bystanders or study director;
- personality variables: influence on expectation by positive or negative affectivity.

In the case of only subjective symptoms being reported, clear to moderate subjective irritation should be selected as POD rather than very slight to slight irritation as this level of response is often already reported at near zero exposure (Paustenbach *et al*, 1997; Arts *et al*, 2006b).

Exposure duration

The exposure duration selected for the POD for acute effects should be relevant to the likely/typical exposure duration for the target group (worker or general population). Exposure durations of 0.5-4 hours should generally be used for deriving the $DNEL_{acute}$ for the general population. A short duration would be applicable to substances/products for which it is known that there are only one single use for short duration tasks.

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Acute systemic effects
No general guidance can be provided for AF for systemic effects in, for example, epidemiological studies as they require a case-by-case decision.

5.6 Summary

Table 10 presents an overview of the human AF (described above). These AF should not be regarded as 'default' for all human studies but rather represent the typical factors that might be applied to studies with recognised deficiencies. These AF apply to both the development of a $DNEL_{long\text{-}term}$ and a $DNEL_{acute}$ (assuming that a substance exhibits both types of effect).

Table 10: Typical assessment factors applied to human data

Nature of assessment factor			AF* applied to account for deficiency
Intraspecies	-	worker to worker	1
	-	worker to general population	2
	-	general population to general population	1
Duration of exposure	-	sub/semi-chronic to chronic	2
	-	chronic to lifetime	1
Dose-response (issues related to reliability of dose-response)	-	LOAEL / NOAEL extrapolation	2**
	-	steep dose-response curve	2
Quality of whole database	-	issues related to completeness of available data	***
	-	issues related to consistency of available data	****
	-	issues related to reliability of available data	2
	-	study substantially influenced by healthy worker effect	2
	-	small study size	3

* Typical factor applied rather than default for all situations
** Typically a value of 2 is sufficient, but if information on the dose-response curve is available a more appropriate AF should be used.
*** No general AF can be recommended; expert judgement is required on a case-by-case basis.
**** No general AF can be recommended; if the human data are inconsistent, refer to animal data.

The overall AF is obtained in principle by simple multiplication of individual AF discussed in the previous paragraphs. However, care should be taken to avoid taking double account of several aspects when multiplying the individual factors. Specific caution on this was expressed in a systematic review of OEL based on human data for 12 compounds recommended by the UK Health and Safety Commission's Working Group on the Assessment of Toxic Chemicals (WATCH) and the Advisory Committee on Toxic Substances (ACTS), in which it was noted that the uncertainty factor applied to derive the OEL was 2 or less, indicating that the overall AF applied to human data are rather small (Fairhurst, 1995).

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APPENDIX A

Comparison of the methodology used by SCOEL in deriving IOELV with the REACH TGD in deriving DNEL using R.8 default AF

Introduction

SCOEL evaluates the toxicological data on chemicals as requested by the EU Commission and proposes OEL. If possible the limit proposed is based solely on scientific considerations. If the database leads to the conclusion that it is possible to identify a clear threshold-dose below which exposure to the substance is not expected to lead to adverse effects, SCOEL is able to propose health-based IOELV, using uncertainty factors (UF) on a case-by-case basis to provide adequate protection in the occupational situation. If a threshold cannot be established, for example for genotoxicity, carcinogenicity or respiratory sensitisation, an EU BOELV may be proposed taking into account socio-economic factors and technical feasibility.

Method

The Task Force examined summary documents prepared by SCOEL to support their proposals for substances which are included in the second and third list of IOELV (EU, 2006b; 2009b). Using the same key study(ies), the Task Force calculated DNEL values using the default AF as given in the REACH TGD. The SCOEL information-based UF were compared with the REACH TGD default AF, to evaluate the effect on the final OEL by applying the respective methodology. In addition, a comparison was made with the AF proposed by ECETOC.

Substances were grouped according to the type of study and endpoint on which the evaluation was based, i.e. human data or animal studies; systemic toxicity or local irritation. In each case, the assessments were analysed to determine the impact of AF chosen by each methodology, for individual variation (interspecies and intraspecies) and uncertainty (route-to-route, study duration, dose-response, database quality).

Discussion

The summary table below and the individual evaluations confirm that, as would be expected, following the REACH TGD default procedure (selection of a single key study, modification of starting point, and application of default AF) results in DNEL which are, in general, considerably more conservative than the IOELV obtained from expert judgement. Similarly, the default AF proposed in this document will, in most cases, also lead to lower DNEL. The differences in the SCOEL evaluations and the REACH TGD default approach are, in principle, as follows:

- In many cases, SCOEL did not define a single ‘key study’ and applied AF to such a study when deriving an exposure level but used an expert approach taking into account the whole database. Important studies, uncertainty and strengths of the whole database were evaluated in the context of all available information to derive a starting point for further evaluation.

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- The majority of the SCOEL assessments were based on inhalation data. In the few cases where route-to-route extrapolation was required, SCOEL considered the need for a correction for bioavailability on a case-by-case basis.

- SCOEL did not modify the starting point to take account of different daily exposure durations (typically 6 hours/day for animal study versus 8 hours/working day). Neither did they modify for inhalation rate during light work (x 0.67). Using the REACH TGD modification of POD, where applicable, often resulted in a modified N(L)OAEC of approximately half the experimental value.

- SCOEL generally used a single uncertainty factor to take account of all variation and uncertainties in the database rather than multiplying individual AF. This practice tended to result in a lower overall AF. In the examples discussed below, the uncertainties identified by SCOEL ranged from an overall factor of 1 to an overall factor of 50 with the majority of uncertainty factors between 1 and 3.

The Task Force evaluated the SCOEL documents with respect to the references to the 'default' factors applied by SCOEL.

Interspecies AF allometric scaling

- In general, SCOEL did not apply an allometric interspecies AF but discussed the whole database to conclude on uncertainties. SCOEL evaluated the whole database and discussed, in particular, human exposure data in the context of the NOAEL from animal studies.

Interspecies AF additional uncertainty (2.5)

- SCOEL did not apply a default factor for additional uncertainty but evaluated the whole database and included any uncertainty in this single factor. Since the majority of the overall factors applied by SCOEL are between 1 and 3, it can be concluded that no default factor for 'additional uncertainty' was taken into account by SCOEL. The procedure of SCOEL corresponds to the approach proposed in this document.

- It is of particular interest that SCOEL did not include an AF for interspecies uncertainty for local effects observed in animal studies in contrast to REACH TGD. SCOEL even indicates that humans could be less sensitive than rats to nasal olfactory epithelium inflammation, *"based on what is understood of general differences in inhaled particle deposition between the two species"* (SCOEL/SUM/113). The procedure of SCOEL corresponds to the approach proposed in this document.

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Intraspecies AF

- SCOEL did not discuss an intraspecies AF (REACH TGD default AF 5). SCOEL did not apply any default intraspecies factor independent of the starting point (i.e. animal studies and human data). Again, because the majority of the overall factors applied by SCOEL are between 1 and 3 it can be concluded that no default intraspecies AF was taken into account. Since some human data are discussed in all examples, it can be concluded that SCOEL did not apply an intraspecies factor when human data are available (in the majority of the examples these are worker studies). The procedure of SCOEL corresponds to the approach proposed in this document.

Exposure duration AF

- SCOEL generally did not use a separate AF for study duration (e.g. AF 2 for sub-chronic to chronic study). This also applies to situations where human exposure data provided the key information. Where local respiratory irritation was the key effect, concentration rather than exposure duration is likely to be critical, implying that no AF would be required. This is, overall, in agreement with the REACH TGD related to derivation of DNEL/DMEL from human data (ECHA, 2010). It indicates that, provided the information in a human study covers a sufficient time span, there is generally no need to introduce an AF to account for differences in duration of exposure for the study population and the scenario under consideration (target population).

Dose-response AF

- SCOEL did not apply a default AF to derive a NOAEL based on a LOAEL from animal studies or human data. The severity of the effect, the dose-response curve and the whole database were taken into account rather than a ‘default’ factor.

General conclusion

SCOEL identified important studies and discussed the data in the context of the whole database to derive the starting point and identified strengths and weaknesses of the database which results in an overall uncertainty factor. Applying REACH TGD’s default AF to the examples, results in DNEL which are, in general, considerably more conservative than the IOELV obtained from expert judgement after assessment of the whole database.

Comparison of the methodology used by SCOEL in deriving IOELV with the ECETOC guidance in deriving DNEL as discussed in ECETOC TR 86 and in this Technical Report

Evaluations based on animal data

- As discussed above, SCOEL did not modify the starting point. Modification of the starting point (different daily exposure durations and light activity during work) resulted in a modified N(L)OAEC approximately half the experimental value.

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- Overall, AF according to ECETOC are lower than the default AF given in the REACH TGD and in general higher than the uncertainty factors derived by SCOEL.

- In only one out of the examples given below, the DNEL is higher than the IOELV, i.e. in the case of pyrethrum the IOELV is 1 mg/m^3 and the DNEL according to ECETOC AF is 5.8 mg/m^3. A further evaluation of this example indicates that substance-specific information has to be considered to derive informed AF. SCOEL applied a high uncertainty factor of 50 because a) the POD is derived from an oral study and acute toxicity data indicate that pyrethrum is less toxic via the oral route than via parental routes (probably as a result of efficient first-path metabolism); b) gastrointestinal absorption after oral dosing is approximately 46% (no data on absorption after exposure by inhalation); c) no inhalation studies are available; and d) an ADI value (0 - 0.04 mg/kg bw/day) derived by WHO-FAO is available. Overall, this example highlights that informed AF should be derived whenever sufficient substance-specific information is available.

- In conclusion, DNEL derived from ECETOC AF are closer to the IOELV than the DNEL derived from REACH TGD default factors.

Evaluations mainly based on human data

- Whenever human data are available, SCOEL discussed the whole database taking into account human and animal data to derive a starting point but did not define a single ‘key-study’. SCOEL applied uncertainty factors based on an expert evaluation of the whole database. Strengths and weaknesses of the whole database have to be considered to derive informed AF and no default factors should be applied.

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Table A: SCOEL exposure limits, REACH TGD and ECETOC DNEL derived for example compounds

Compound	CAS	Annex I Classification (human health part only)	SCOEL Exposure Limit (worker)				DNEL (worker, long-term) based on REACH TGD default AF [mg/m^3 - ppm]	IOELV/ DNEL (worker, long-term)	DNEL based on ECETOC AF
			defined by [reference]	local or systemic	key study; effect	IOELV			
Key Effect: Systemic/Human									
Carbon disulphide	75-15-0	Repr. Cat. 3 R62-63 T; R48/23 Xi; R36/38	SCOEL/SUM/82	systemic	human; neurotoxicity, cardiotoxicity in workers	15 mg/m^3	2 mg/m^3	7.5	*
2-Ethoxyethanol	110-80-5	R10 Repr. Cat. 2 R60-61 Xn; R20/21/22	SCOEL/SUM/116	systemic	Human haematology and reproductive toxicity in workers	2 ppm	0.36 ppm	5.5	*
2-Ethoxyethylacetate	111-15-9								
n-Hexane	110-54-3	Repr. Cat. 3; R62 Xn; R48/20-65 Xi; R38 R67	SEG/SUM/52C	systemic	human; peripheral neuropathy in workers	72 mg/m^3	17 mg/m^3	4.2	*

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Table A: SCOEL exposure limits, REACH TGD and ECETOC DNEL derived for example compounds (cont'd)

2-Methoxyethanol	109-86-4	Repr. Cat. 2 R60-61 Xn; R20/21/22	SCOEL/SUM/120C	systemic	human haematology and reproductive toxicity in workers	1 ppm	0.27 ppm	3.7	*
2-Methoxyethylacetate	110-49-6								
Toluene	108-88-3	Repr. Cat. 3; R63 Xn; R48/20-65 Xi; R38; R67	SCOEL/SUM/18	systemic	human data, performance of workers	50 ppm	10 ppm	5	*

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Table A: SCOEL exposure limits, REACH TGD and ECETOC DNEL derived for example compounds (cont'd)

Key Effect: Systemic/Animal									
Cyanamide	420-04-2	T; R25 Xn; R21 Xi; R36/38 R43	SCOEL/SUM/100	systemic	dog, 1-year; hematological effects	1 mg/m^3	0.04 mg/m^3	25	**0.3 mg/m^3**
N,N-Dimethylformamide (DMF)	68-12-2	Repr. Cat. 2; R61 Xn; R20/21 Xi; R36	SCOEL/SUM/121	systemic	rat and mouse, chronic inhalation study; liver effects	5 ppm	0.32 ppm	17	**1.3 ppm**
((2-(2-Methoxyethoxy)ethanol) (DEGME)	111-77-3	Repr. Cat. 3; R63	SCOEL/SUM/99	systemic	rabbit dermal developmental toxicity study; foetotoxicity	50 mg/m^3	6 mg/m^3	8.3	**50 mg/m^3**
Monochlorobenzene	108-90-7	Xn; R20	SCOEL/SUM/42	systemic	rat, two-gen inhalation study; liver effects	5 ppm	0.5 ppm	10	**2 ppm**
Pentanes	109-66-0 78-78-4 590-35-2	Xn; R65 R66 R67	SEG/SUM/79	no effect	rats, 30-week inhalation study; no effect	3000 mg/m^3	600 mg/m^3	5	**2500 mg/m^3**
Pyrethrum	8003-34-7	not listed in ESIS	SCOEL/SUM/95	systemic	rat, chronic dietary study; liver effects	1 mg/m^3	0.7 mg/m^3	1.40	**5.8 mg/m^3**

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Table A: SCOEL exposure limits, REACH TGD and ECETOC DNEL derived for example compounds (cont'd)

Key Effect: Local/Human									
Diethylamine	109-89-7	Xn; R20/21/22 C; R35	SCOEL/SUM/91	sensory irritation	human data; self-reported irritation	15 mg/m^3	10 mg/m^3 (short-term)	15	*
Formaldehyde	50-00-0	Carc. Cat. 3 R40 T; R23/24/25 C; R34 R43	SCOEL/SUM/125	local irritation	human volunteer data; eye irritation	0.2 ppm	0.1 ppm (short-term)	2	*
Hydrogen peroxide	7722-84-1	C; R35 Xn R20/22	SCOEL /SUM/134	local irritation	human worker and volunteers	1 ppm	0.2 ppm	5	*
Methyl methacrylate	80-62-6	Xi; R37/38 R43	SCOEL/SUM/126	local irritation	human data; nasal olfactory epithelium	50 ppm	10 ppm	5	*
Vinyl acetate	108-05-4	-	SCOEL/SUM/122	local irritation	human worker	5 ppm	2 ppm	2.5	*

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Table A: SCOEL exposure limits, REACH TGD and ECETOC DNEL derived for example compounds (cont'd)

Key Effect: Local/Animal									
Bisphenol A	80-05-7	Repr. Cat. 3; R62 Xi; R37-41 R43	SCOEL/SUM/113	local irritation	rat, 90-day inhalation; olfactory epithelium inflammation	10 mg/m^3	0.27 mg/m^3	37	**2.2 mg/m^3**
((2-(2-Butoxyethoxy)ethanol) (DEGBE)	112-34-5	Xi; R36	SCOEL/SUM/101	local irritation	rat 90-day inhalation study; respiratory irritation	67.5 mg/m^3	2.5 mg/m^3	27	**21 mg/m^3**
Ethyl acrylate	140-88-5	Xn; R20/21/22 Xi; R36/37/38 R43	SCOEL/SUM/47	local irritation	hyperplasia and metaplasia of the nasal mucosa	5 ppm	0.27 ppm	18.5	**1.1 ppm**
Hydrogen sulphide	7783-06-4	T; R26	SCOEL/SUM/124	local irritation	rats, sub-chronic inhalation study; nasal lesions	5 ppm	0.17 ppm	29	**2.2 ppm**
Methyl acrylate	96-33-3	Xn; R20/21/22 Xi; R36/37/38 R43	SCOEL/SUM/46	local irritation	olfactory epithelium irritation	5 ppm	0.27 ppm	18.5	**1.1 ppm**
Phenol	108-95-2	Muta. Cat. 3; R68 T; R23/24/25 Xn; R48/20/21/22 C; R34	SCOEL/SUM/16	local irritation	monkey, 90-day inhalation study: no effect; r at irritation and CNS at higher conc.	2 ppm	0.14 ppm	15	**1.1 ppm**
Sulphuric acid	7664-93-9	C; R35	SCOEL/SUM/105	local irritation	animal, but no specific study	0.05 mg/m^3	0.0009 mg/m^3	55	**0.02 mg/m^3**

* SCOEL identified relevant human data as POD. Strengths and weaknesses of human studies have to be judged by expert evaluation and the whole database has to be taken into account to derive a DNEL; no default factors should be applied.

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Carbondisulphide (CAS 75-15-0)

Comparison of IOELV, $DNEL_{long\text{-}term\ worker\ inhalation}$ using REACH TGD default AF and ECETOC AF

General remarks:

This evaluation is based on the relevant dose descriptor identified by SCOEL (SCOEL/SUM/82) and the application of default factors. No compound specific information was considered in steps 2 and 3.

1) Relevant dose descriptor as defined by SCOEL:

The critical health effects in humans are neurotoxicity and cardiotoxicity. Overall, SCOEL concludes that *"the threshold/NOAEL for the earliest non-clinical changes is in the range of 10-30 mg/m³ (3-10 ppm), with the more reliable human studies relating to the top end of this range."* The largest studies are from Germany with about 240 exposed and 220 control workers (group of Drexler and co-workers) and from Japan with about 430 exposed and 400 control workers (group of Omae and Takebayashi and co-workers).

2) Modification of starting point:

SCOEL	REACH TGD default values	ECETOC
SCOEL did not modify the starting point **10-30 mg/m³**	No default modification needed; occupational studies **10 mg/m³ ***	Human data

* Lowest threshold/NOAEL level discussed by SCOEL

3) Assessment factors (AF):

SCOEL	REACH TGD default values	ECETOC
An AF of 2 was applied by SCOEL to the high end of exposures where non-clinical effects might have started **Overall factor: 2**	Route-to-route: 1 Interspecies: 1 Intraspecies (worker): ≤5* Exposure duration: 1** Dose-response: 1 Quality of database: 1 **Overall AF: 5**	Strengths and weaknesses of human studies have to be judged by expert evaluation and the whole database has to be taken into account to define assessment factors and to derive a DNEL.

* REACH TGD on derivation of DNEL/DMEL from human data (ECHA, 2010) indicates on pg. 25 that an AF <5 might be applied based on expert judgment: *"Use of AFs lower than the standard assessment factors is appropriate when it can be shown that <u>some</u> of the factors that cause the intraspecies variation in the target population, such as gender, age, nutritional status, health, susceptibility and genetic polymorphism have been covered in the study population. When this is the case, a value lower than the standard assessment factor should be selected and justified based on expert judgment."*

** REACH TGD on derivation of DNEL/DMEL from human data (ECHA, 2010) indicates on pg. 27: "*Provided that the information in a human study covers a sufficient time span, there is generally no need to introduce an assessment factor to account for differences in duration of exposure for the study population and scenario under consideration (target population).*"

4) Exposure limits:

SCOEL	REACH TGD	ECETOC
IOELV **15 mg/m³ (5 ppm)**	Default $DNEL_{long\text{-}term\ worker\ inhalation}$ **2 mg/m³**	

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2-Ethoxyethanol / 2-Ethoxyethylacetate (CAS 110-80-5 / 111-15-9)
Comparison of IOELV, $DNEL_{long\text{-}term\ worker\ inhalation}$ using REACH TGD default AF and ECETOC AF

General remarks:
This evaluation is based on the relevant dose descriptor identified by SCOEL (SCOEL/SUM/116 – for public consultation) and the application of default factors. No compound specific information was considered in steps 2 and 3.

1) Relevant dose descriptor as defined by SCOEL:
Hematologic effects were observed in workers at 2.6 ppm and a level of no effects of 1.8 ppm was derived. Effects on sperm parameters were not significant but could not be excluded at 6.6 ppm.

2) Modification of starting point:

SCOEL	REACH TGD default values	ECETOC
SCOEL did not modify the starting point **1.8 ppm**	No default modification needed; occupational study **1.8 ppm**	Human data

3) Assessment factors (AF):

SCOEL	REACH TGD default values	ECETOC
Overall factor: 1	Route-to-route: 1 Interspecies: 1 Intraspecies (worker): ≤5* Exposure duration: 1** Dose-response: 1 Quality of database: 1 **Overall AF: 5**	Strengths and weaknesses of human studies have to be judged by expert evaluation and the whole database has to be taken into account to define assessment factors and to derive a DNEL.

* REACH TGD on derivation of DNEL/DMEL from human data (ECHA, 2010) indicates on pg. 25 that an AF <5 might be applied based on expert judgment: "*Use of AFs lower than the standard assessment factors is appropriate when it can be shown that <u>some</u> of the factors that cause the intraspecies variation in the target population, such as gender, age, nutritional status, health, susceptibility and genetic polymorphism have been covered in the study population. When this is the case, a value lower than the standard assessment factor should be selected and justified based on expert judgment.*"
** REACH TGD on derivation of DNEL/DMEL from human data (ECHA, 2010) indicates on pg. 27: "*Provided that the information in a human study covers a sufficient time span, there is generally no need to introduce an assessment factor to account for differences in duration of exposure for the study population and scenario under consideration (target population).*"

4) Exposure limits:

SCOEL	REACH TGD	ECETOC
IOELV **2 ppm**	Default $DNEL_{long\text{-}term\ worker\ inhalation}$ **0.36 ppm**	

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n-Hexane (CAS 110-54-3)

Comparison of IOELV, $DNEL_{long\text{-}term\ worker\ inhalation}$ using REACH TGD default AF and ECETOC AF

General remarks:
This evaluation is based on the relevant dose descriptor identified by SCOEL (SEG/SUM/52C) and the application of default factors. No compound specific information was considered in steps 2 and 3.

1) Relevant dose descriptor as defined by SCOEL:
The critical effect identified by SCOEL was the development of early, pre-clinical signs of peripheral neuropathy following exposure by inhalation. The SCOEL approach was to use urinary metabolite information indicating a greater propensity for effects to be associated with urinary levels greater than approximately 7.5 mg/l 2,5-hexane dione, and a urinary level of 7.5 mg/l corresponds to an 8-hour time-weighted average of approximately 250 mg/m^3 (70 ppm). SCOEL considered 250 mg/m^3 (70 ppm) as the LOAEL for further calculations. The worker population investigated in the key study handled solvents approximately 7 hours/day, 5 days/week, for periods of time ranging from 1 to 28 years with a mean exposure of 12.4 years.

2) Modification of starting point:

SCOEL	REACH TGD default values	ECETOC
SCOEL did not modify the starting point **250 mg/m^3**	No default modification needed; occupational study **250 mg/m^3**	Human data

3) Assessment factors (AF):

SCOEL	REACH TGD default values	ECETOC
AF of 2 and a 'rounding convention' of 1.75 **Overall factor: 3.5**	Route-to-route: 1 Interspecies: 1 Intraspecies (worker): ≤5* Exposure duration: 1** Dose-response: 3*** Quality of database: 1 **Overall AF: 15**	Strengths and weaknesses of human studies have to be judged by expert evaluation and the whole database has to be taken into account to define assessment factors and to derive a DNEL.

* REACH TGD on derivation of DNEL/DMEL from human data (ECHA, 2010) indicates on pg. 25 that an AF <5 might be applied based on expert judgment: "*Use of AFs lower than the standard assessment factors is appropriate when it can be shown that <u>some</u> of the factors that cause the intraspecies variation in the target population, such as gender, age, nutritional status, health, susceptibility and genetic polymorphism have been covered in the study population. When this is the case, a value lower than the standard assessment factor should be selected and justified based on expert judgment.*"
** REACH TGD on derivation of DNEL/DMEL from human data (ECHA, 2010) indicates on pg. 27: "*Provided that the information in a human study covers a sufficient time span, there is generally no need to introduce an assessment factor to account for differences in duration of exposure for the study population and scenario under consideration (target population).*"
***REACH TGD on derivation of DNEL/DMEL from human data (ECHA, 2010) indicates on pg. 28: "*It is proposed that when the starting point for the DNEL calculation is a LOAEL, an assessment factor ranging from 3 (as minimum/majority of cases) to 10 (as maximum/exceptional cases) is applied.*"

4) Exposure limits:

SCOEL	REACH TGD	ECETOC
IOELV **72 mg/m^3**	Default $DNEL_{long\text{-}term\ worker\ inhalation}$ **17 mg/m^3**	

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2-Methoxyethanol / 2-Methoxyethylacetate (CAS 109-86-4 / 110-49-6)
Comparison of IOELV, $DNEL_{long\text{-}term\ worker\ inhalation}$ using REACH TGD default AF and ECETOC AF

General remarks:
This evaluation is based on the relevant dose descriptor identified by SCOEL (SCOEL/SUM/120C) and the application of default factors. No compound specific information was considered in steps 2 and 3.

1) Relevant dose descriptor as defined by SCOEL:
SCOEL judged from both animal data and experience of occupational exposure, the critical effects of 2ME are its toxic effects on reproduction and blood formation. SCOEL derived an IOELV based on haematological effects seen in workers at 4 ppm.

2) Modification of starting point:

SCOEL	REACH TGD default values	ECETOC
SCOEL did not modify the starting point **4 ppm**	No default modification needed; occupational study **4 ppm**	Human data

3) Assessment factors (AF):

SCOEL	REACH TGD default values	ECETOC
Overall factor: 4	Route-to-route: 1 Interspecies: 1 Intraspecies (worker): ≤5* Exposure duration: 1** Dose-response: 3*** Quality of database: 1 **Overall AF: 15**	Strengths and weaknesses of human studies have to be judged by expert evaluation and the whole database has to be taken into account to define assessment factors and to derive a DNEL.

* REACH TGD on derivation of DNEL/DMEL from human data (ECHA, 2010) indicates on pg. 25 that an AF <5 might be applied based on expert judgment: "*Use of AFs lower than the standard assessment factors is appropriate when it can be shown that <u>some</u> of the factors that cause the intraspecies variation in the target population, such as gender, age, nutritional status, health, susceptibility and genetic polymorphism have been covered in the study population. When this is the case, a value lower than the standard assessment factor should be selected and justified based on expert judgment.*"
** REACH TGD on derivation of DNEL/DMEL from human data (ECHA, 2010) indicates on pg. 27: "*Provided that the information in a human study covers a sufficient time span, there is generally no need to introduce an assessment factor to account for differences in duration of exposure for the study population and scenario under consideration (target population).*"
***REACH TGD on derivation of DNEL/DMEL from human data (ECHA, 2010) indicates on pg. 28: "*It is proposed that when the starting point for the DNEL calculation is a LOAEL, an assessment factor ranging from 3 (as minimum/majority of cases) to 10 (as maximum/exceptional cases) is applied.*"

4) Exposure limits:

SCOEL	REACH TGD	ECETOC
IOELV **1 ppm**	Default $DNEL_{long\text{-}term\ worker\ inhalation}$ **0.27 ppm**	

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Toluene (CAS 108-88-3)
Comparison of IOELV, $DNEL_{long\text{-}term\ worker\ inhalation}$ using REACH TGD default AF and ECETOC AF

General remarks:
This evaluation is based on the relevant dose descriptor identified by SCOEL (SCOEL/SUM/18) and the application of default factors. No compound specific information was considered in steps 2 and 3.

1) Relevant dose descriptor as defined by SCOEL:
The critical effect identified by SCOEL was changes in performance in human volunteers and workers indicative of effects on the CNS from concentrations of about 75 ppm. There was no reliable evidence of effects in print workers at or below toluene concentrations of 50 ppm.

2) Modification of starting point:

SCOEL	REACH TGD default values	ECETOC
SCOEL did not modify the starting point **50 ppm**	No default modification needed; occupational exposure **50 ppm**	Human data

* "*Modification is generally also not needed when the dose descriptor is based on human data (e.g., case studies).*" (REACH TGD, Chapter R.8, p.24)

3) Assessment factors (AF):

SCOEL	REACH TGD default values	ECETOC
Overall factor: 1	Route-to-route: 1 Interspecies: 1 Intraspecies (worker): ≤5* Exposure duration: 1** Dose-response: 1 Quality of database: 1 **Overall AF: 5**	Strengths and weaknesses of human studies have to be judged by expert evaluation and the whole database has to be taken into account to define assessment factors and to derive a DNEL.

* REACH TGD on derivation of DNEL/DMEL from human data (ECHA, 2010) indicates on pg. 25 that an AF <5 might be applied based on expert judgment: "*Use of AFs lower than the standard assessment factors is appropriate when it can be shown that <u>some</u> of the factors that cause the intraspecies variation in the target population, such as gender, age, nutritional status, health, susceptibility and genetic polymorphism have been covered in the study population. When this is the case, a value lower than the standard assessment factor should be selected and justified based on expert judgment.*"
** REACH TGD on derivation of DNEL/DMEL from human data (ECHA, 2010) indicates on pg. 27: "*Provided that the information in a human study covers a sufficient time span, there is generally no need to introduce an assessment factor to account for differences in duration of exposure for the study population and scenario under consideration (target population).*"

4) Exposure limits:

SCOEL	REACH TGD	ECETOC
IOELV **50 ppm**	Default $DNEL_{long\text{-}term\ worker\ inhalation}$ **10 ppm***	

* REACH TGD on derivation of DNEL/DMEL from human data (ECHA, 2010) discusses in Appendix R.8-16 toluene as an example on how to deviate from the default factors based on the discussion in the related EU Risk Assessment Report. A human study with a LOAEC of 88 ppm was taken as a key study; the EU Risk Assessment Report defines the minimum Margins of Safety (purpose of MOSmin in the EU risk assessment was the same as the overall Assessment Factor) for toluene as 5 for workers. This single factor covers (i) some of the intraspecies variation and (ii) the step from LOAEC to NOAEL.

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Cyanamide (CAS 420-04-2)

Comparison of IOELV, $DNEL_{long\text{-}term\ worker\ inhalation}$ using REACH TGD default AF and ECETOC AF

General remarks:

This evaluation is based on the relevant dose descriptor identified by SCOEL (SCOEL/SUM/100) and the application of default factors. No compound specific information was considered in steps 2 and 3.

1) Relevant dose descriptor as defined by SCOEL:

Hematological effects in a 1-year dog feeding study. NOAEL 0.2 mg/kg bw/day.

2) Modification of starting point:

SCOEL	REACH TGD default values	ECETOC
x 70 (human bw) ÷ 10 (10 m^3 air volume during a working day of 8 hours) **1.4 mg/m^3**	x 70 (human bw) ÷ 10 (10 m^3 air volume during a working day of 8 hours) **1.4 mg/m^3**	x 70 (human bw) ÷ 10 (10 m^3 air volume during a working day of 8 hours) **1.4 mg/m^3**

3) Assessment factors (AF):

SCOEL	REACH TGD default values	ECETOC
	Route-to-route: 2 Allometric scaling: 1.4* Additional uncertainty: 2.5 Intraspecies (worker): 5 Exposure duration: 1 Dose-response: 1 Quality of database: 1	Route-to-route: 1 Interspecies: 1.4* Intraspecies (worker): 3 Exposure duration: 1 Dose-response: 1 Quality of database: 1
Overall factor: 1.4	**Overall AF: 35**	**Overall AF: 4.2**

* Default factor for extrapolation from dogs to humans. The default factor of REACH TGD is also used for ECETOC, although ECETOC tends to propose 1.3

4) Exposure limits:

SCOEL	REACH TGD	ECETOC
IOELV **1 mg/m^3**	Default $DNEL_{long\text{-}term\ worker\ inhalation}$ **0.04 mg/m^3**	$DNEL_{long\text{-}term\ worker\ inhalation}$ **0.3 mg/m^3**

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N, N-Dimethylformamide - DMF (CAS 68-12-2)

Comparison of IOELV, $DNEL_{long\text{-}term\ worker\ inhalation}$ using REACH TGD default AF and ECETOC AF

General remarks:

This evaluation is based on the relevant dose descriptor identified by SCOEL (SCOEL/SUM/121) and the application of default factors. No compound specific information was considered in steps 2 and 3.

1) Relevant dose descriptor as defined by SCOEL:

Derivation of the IOELV is based on a long-term study in rats over 2 years and mice over 18 months at 0, 25, 100, or 400 ppm DMF (6 hours/day, 5 day/week). Compound related morphological changes were observed only in the liver. In this study 25 ppm was the NOAEL for rats and a LOAEL for mice. A benchmark calculation for a benchmark response of 5% extra risk gave a BMDL of 7.8 ppm and a BMD of 14.7 ppm for mice.

2) Modification of starting point:

SCOEL	REACH TGD default values	ECETOC
SCOEL did not modify the starting point **7.8 ppm**	x 6/8 (6 hours exposure in animal experiment / 8 hours exposure per day for worker) x 6.7/10 (light activity) **3.9 ppm**	x 6/8 (6 hours exposure in volunteers / 8 hours exposure per day for worker) x 6.7/10 (light activity) **3.9 ppm**

3) Assessment factors (AF):

SCOEL	REACH TGD default values	ECETOC
	Allometric scaling: 1* Additional uncertainty: 2.5 Intraspecies (worker): 5 Exposure duration: 1 Dose-response: 1 Quality of database: 1 **Overall AF: 12.5**	Interspecies: 1* Intraspecies (worker): 3 Exposure duration: 1 Dose-response: 1 Quality of database: 1 **Overall AF: 3**
Overall factor: 1		

* Inhalation experiment in animals

4) Exposure limits:

SCOEL	REACH TGD	ECETOC
IOELV **5 ppm**	Default $DNEL_{long\text{-}term\ worker\ inhalation}$ **0.32 ppm (**0.62 ppm***)**	$DNEL_{long\text{-}term\ worker\ inhalation}$ **1.3 ppm (**2.6ppm***)**

* DNEL using default AF and relevant dose descriptor WITHOUT modification (step 2)

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((2-(2-Methoxyethoxy)ethanol) - DEGME (CAS 111-77-3)

Comparison of IOELV, $DNEL_{long\text{-}term\ worker\ inhalation}$ using REACH TGD default AF and ECETOC AF

General remarks:

This evaluation is based on the relevant dose descriptor identified by SCOEL (SCOEL/SUM/99) and the application of default factors. No compound specific information was considered in steps 2 and 3.

1) Relevant dose descriptor as defined by SCOEL:

The critical effect identified by SCOEL was foetotoxicity in developmental toxicity studies. Delayed ossification and visceral malformations were reported at gavage dose of 600 mg/kg bw/day in rats, and delayed ossification reported from dermal application at 250 mg/kg bw/day in rabbits. SCOEL considered that absorption of DEGME was 100% by all routes and used route-to-route extrapolation to define the 'critical inhalation exposure level at the workplace'. The key study was the developmental toxicity study by the dermal route in the rabbit (GD 6-18) giving $NOAEL_{development}$ 50 mg/kg bw/day and $NOAEL_{maternal}$ 250 mg/kg bw/day.

2) Modification of starting point:

SCOEL	REACH TGD default values	ECETOC
x 70 (human bw) ÷ 10 (10 m^3 air volume during a working day of 8 hours) **350 mg/m^3**	x 70 (human bw) ÷ 10 (10 m^3 air volume during a working day of 8 hours) **350 mg/m^3**	x 70 (human bw) ÷ 10 (10 m^3 air volume during a working day of 8 hours) **350 mg/m^3**

3) Assessment factors (AF):

SCOEL	REACH TGD default values	ECETOC
	Route-to-route: 2* Allometric scaling: 2.4** Additional uncertainty: 2.5 Intraspecies (worker): 5 Exposure duration: 1*** Dose-response: 1 Quality of database: 1	Route-to-route: 1***** Interspecies: 2.4**** Intraspecies (worker): 3 Exposure duration: 1 Dose-response: 1 Quality of database: 1
Overall factor: 5	**Overall AF: 60**	**Overall AF: 7.2**

* No default factor for dermal ≥ inhalation but (dermal -> oral: 1 and oral-> inhalation: 2)
** Default factor for rabbit ≥ human extrapolation
*** Developmental study (in rabbits; GD 6-18)
**** No AF given for rabbits in ECETOC TR 86 (2003)
***** 100% absorption assumed for all routes

4) Exposure limits:

SCOEL	REACH TGD	ECETOC
IOELV **50 mg/m^3**	Default $DNEL_{long\text{-}term\ worker\ inhalation}$ **6 mg/m^3**	$DNEL_{long\text{-}term\ worker\ inhalation}$ **50 mg/m^3**

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Monochlorobenzene (CAS 108-90-7)

Comparison of IOELV, $DNEL_{long\text{-}term\ worker\ inhalation}$ using REACH TGD default AF and ECETOC AF

General remarks:

This evaluation is based on the relevant dose descriptor identified by SCOEL (SCOEL/SUM/42) and the application of default factors. No compound specific information was considered in steps 2 and 3.

1) Relevant dose descriptor as defined by SCOEL:

SCOEL selected the LOAEC of 50 ppm obtained in a two generation rat inhalation reproduction study as the starting point. The critical effect is increased liver weight; at higher doses in addition liver histopathology and kidney weight and histopathology; no prenatal or developmental effects.

2) Modification of starting point:

SCOEL	REACH TGD default values	ECETOC
SCOEL did not modify the starting point **50 ppm**	x 6/8 (6 hours exposure in animal experiment / 8 hours exposure per day for worker) x 7/5 (animals were exposed 7 days per week / 5 days per week exposure for workers) x 6.7/10 (light activity) **35.2 ppm**	x 6/8 (6 hours exposure in animals / 8 hours exposure per day for worker) x 7/5 (animals were exposed 7 days per week / 5 days per week exposure for workers) x 6.7/10 (light activity) **35.2 ppm**

3) Assessment factors (AF):

SCOEL	REACH TGD default values	ECETOC
Uncertainty factor for intra-interspecies variability and for the absence of a NOEAL in the selected study. **Overall factor: 10**	Allometric scaling: 1* Additional uncertainty: 2.5 Intraspecies (worker): 5 Exposure duration: 2** Dose-response: 3*** Quality of database: 1 **Overall AF: 75**	Interspecies: 1* Intraspecies (worker): 3 Exposure duration: 2** Dose-response: 3*** Quality of database: 1 **Overall AF: 18**

* Inhalation experiment in animals
** Extrapolation from two-generation study to chronic exposure. The critical effect is increased liver weight; at higher doses in addition liver histopathology and kidney weight and histopathology were reported; no prenatal or developmental effects. A time-extrapolation factor is taken into account for these systemic effects based on the sub-chronic exposure period of the parental animals in a guideline two-generation study; males approx. 12 weeks; females approx. 18 weeks.
*** LOAEC $\geq$ NOAEC; REACH TGD, Chapter R.8, p.36: "*It is suggested to use an assessment factor between 3 (as minimum/majority of cases) and 10 (as maximum/exceptional cases).*"

4) Exposure limits:

SCOEL	REACH TGD	ECETOC
IOELV **5 ppm**	Default $DNEL_{long\text{-}term\ worker\ inhalation}$ **0.5 ppm** (0.66 ppm*)	$DNEL_{long\text{-}term\ worker\ inhalation}$ **2 ppm** (2.8 ppm*)

* DNEL using default AF and relevant dose descriptor WITHOUT modification (step 2).

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Pentanes (CAS 109-66-0; 78-78-4; 590-35-2)

Comparison of IOELV, $DNEL_{long\text{-}term\ worker\ inhalation}$ using REACH TGD default AF and ECETOC AF

General remarks:

This evaluation is based on the relevant dose descriptor identified by SCOEL (SEG/SUM/79) and the application of default factors. No compound specific information was considered in steps 2 and 3.

1) Relevant dose descriptor as defined by SCOEL:

The critical effect identified by SCOEL is the absence of any signs of toxicity in rats exposed to 9,000 mg/m^3 of pentane during 10 hours/day, 5 days/week, 30 weeks, or 11,800 mg/m^3 of a mixture of alkanes containing 25% n-pentane and 25% isopentane (the other 50% was equal amounts of n-butane and isobutene) during 6 hours/day, 5 days/week, 13 weeks.

2) Modification of starting point:

SCOEL	REACH TGD	ECETOC
SCOEL did not modify the starting point **9,000 mg/m^3**	x 10/8 (10 hours exposure in animal experiment / 8 hours exposure per day for worker) x 6.7/10 (light activity) **7537 mg/m^3**	x 10/8 (10 hours exposure in animal experiment / 8 hours exposure per day for worker) x 6.7/10 (light activity) **7537 mg/m^3**

3) Assessment factors (AF):

SCOEL	REACH TGD default values	ECETOC
Overall factor: 3	Allometric scaling: 1* Additional uncertainty: 2.5 Intraspecies (worker): 5 Exposure duration: 1** Dose-response: 1 Quality of database: 1 **Overall AF: 12.5**	Interspecies: 1* Intraspecies (worker): 3 Exposure duration: 1 Dose-response: 1** Quality of database: 1 **Overall AF: 3**

* Inhalation experiment in animals
** Animals were exposed for 30 weeks.

4) Exposure limits:

SCOEL	REACH TGD	ECETOC
IOELV **3000 mg/m^3**	Default $DNEL_{long\text{-}term\ worker\ inhalation}$ **600 mg/m^3 (**720 mg/m^3*)	$DNEL_{long\text{-}term\ worker\ inhalation}$ **2500 mg/m^3 (**3000 mg/m^3*)

* DNEL using default AF and relevant dose descriptor WITHOUT modification (step 2).

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Pyrethrum (CAS 8003-34-7)
Comparison of IOELV, $DNEL_{long\text{-}term\ worker\ inhalation}$ using REACH TGD default AF and ECETOC AF

General remarks:
This evaluation is based on the relevant dose descriptor identified by SCOEL (SCOEL/SUM/95) and the application of default factors. No compound specific information was considered in steps 2 and 3.

1) Relevant dose descriptor as defined by SCOEL:
Slight liver damage was observed in a dietary 2-year study in rats; NOAEL = 10 mg/kg/day

2) Modification of starting point:

SCOEL	REACH TGD default values	ECETOC
x 70 (human bw) ÷ 10 (10 m^3 air volume during a working day of 8 hours) **70 mg/m^3**	x 70 (human bw) ÷ 10 (10 m^3 air volume during a working day of 8 hours) **70 mg/m^3**	x 70 (human bw) ÷ 10 (10 m^3 air volume during a working day of 8 hours) **70 mg/m^3**

3) Assessment factors (AF):

SCOEL	REACH TGD default values	ECETOC
	Route-to-route: 2 Allometric scaling: 4 Additional uncertainty: 2.5 Intraspecies (worker): 5 Exposure duration: 1 Dose-response: 1 Quality of database: 1	Route-to-route: 1 Interspecies: 4 Intraspecies (worker): 3 Exposure duration: 1 Dose-response: 1 Quality of database: 1
Overall factor: 50*	**Overall AF: 100**	**Overall AF: 12**

* This high overall factor is applied by SCOEL because 1) the POD is derived from an oral study and acute toxicity data indicate that pyrethrum is less toxic via the oral route than via parental routes (probably as a result of efficient first-path metabolism) 2) gastrointestinal absorption after oral dosing is approx. 46% (no data on absorption after exposure by inhalation), 3) no inhalation studies are available, and 4) an ADI value (0 – 0.04 mg/kg bw/day) is available derived from WHO-FAO.

4) Exposure limits:

SCOEL	REACH TGD	ECETOC
IOELV **1 mg/m^3**	Default $DNEL_{long\text{-}term\ worker\ inhalation}$ **0.7 mg/m^3**	$DNEL_{long\text{-}term\ worker\ inhalation}$ **5.8 mg/m^3**

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Diethylamine (CAS 109-89-7)

Comparison of IOELV, $DNEL_{long\text{-}term\ worker\ inhalation}$ using REACH TGD default AF and ECETOC AF

General remarks:

This evaluation is based on the relevant dose descriptor identified by SCOEL (SCOEL/SUM/91) and the application of default factors. No compound specific information was considered in steps 2 and 3.

1) Relevant dose descriptor as defined by SCOEL:

Human volunteers exposed to 75 mg/m³ for 15 min experienced no change in nasal air volume and nasal airway resistance; if exposed for 60 minutes to increasing concentrations from 0 - 36 mg/m³ there was odour perception and self-reported irritation.

2) Modification of starting point:

SCOEL	REACH TGD default values	ECETOC
SCOEL did not modify the starting point **75 mg/m³**	Local effects in volunteers; no time-scaling x 6.7/10 (light activity) **50 mg/m³**	Human Data

3) Assessment factors (AF):

SCOEL	REACH TGD default values	ECETOC
Overall factor: 5	Interspecies: 1 Intraspecies (worker): ≤5* Exposure duration: 1** Dose-response: 1 Quality of database: 1 **Overall AF: 5** (acute effects)	Strengths and weaknesses of human studies have to be judged by expert evaluation and the whole database has to be taken into account to define assessment factors and to derive a DNEL.

* REACH TGD on derivation of DNEL/DMEL from human data (ECHA, 2010) indicates on pg. 25 that an AF <5 might be applied based on expert judgment: "*Use of AFs lower than the standard assessment factors is appropriate when it can be shown that some of the factors that cause the intraspecies variation in the target population, such as gender, age, nutritional status, health, susceptibility and genetic polymorphism have been covered in the study population. When this is the case, a value lower than the standard assessment factor should be selected and justified based on expert judgment.*"

** REACH TGD on derivation of DNEL/DMEL from human data (ECHA, 2010) indicates on pg. 27: "*A NOAEL for an acute endpoint (NOAEL following short term exposure only) should not be used as the basis for the derivation of a $DNEL_{long\text{-}term}$. If the study design does not allow to adequately address any latency of the observed effect, then these data should not be used for deriving a $DNEL_{long\text{-}term.}$*"

4) Exposure limits:

SCOEL	REACH TGD	ECETOC
IOELV **15 mg/m³**	Default $DNEL_{long\text{-}term\ worker\ inhalation}$ should not be calculated based on a human NOAEL for an acute endpoint* Default $DNEL_{short\text{-}term\ worker\ inhalation}$ **10 mg/m³ (**15 mg/m³**)	

* REACH TGD on derivation of DNEL/DMEL from human data, pg. 27 (ECHA, 2010).

** DNEL using default AF and relevant dose descriptor WITHOUT modification (step 2).

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Formaldehyde (CAS 50-00-0)

Comparison of IOELV, $DNEL_{long\text{-}term\ worker\ inhalation}$ using REACH TGD default AF and ECETOC AF

General remarks:

This evaluation is based on the relevant dose descriptor identified by SCOEL (SCOEL/SUM/125) and the application of default factors. No compound specific information was considered in steps 2 and 3.

1) Relevant dose descriptor as defined by SCOEL:

SCOEL concluded that on the basis of studies with volunteers, concentrations between 0.5 and 1 ppm, exposure for up to 6 hours, can produce eye irritation in 5 to 25 % of the exposed persons. (The derived IOELV takes the carcinogenic risk into account; SCOEL states that the database is insufficient to derive directly an IOELV for irritating effects on the respirator tract but used irritating effects on the eye 'a more sensitive' effect to derive an IOELV.)

2) Modification of starting point:

SCOEL	REACH TGD default values	ECETOC
SCOEL did not modify the starting point **0.5 ppm**	Local effects on eye **0.5 ppm**	Human data

3) Assessment factors (AF):

SCOEL	REACH TGD default values	ECETOC
Overall factor: 2.5	Interspecies: 1 Intraspecies (worker): ≤5* Exposure duration: 1** Dose-response: 1 Quality of database: 1 **Overall AF: 5** (acute effects)	Strengths and weaknesses of human studies have to be judged by expert evaluation and the whole database has to be taken into account to define assessment factors and to derive a DNEL.

* REACH TGD on derivation of DNEL/DMEL from human data (ECHA, 2010) indicates on pg. 25 that an AF <5 might be applied based on expert judgment: "*Use of AFs lower than the standard assessment factors is appropriate when it can be shown that some of the factors that cause the intraspecies variation in the target population, such as gender, age, nutritional status, health, susceptibility and genetic polymorphism have been covered in the study population. When this is the case, a value lower than the standard assessment factor should be selected and justified based on expert judgment.*"

** Local eye irritation in humans: REACH TGD on derivation of DNEL/DMEL from human data (ECHA, 2010) indicates on pg. 27: "*Whether the duration of a human study can be considered sufficient will also depend on the type of effect under consideration. Acute effects, e.g. effects on the central nervous system caused by solvents or skin and eye irritation/corrosion can usually be observed within a few days. A NOAEL for an acute endpoint (NOAEL following short term exposure only) should not be used as the basis for the derivation of a* $DNEL_{long\text{-}term}$*. If the study design does not allow to adequately address any latency of the observed effect, then these data should not be used for deriving a* $DNEL_{long\text{-}term}$*.*"

4) Exposure limits:

SCOEL	REACH TGD	ECETOC
IOELV **0.2 ppm**	Default $DNEL_{long\text{-}term\ worker\ inhalation}$ should not be calculated based on a human NOAEL for an acute endpoint* Default $DNEL_{short\text{-}term\ worker\ inhalation}$ **0.1 ppm**	

* REACH TGD on derivation of DNEL/DMEL from human data, pg. 27 (ECHA, 2010).

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Hydrogen peroxide (CAS 7722-84-1)
Comparison of IOELV, $DNEL_{long\text{-}term\ worker\ inhalation}$ using REACH TGD default AF and ECETOC AF

General remarks:
This evaluation is based on the relevant dose descriptor identified by SCOEL (SCOEL/SUM/134) and the application of default factors. No compound specific information was considered in steps 2 and 3.

1) Relevant dose descriptor as defined by SCOEL:
The critical effect identified by SCOEL is the respiratory tract and lung irritation following repeated exposure to H_2O_2 by inhalation. The review of available human data carried out by SCOEL indicates that no respiratory tract irritation and pulmonary function alterations were observed in volunteers or humans occupationally exposed to 8-hour TWA concentrations below 1.4 mg/m^3 (1 ppm).

2) Modification of starting point:

SCOEL	REACH TGD default values	ECETOC
SCOEL did not modify the starting point **1 ppm**	No default modification needed; occupational study **1 ppm**	Human data

3) Assessment factors (AF):

SCOEL	REACH TGD default values	ECETOC
Overall factor: 1	Route-to-route: 1 Interspecies: 1 Intraspecies (worker): ≤5* Exposure duration: 1** Dose-response: 1 Quality of database: 1 **Overall AF: 5**	Strengths and weaknesses of human studies have to be judged by expert evaluation and the whole database has to be taken into account to define assessment factors and to derive a DNEL.

* REACH TGD on derivation of DNEL/DMEL from human data (ECHA, 2010) indicates on pg. 25 that an AF <5 might be applied based on expert judgment: "*Use of AFs lower than the standard assessment factors is appropriate when it can be shown that some of the factors that cause the intraspecies variation in the target population, such as gender, age, nutritional status, health, susceptibility and genetic polymorphism have been covered in the study population. When this is the case, a value lower than the standard assessment factor should be selected and justified based on expert judgment.*"
** REACH TGD on derivation of DNEL/DMEL from human data (ECHA, 2010) indicates on pg. 27: "*Provided that the information in a human study covers a sufficient time span, there is generally no need to introduce an assessment factor to account for differences in duration of exposure for the study population and scenario under consideration (target population).*"

4) Exposure limits:

SCOEL	REACH TGD	ECETOC
IOELV **1 ppm**	Default $DNEL_{long\text{-}term\ worker\ inhalation}$ **0.2 ppm***	

* REACH TGD on derivation of DNEL/DMEL from human data (ECHA, 2010) discusses in Appendix R.8-16 hydrogen peroxide as an example on how to deviate from the default factors based on the discussion in the related EU Risk Assessment Report. "*Because of the uncertainties and/or preliminary nature of the human data, they were not taken into account in the risk characterisation in that risk assessment report. Instead, more robust animal data were used to characterise the repeated dose inhalation toxicity of hydrogen peroxide. Interestingly, the effect concentrations in animal compared to human studies are rather consistent. Whether human data was dealt with in the Weight of Evidence analysis is not explained in the risk assessment report. This example illustrates that a study with small sample size, where all relevant parameters/observations are not covered is not a valid basis for obtaining a NOAEL or dose descriptor.*"

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Methyl methacrylate (CAS 80-62-6)

Comparison of IOELV, DNEL$_{\text{long-term worker inhalation}}$ using REACH TGD default AF and ECETOC AF

General remarks:

This evaluation is based on the relevant dose descriptor identified by SCOEL (SCOEL/SUM/126) and the application of default factors. No compound specific information was considered in steps 2 and 3.

1) Relevant dose descriptor as defined by SCOEL:

The critical effect identified by SCOEL was focal lesion of the olfactory region of the nasal epithelium in both rats and mice following repeated exposure as a consequence of local metabolism of MMA to methacrylic acid by carboxylesterases in the nasal epithelial cells. For defining the 'critical inhalation exposure level at the workplace' a reliable NOAEC of 25 ppm and LOAEC of 100 ppm was available from a 2-year inhalation study in rats. SCOEL judged that 'extensive' PBPK modelling work predicted that on kinetic grounds, for a given level of exposure to MMA, human nasal olfactory epithelium will be at least 3 times less sensitive than that of rats to the toxicity of MMA. SCOEL also judged that the available studies of workforces provided reassuring evidence that workers exposed to MMA levels of up to approximately 50 ppm have not suffered any respiratory ill-health consequences related to their long-term exposure with the occasional respiratory symptoms reported seem to be clearly connected with short-term peak exposures and the sensory irritant potential of MMA which starts to be expressed at concentrations somewhere in excess of 100 ppm.

2) Modification of starting point:

SCOEL	REACH TGD default values	ECETOC
SCOEL did not modify the starting point **50 ppm**	No default modification needed; occupational studies **50 ppm**	Human data

3) Assessment factors (AF):

SCOEL	REACH TGD default values	ECETOC
Overall factor: 1	Route-to-route: 1 Interspecies: 1 Intraspecies (worker): ≤5* Exposure duration: 1** Dose-response: 1 Quality of database: 1 **Overall AF: 5**	Strengths and weaknesses of human studies have to be judged by expert evaluation and the whole database has to be taken into account to define assessment factors and to derive a DNEL.

* REACH TGD on derivation of DNEL/DMEL from human data (ECHA, 2010) indicates on pg. 25 that an AF <5 might be applied based on expert judgment: "*Use of AFs lower than the standard assessment factors is appropriate when it can be shown that some of the factors that cause the intraspecies variation in the target population, such as gender, age, nutritional status, health, susceptibility and genetic polymorphism have been covered in the study population. When this is the case, a value lower than the standard assessment factor should be selected and justified based on expert judgment.*"

** REACH TGD on derivation of DNEL/DMEL from human data (ECHA, 2010) indicates on pg. 27: "*Provided that the information in a human study covers a sufficient time span, there is generally no need to introduce an assessment factor to account for differences in duration of exposure for the study population and scenario under consideration (target population).*"

4) Exposure limits:

SCOEL	REACH TGD	ECETOC
IOELV **50 ppm**	Default DNEL$_{\text{long-term worker inhalation}}$ **10 ppm**	

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Vinyl acetate (CAS 108-05-4)

Comparison of IOELV, $DNEL_{long\text{-}term\ worker\ inhalation}$ using REACH TGD default AF and ECETOC AF

General remarks:

This evaluation is based on the relevant dose descriptor identified by SCOEL (SCOEL/SUM/122) and the application of default factors. No compound specific information was considered in steps 2 and 3.

1) Relevant dose descriptor as defined by SCOEL:

Two-year inhalation experiments in mice and rat have proven a concentration of 50 ppm to be a NOAEL with respect to local histopathological changes of the nose and lungs. A cancer risk at low, non irritating concentrations appears negligible. SCOEL concluded that there are limited observations in humans of an NOAEL for irritancy at 10 ppm; this value was used as a starting point.

2) Modification of starting point:

SCOEL	REACH TGD default values	ECETOC
SCOEL did not modify the starting point **10 ppm**	No default modification needed; occupational study **10 ppm**	Human data

3) Assessment factors (AF):

SCOEL	REACH TGD default values	ECETOC
Overall factor: 2	Interspecies: 1 Intraspecies (worker): ≤5* Exposure duration: 1** Dose-response: 1 Quality of database: 1 **Overall AF: 5**	Strengths and weaknesses of human studies have to be judged by expert evaluation and the whole database has to be taken into account to define assessment factors and to derive a DNEL.

* REACH TGD on derivation of DNEL/DMEL from human data (ECHA, 2010) indicates on pg. 25 that an AF <5 might be applied based on expert judgment: "*Use of AFs lower than the standard assessment factors is appropriate when it can be shown that some of the factors that cause the intraspecies variation in the target population, such as gender, age, nutritional status, health, susceptibility and genetic polymorphism have been covered in the study population. When this is the case, a value lower than the standard assessment factor should be selected and justified based on expert judgment.*"

** REACH TGD on derivation of DNEL/DMEL from human data (ECHA, 2010) indicates on pg. 27: "*Provided that the information in a human study covers a sufficient time span, there is generally no need to introduce an assessment factor to account for differences in duration of exposure for the study population and scenario under consideration (target population).*"

4) Exposure limits:

SCOEL	REACH TGD	ECETOC
IOELV **5 ppm**	Default $DNEL_{long\text{-}term\ worker\ inhalation}$ **2 ppm**	

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Bisphenol A (CAS 80-05-7)

Comparison of IOELV, $DNEL_{long\text{-}term\ worker\ inhalation}$ using REACH TGD default AF and ECETOC AF

General remarks:

This evaluation is based on the relevant dose descriptor identified by SCOEL (SCOEL/SUM/113) and the application of default factors. No compound specific information was considered in steps 2 and 3.

1) Relevant dose descriptor as defined by SCOEL:

NOAEC = 10 mg/m^3 (mild olfactory epithelium inflammation at 50 mg/m^3); inhalation study, rats, 13 weeks; 6 hours/day; 5 days/week

2) Modification of starting point:

SCOEL	REACH TGD default values	ECETOC
SCOEL did not modify the starting point **10 mg/m^3**	Local effects; no time-scaling x 6.7/10 (light activity) **6.7 mg/m^3**	Local effects; no time-scaling x 6.7/10 (light activity) **6.7 mg/m^3**

3) Assessment factors (AF):

SCOEL	REACH TGD default values	ECETOC
	Allometric scaling: 1*	Interspecies: 1
	Additional uncertainty: 2.5	
	Intraspecies (worker): 5	Intraspecies (worker): 3
	Exposure duration: 2	Exposure duration: 1
	Dose-response: 1	Dose-response: 1
	Quality of database: 1	Quality of database: 1
Overall factor: 1	**Overall AF: 25**	**Overall AF: 3**

* Inhalation experiment in animals

4) Exposure limits:

SCOEL	REACH TGD	ECETOC
IOELV **10 mg/m^3**	Default $DNEL_{long\text{-}term\ worker\ inhalation}$ **0.27 mg/m^3 (**0.4 mg/m^3***)**	$DNEL_{long\text{-}term\ worker\ inhalation}$ **2.2 mg/m^3 (**3.3 mg/m^3***)**

* DNEL using default AF and relevant dose descriptor WITHOUT modification (step 2).

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((2-(2-Butoxyethoxy)ethanol) - DEGBE (CAS 112-34-5)

Comparison of IOELV, $DNEL_{long\text{-}term\ worker\ inhalation}$ using REACH TGD default AF and ECETOC AF

General remarks:

This evaluation is based on the relevant dose descriptor identified by SCOEL (SCOEL/SUM/101) and the application of default factors. No compound specific information was considered in steps 2 and 3.

1) Relevant dose descriptor as defined by SCOEL:

The critical effect identified by SCOEL is local irritation in the lungs observed in studies with exposure concentrations that lead to the formation of aerosols (i.e. concentrations > 100 mg/m^3). The key study was a 90-day inhalation study in rats, exposed 6 hours/day, 5 days/week, in which a NOEL of 94 mg/m^3 was observed.

2) Modification of starting point:

SCOEL	REACH TGD default values	ECETOC
SCOEL did not modify the starting point **94 mg/m^3**	Local effects; no time-scaling x 6.7/10 (light activity) **63 mg/m^3**	Local effects; no time-scaling x 6.7/10 (light activity) **63 mg/m^3**

3) Assessment factors (AF):

SCOEL	REACH TGD default values	ECETOC
	Allometric scaling: 1* Additional uncertainty: 2.5 Intraspecies (worker): 5 Exposure duration: 2 Dose-response: 1 Quality of database: 1	Interspecies: 1 Intraspecies (worker): 3 Exposure duration: 1** Dose-response: 1 Quality of database: 1
Overall factor: 1	**Overall AF: 25**	**Overall AF: 3**

* Inhalation experiment in animals
** Local effects

4) Exposure limits:

SCOEL	REACH TGD	ECETOC
IOELV **67.5 mg/m^3**	Default $DNEL_{long\text{-}term\ worker\ inhalation}$ **2.5 mg/m^3 (**3.8 mg/m^3*)	$DNEL_{long\text{-}term\ worker\ inhalation}$ **21 mg/m^3 (**31 mg/m^3***)

* DNEL using default AF and relevant dose descriptor WITHOUT modification (step 2).

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Ethyl acrylate (CAS 140-88-5)

Comparison of IOELV, $DNEL_{long\text{-}term\ worker\ inhalation}$ using REACH TGD default AF and ECETOC AF

General remarks:

This evaluation is based on the relevant dose descriptor identified by SCOEL (SCOEL/SUM/47) and the application of default factors. No compound specific information was considered in steps 2 and 3.

1) Relevant dose descriptor as defined by SCOEL:

NOAEC 5 ppm (LOAEC 25 ppm) for slight to moderate hyperplasia and metaplasia of the nasal mucosa in rats and mice after 24 or 27 months of exposure.

2) Modification of starting point:

SCOEL	REACH TGD default values	ECETOC
SCOEL did not modify the starting point **5 ppm**	Local effects; no time-scaling x 6.7/10 (light activity) **3.35 ppm**	Local effects; no time-scaling x 6.7/10 (light activity) **3.35 ppm**

3) Assessment factors (AF):

SCOEL	REACH TGD default values	ECETOC
	Allometric scaling: 1* Additional uncertainty: 2.5 Intraspecies (worker): 5 Exposure duration: 1 Dose-response: 1 Quality of database: 1	Interspecies: 1* Intraspecies (worker): 3 Exposure duration: 1 Dose-response: 1 Quality of database: 1
Overall factor: 1	**Overall AF: 12.5**	**Overall AF: 3**

* Inhalation experiment in animals

4) Exposure limits:

SCOEL	REACH TGD	ECETOC
IOELV **5 ppm**	Default $DNEL_{long\text{-}term\ worker\ inhalation}$ **0.27 ppm (**0.4 ppm***)**	$DNEL_{long\text{-}term\ worker\ inhalation}$ **1.1 ppm (**1.7 ppm***)**

* DNEL using default AF and relevant dose descriptor WITHOUT modification (step 2).

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Hydrogen sulphide (CAS 7783-06-4)

Comparison of IOELV, $DNEL_{long\text{-}term\ worker\ inhalation}$ using REACH TGD default AF and ECETOC AF

General remarks:

This evaluation is based on the relevant dose descriptor identified by SCOEL (SCOEL/SUM/124) and the application of default factors. No compound specific information was considered in steps 2 and 3.

1) Relevant dose descriptor as defined by SCOEL:

The critical effect identified by SCOEL is nasal lesions (olfactory neuron loss and basal cell hyperplasia) in a sub-chronic repeated-dose study in rats. The animals were exposed for 6 hours/day, 7 days/week for 10 weeks to 14, 42 and 112 mg/m^3 of H_2S and the NOAEL was 14 mg/m^3 (10 ppm).

2) Modification of starting point:

SCOEL	REACH TGD default values	ECETOC
SCOEL did not modify the starting point **10 ppm**	Local effects; no time-scaling x 6.7/10 (light activity) **6.7 ppm**	Local effects; no time-scaling x 6.7/10 (light activity) **6.7 ppm**

3) Assessment factors (AF):

SCOEL	REACH TGD default values	ECETOC
	Allometric scaling: 1* Additional uncertainty: 2.5 Intraspecies (worker): 5 Exposure duration: 3.3** Dose-response: 1 Quality of database: 1	Interspecies: 1 Intraspecies (worker): 3 Exposure duration: 1 Dose-response: 1*** Quality of database: 1
Overall factor: 2	**Overall AF: 41.25**	**Overall AF: 3**

* Inhalation experiment in animals
** No default factor for 70-day studies given but a factor of 3.3 seems appropriate based on the REACH TGD.
*** Local effects

4) Exposure limits:

SCOEL	REACH TGD default values	ECETOC
IOELV **5 ppm**	Default $DNEL_{long\text{-}term\ worker\ inhalation}$ **0.17 ppm (**0.24 ppm***)**	$DNEL_{long\text{-}term\ worker\ inhalation}$ **2.2 ppm (**3.3 ppm***)**

* DNEL using default AF and relevant dose descriptor WITHOUT modification (step 2).

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Methyl acrylate (CAS 96-33-3)

Comparison of IOELV, $DNEL_{long\text{-}term\ worker\ inhalation}$ using REACH TGD default AF and ECETOC AF

General remarks:

This evaluation is based on the relevant dose descriptor identified by SCOEL (SCOEL/SUM/46) and the application of default factors. No compound specific information was considered in steps 2 and 3.

1) Relevant dose descriptor as defined by SCOEL:

LOAEC 15 ppm; Inhalation study, rats, 2 years; local effects slight irritation on olfactory epithelium

2) Modification of starting point:

SCOEL	REACH TGD default values	ECETOC
SCOEL did not modify the starting point **15 ppm**	Local effects; no time-scaling x 6.7/10 (light activity) **10 ppm**	Local effects; no time-scaling x 6.7/10 (light activity) **10 ppm**

3) Assessment factors (AF):

SCOEL	REACH TGD default values	ECETOC
Uncertainty factor for LOAEL to NOAEL extrapolation (2) and preferred value approach. **Overall factor: 3**	Allometric scaling: 1* Additional uncertainty: 2.5 Intraspecies (worker): 5 Exposure duration: 1 Dose-response: 3** Quality of database: 1 **Overall AF: 37.5**	Interspecies: 1* Intraspecies (worker): 3 Exposure duration: 1 Dose-response: 3 Quality of database: 1 **Overall AF: 9**

* Inhalation experiment in animals

** LOAEC ≥ NOAEC; REACH TGD, Chapter R.8, p.36: *"It is suggested to use an assessment factor between 3 (as minimum/majority of cases) and 10 (as maximum/exceptional cases)."*

4) Exposure limits:

SCOEL	REACH TGD	ECETOC
IOELV **5 ppm**	Default $DNEL_{long\text{-}term\ worker\ inhalation}$ **0.27 ppm (**0.4 ppm***)**	$DNEL_{long\text{-}term\ worker\ inhalation}$ **1.1 ppm (**1.7 ppm***)**

* DNEL using default AF and relevant dose descriptor WITHOUT modification (step 2).

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Phenol (CAS 108-95-2)

Comparison of IOELV, $DNEL_{long\text{-}term\ worker\ inhalation}$ using REACH TGD default AF and ECETOC AF

General remarks:

This evaluation is based on the relevant dose descriptor identified by SCOEL (SCOEL/SUM/16) and the application of default factors. No compound specific information was considered in steps 2 and 3.

1) Relevant dose descriptor as defined by SCOEL:

SCOEL considered that repeated daily exposure to 5 ppm (20 mg/m^3) phenol would probably produce no local or systemic toxicity in experimental animals. For defining the 'critical inhalation exposure level at the workplace' the study of Sandage, (1961) in rhesus monkeys, rats and mice continuously exposed to 5 ppm (20 mg/m^3) phenol for 90 days is used as starting point. SCOEL considered local irritation as the most critical toxicological effect.

2) Modification of starting point:

SCOEL	REACH TGD default values	ECETOC
SCOEL did not modify the starting point **5 ppm**	Local effects; no time-scaling x 6.7/10 (light activity) **3.35 ppm**	Local effects; no time-scaling x 6.7/10 (light activity) **3.35 ppm**

3) Assessment factors (AF):

SCOEL	REACH TGD default values	ECETOC
Overall factor: 2	Allometric scaling: 1* Additional uncertainty: 2.5 Intraspecies (worker): 5 Exposure duration: 2 Dose-response: 1 Quality of database: 1 **Overall AF: 25**	Interspecies: 1 Intraspecies (worker): 3 Exposure duration: 1** Dose-response: 1 Quality of database: 1 **Overall AF: 3**

* Inhalation experiment in animals
** No extrapolation due to local effects

4) Exposure limits:

SCOEL	REACH TGD	ECETOC
IOELV **2 ppm**	Default $DNEL_{long\text{-}term\ worker\ inhalation}$ **0.14 ppm (**0.2 ppm***)**	$DNEL_{long\text{-}term\ worker\ inhalation}$ **1.1 ppm (**1.7 ppm***)**

* DNEL using default AF and relevant dose descriptor WITHOUT modification (step 2).

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Sulphuric acid (CAS 7664-93-9)
Comparison of IOELV, $DNEL_{long\text{-}term\ worker\ inhalation}$ using REACH TGD default AF and ECETOC AF

General remarks:
This evaluation is based on the relevant dose descriptor identified by SCOEL (SCOEL/SUM/105) and the application of default factors. No compound specific information was considered in steps 2 and 3.

1) Relevant dose descriptor as defined by SCOEL:
The critical end point identified by SCOEL was based on the observation of various effects in the respiratory tract in various species, including humans, bearing the concern for potential human carcinogenicity in mind. It was concluded that (the evidence suggested that) there was a possibility of effects (in humans) of some health significance even at concentrations down to about 0.1 mg/m³. It could be deduced that this conclusion was equivalent to the statement that the NOAEC for sulphuric acid aerosols in humans is 0.1 mg/m³.

A 28-day repeated-dose inhalation toxicity study on aerosols of sulphuric acid in the rat was identified by SCOEL as an important study. This study showed evidence of slight changes in the laryngeal epithelium (minimal metaplasia of the squamous epithelium in the absence of increased cell proliferation) following exposure at the lowest concentration tested (0.3 mg/m³). This study was used as a starting point for default DNEL calculations.

2) Modification of starting point:

SCOEL	REACH TGD default values	ECETOC
SCOEL did not modify the starting point **0.3 mg/m³**	Local effects; no time-scaling x 6.7/10 (light activity) **0.2 mg/m³**	Local effects; no time-scaling x 6.7/10 (light activity) **0.2 mg/m³**

3) Assessment factors (AF):

SCOEL	REACH TGD default values	ECETOC
	Allometric scaling: 1*	Interspecies: 1
	Additional uncertainty: 2.5	
	Intraspecies (worker): 5	Intraspecies (worker): 3
	Exposure duration: 6	Exposure duration: 1***
	Dose-response: 3**	Dose-response: 3
	Quality of database: 1	Quality of database: 1
Overall factor: 6	**Overall AF: 225**	**Overall AF: 9**

* Inhalation experiment in animals
** LOAEC ≥ NOAEC; REACH TGD, Chapter R.8, p. 36: "*It is suggested to use an assessment factor between 3 (as minimum/majority of cases) and 10 (as maximum/exceptional cases).*"
*** No extrapolation due to local effects

4) Exposure limits:

SCOEL	REACH TGD	ECETOC
IOELV **0.05 mg/m³**	Default $DNEL_{long\text{-}term\ worker\ inhalation}$ **0.0009 mg/m³** (0.0013 mg/m³*)	$DNEL_{long\text{-}term\ worker\ inhalation}$ **0.02 mg/m³** (0.03 mg/m³*)

* DNEL using default AF and relevant dose descriptor WITHOUT modification (step 2).

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Appendix B

Quantitative assessment of the time dependency of the development of local effects in the upper respiratory tract (from NTP studies)

Introduction

In the paper of Kalberlah and Schneider (1998), a quantification of extrapolation factors was made. The time dependency of the development of local effects was also included in these analyses using NTP inhalation studies with rats and/or mice; see Kalberlah and Schneider (1998) Annex 4. The evaluation by Kalberlah and Schneider does not support a default factor of 1 as proposed in ECETOC TR 86 (2003). In the latter, a clear position was taken regarding the default AF to be used for duration extrapolation for local effects, i.e. no AF below the threshold of cytotoxicity. Therefore, the Task Force decided to take a closer look at the database used by Kalberlah and Schneider.

Method

For a quantitative assessment of time dependency of the development of local effects in the upper respiratory tract, at least two studies with different study duration are needed. Local effects should be observed in these studies. So, studies with no signs of any local effects up to the highest dose level cannot be used for the determination of an AF for differences in duration of exposure. Also studies in which local effects are observed at the lowest dose level tested cannot be used, because of the absence of a clear-cut point between effects and no effects.

For 19 substances, the NTP studies were screened for local toxicity. The data used by Kalberlah and Schneider and additional details taken from the NTP study reports were summarised for each substance and test species.

Discussion and conclusion

It should be recognised that the NTP studies were performed for the purpose of assessing the carcinogenic potential in animals rather than with the aim to establish NOEL for local effects and, consequently, this has a major bearing on their value in establishing AF for time extrapolation for local effects. Typically, the level of investigation (number of animals or concentration levels studied, range of local target tissues evaluated and histopathological investigation) as well as the level of detail reported was greatest in chronic NTP studies, and particularly for those chemicals where local effects (irritancy and hyperplasia) were suspected to play a role in the carcinogenic mechanism. In the case of sub-chronic studies, the extent of investigation was often more limited than in the chronic study and focused primarily on establishing the concentration range for systemic and local effects. In marked contrast, the extent of investigation and/or reporting of local effects in the sub-acute studies was extremely limited, if at all. This may not be surprising considering the aim of these studies, i.e. to identify target organs and set concentration levels for the subsequent 90-day studies. The different study aims, concentration ranges and level of

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investigation between the studies prevent any meaningful direct comparison between many of the studies. The number of studies remaining that could be used in this regard is possibly too limited to draw any firm conclusions regarding AF. It was noted that in several of the NTP reports on chronic studies background infections might have confounded the LOEL/NOEL for local effects in longer duration studies, particularly in the rat nose.

During the review, no literature searches were conducted for the substances included in the NTP analysis. In two cases, the reviewers were aware of additional studies that were critical to the assessment and these are included for completeness.

Table B: Overview on evaluation of NTP studies (references see tables on the individual studies)

Substance	CAS no.	Rat	Mouse	Comments
1,2-Dibromo-3-chloro-propane	96-12-8	NOEC not determined.	NOEC not determined.	Effects at all concentrations. No dose response from either study.
1,2-Dibromo-ethane	106-93-4	NOEC not determined.	NOEC not determined.	No comparable NOECs. Uncertainty over sensitivity of sub-chronic study.
Propylene oxide	75-56-9	NOEC confounded by infection.	$AF_{sub\text{-}chronic/chronic}$ >= 2.	Rat chronic NOEC confounded by infection.
1,3- Butadiene	106-99-0	No studies.	Local effects only observed in the presence of overwhelming systemic toxicity.	AF may be compromised by systemic toxicity.
Dichloromethane	75-09-2	Only NOEC for local effects in chronic study.	No local effects.	
Perchloroethylene	127-18-4	Insufficient histopathology in sub-chronic study; chronic NOAEL confounded by infection.	No local effects.	Insufficient data to draw any conclusion on time extrapolation.
Methyl methacrylate	80-62-6	NOEC not determined.	NOEC not determined.	Additional studies support $AF_{acute/chronic}$ 1.
Ethylene oxide	75-21-8	No studies.	Insufficient data to make comparison with sub-acute study.	Comparison of suchronic and chronic data support an AF =1.
1,2-Epoxybutane	106-88-7	Not clear due to infection.	NOEC not determined.	Insufficient data to draw any conclusion on time extrapolation.
Chloroethane	75-00-3	No local effects.	No local effects.	Insufficient data to draw any conclusion on time extrapolation.
Bromoethane	74-96-4	Not clear due to infection.	Not clear due to infection.	Insufficient data to draw any conclusion on time extrapolation.

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Substance	CAS no.	Rat	Mouse	Comments
Vinyl toluene	25013-15-4	Different local effects and NOEC precluding direct comparison.	NOEC not determined.	Insufficient data to make comparison in rat. No comparable NOEC in mouse.
Toluene	108-88-3	Nasal tissues not studied in sub-chronic study.	No local effects.	Insufficient data to make comparison in rat. No local effects in mouse.
Allyl glycidyl ether	106-92-3	NOEC not determined.	NOEC not determined.	Insufficient data to make comparison.
O-Chlorobenzal-malonitrile	2698-41-1	NOEC not determined.	$AF_{sub\text{-}chronic/chronic}$ 2.	Insufficient data to make comparison.
2-Chloro-acetophenone	532-27-4	Nasal tissues may not have been studied in sub-acute and sub-chronic studies. Chronic LOEC confounded by infection.	Nasal tissues may not have been studied in sub-acute and sub-chronic studies.	Insufficient data to make comparison.
1-Epinephrine hydrochloride	55-31-2	NOEC not determined.	NOEC not determined.	Insufficient data to make comparison.
Methyl bromide	74-83-9	No studies available.	No local effects in sub-acute and sub-chronic study; no chronic study available.	Insufficient data to make comparison.
Tetranitromethane	509-14-8	Not clear due to infection.	Not clear due to infection.	Insufficient data to make comparison.

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1,2-Dibromo-3-chloro-propane (CAS 96-12-8)

Summary of rat studies in NTP report 206

Key data extracted from Kalberlah and Schneider (1998), table 1a (figures in ppm)

Subacute study	Subchronic study	Chronic study
$NOEC_{local}$ target: n.p.	$NOEC_{local}$ target: 5 lung	$NOEC_{local}$ target: (0.6) nose
$NOEC_{systemic}$ target: n.p.	$NOEC_{systemic}$ target: (1) kidney, liver, b.w.	$NOEC_{systemic}$ target: (0.6) spleen

values in brackets ( ) represents LOAEL; n.p.= not performed; b.w. = change in body weight;
u.s. = unspecified symptoms; -- = no effects observed

Study details of NTP report 206

Subacute study	Subchronic study	Chronic study
	rats (F344) male/female 1, 5, 25 ppm Exposure: 6 hours/day, 5 days/week, 13 weeks Histopathology: lungs, trachea, nasal cavity and sinuses (all killed animals). Not clear of special processing and step cuts were performed.	rats (F344) male/female 0.6, 3.0 ppm Exposure: 6 hours/day, 5 days/week, 76-103 weeks Histopathology: lungs, trachea, nasal cavity and sinuses (all killed animals). Including special processing was conducted with step cuts from the nostril to the cranial vault to ensure adequate tissue sampling and visualization of the extent of tumour.
	The severity and incidence of histopathological changes of nasal cavity were dose related. Necrosis and squamous metaplasia of olfactory, tracheal, and bronchial epithelium were present in the animals receiving 25 ppm. Not clearly stated effects at 1 and 5 ppm. However, states the severity of the proliferative lesions in the epithelium of the nasal cavity of high-dose animals was dose related suggesting effects were present at lower concentrations. $LOEC_{local}$ not indicated.	Dose related increased numbers of cancers in the nasal cavity, tongue, pharynx, larynx, and kidney at both concentrations. In both low-dose and high-dose groups of male and female rats, the combined incidences of nasal tumours were significant at the P<0.001 level. Increase in acute inflammation (males:0/50, 1/50 and 4/50: females 2/50, 1/50 and 7/50), chronic inflammation (males:0/50, 1/50 and 0/50: females 0/50, 0/50 and 6/50) focal hyperplasia (males:0/50, 31/50 and 1/50; females 0/50, 24/50 and 23/50), lung inflammation (males: 0/50, 3/50 and 4/50: females 0/50, 0/50 and 1/50) and chronic pneumonitis (males:5/50, 3/50 and 1/50: females 2/50, 2/50 and 5/50). $LOEC_{local}$ 0.6 ppm.
	NTP (1982a)	NTP (1982a)

Local effects:

As data are lacking for sub-acute exposure, the data can only be used to assess the time dependency of the development of local effects from sub-chronic to chronic exposure. In both studies, effects were observed at the lowest concentration and no NOEC was established. In the chronic study, chronic pneumonitis may have contributed to the effects observed and the

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indicated LOEC. Therefore, the data cannot be used for a quantitative assessment of time dependency for the development of local effects.

Summary of mouse studies in NTP report 206

Key data extracted from Kalberlah and Schneider (1998), table 1a (figures in ppm)

Subacute study	Subchronic study	Chronic study
$NOEC_{local}$ target: n.p.	$NOEC_{local}$ target: 1 lung, nose	$NOEC_{local}$ target: (0.6) lung, nose
$NOEC_{systemic}$ target: n.p.	$NOEC_{systemic}$ target: 1 liver, b.w.	$NOEC_{systemic}$ target: (0.6) stomach

values in brackets ( ) represents LOAEL; n.p.= not performed; b.w. = change in body weight;
u.s. = unspecified symptoms; -- = no effects observed

Study details of NTP report 206

Subacute study	Subchronic study	Chronic study
	mice (B6C3F1) male/female 1, 5, 25 ppm Exposure: 6 hours/day, 5 days/week, 13 weeks Histopathology: lungs, trachea, sinuses and nasal cavity but it is not clear if they performed serial sections of the nasal cavity and turbinates (all killed animals).	mice (B6C3F1) male/female 0.6, 3.0 ppm Exposure: 6 hours/day, 5 days/week, 76-103 weeks. Histopathology: lungs, trachea, nasal cavity and sinuses (all killed animals).
	The severity and incidence of histopathological changes of nasal cavity were dose related. Necrosis of the bronchiolar epithelium was found in both male and female mice exposed to 25 ppm. Additional subsequent pathologic examinations revealed lesions in the epithelium of the nasal cavity of mice exposed to 25 ppm. Regeneration and hyperplasia of the bronchiolar epithelium and megalocytic epithelial cells were found in all 20 of the mice exposed to 5 ppm. $NOEC_{local}$ 1 ppm.	Dose-related increase in the incidence of nasal cavity tumours and respiratory tract tumours in male and female mice. NOEC 0.6 ppm. Non neoplastic lesions: inflammation and hyperplasia of the nasal mucosa and related structures, multifocal hyperplasia in the lungs. Increase in serous inflammation (females: 0/50, 4/50, 4/50), suppurative inflammation (males: 1/50, 1/50 and 1/50: females 0/50, 5/50 and 13/50), focal hyperplasia (males:0/50, 0/50 and 1/50; females: 0/50, 17/50 and 3/50), lung hyperplasia (males: 0/50, 2/50 and 7/50: females 0/50, 5/50 and 11/50) and chronic pneumonitis (males:5/50, 3/50 and 1/50: females 0/50, 2/50 and 2/50). $NOEC_{local}$ 0.6 ppm.
	NTP (1982a)	NTP (1982a)

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Local effects:

As data are lacking for sub-acute exposure, the data can only be used to assess the time dependency of the development of local effects from sub-chronic to chronic exposure. In the chronic study, chronic pneumonitis may have contributed to the effects observed and the indicated NOEC/LOEC. Therefore, the data cannot be used for a quantitative assessment of time dependency for the development of local effects.

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1,2-Dibromo-ethane (CAS 106-93-4)

Summary of rat studies in NTP report 210

Key data extracted from Kalberlah and Schneider (1998), table 1a (figures in ppm)

Subacute study	Subchronic study	Chronic study
$NOEC_{local}$ target: n.p.	$NOEC_{local}$ target: 75 --	$NOEC_{local}$ target: (10) nose, lung
$NOEC_{systemic}$ target: n.p.	$NOEC_{systemic}$ target: (3) b.w.	$NOEC_{systemic}$ target: (10) liver

values in brackets ( ) represents LOAEL; n.p.= not performed; b.w. = change in body weight;
u.s. = unspecified symptoms; -- = no effects observed

Study details of NTP report 210

Subacute study	Subchronic study	Chronic study
	rat (Fischer 344) male/female 3, 15 and 75 ppm Exposure: 13 weeks, 5 days/week, 6 hours/day. Histopathology of local effects included lungs, trachea, nasal cavity and sinuses. It was stated that representative tissues were examined microscopically as described in the section on chronic studies but no details were given.	rat (Fischer 344) male/female: 10 and 40 ppm Exposure: 88-103 weeks, 5 days/week, 6 hours/day. Histopathology of local effects included lungs, trachea, nasal cavity and sinuses. Including special processing was conducted with step cuts from the nostril to the cranial vault to ensure adequate tissue sampling and visualization of the extent of tumour.
	Apart from depression in weight gain, swelling and/or vacuolation of the adrenal cortical cells of the zona fasciculata were detected in 8/10, and slight decreases in follicular size in the thyroid were found in 6/10 animals at 75 ppm. No local effects observed.	Significantly increased incidence of tumours of the nasal cavity in 10 and 40 ppm dose rats. Lung tumours in high-dose female rats. Increase in serous inflammation (males: 0/50, 2/50 and 1/50: females 0/50, 4/50 and 1/50), suppurative inflammation (males: 0/50, 8/50 and 20/50: females 0/50, 1/50 and 15/50), chronic inflammation (males:2/50, 1/50 and 0/50: females 0/50, 2/50 and 1/50) and hyperplasia (males: 0/50, 38/50 and 25/50; females 0/50, 27/50 and 31/50). $NOEC_{local}$ 10 ppm.
	NTP (1982b)	NTP (1982b)

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Additional key studies not addressed in analysis include:

Subacute study	Subchronic study	Chronic study
n.a.	$NOEC_{local}$ target	n.a.
	rat (Fischer 344) male/female 23, 78 and 312 mg/m^3 (3, 10 and 40 ppm). Vehicle: inhalation (no vehicle) Exposure: 6 hours/day, 5 days/week for 13 weeks.	
	NOEC (local): (male/female) 3 ppm. Hyperplasia and necrosis of nasal and bronchial epithelium at 10 and 40 ppm.	
	Nitschke *et al* (1981)	

Local effects:

Data are lacking for sub-acute exposure. In the chronic study, local effects were observed at the lowest concentration. A NOEC was not established. In the NTP sub-chronic study, no local effects were seen up to the highest dose level tested. In the NTP chronic study, tumours were observed at 10 and 40 ppm but no local effects were reported up to the highest concentration of 75 ppm. However, in a further sub-chronic study by Nitsche and co-workers, a NOEC for local effects was observed at 3 ppm with a LOEC at 10 ppm indicting comparable sensitivity of the tissue after sub-chronic and chronic exposure. On balance, the data should not be used for a quantitative assessment of time dependency for the development of local effects.

Summary of mouse studies in NTP report 210

Key data extracted from Kalberlah and Schneider (1998), table 1a (figures in ppm)

Subacute study	Subchronic study	Chronic study
$NOEC_{local}$ target: n.p.	$NOEC_{local}$ target: 15 lung	$NOEC_{local}$ target: (10) lung
$NOEC_{systemic}$ target: n.p.	$NOEC_{systemic}$ target: (3) b.w.	$NOEC_{systemic}$ target: (10) prostata

values in brackets ( ) represents LOAEL; n.p.= not performed; b.w. = change in body weight;
u.s. = unspecified symptoms; -- = no effects observed

Study details of NTP report 210

Subacute study	Subchronic study	Chronic study
	mice (B6C3F1) male/female 3, 15 and 75 ppm Exposure: 13 weeks, 5 days/week, 6 hours/day. Histopathology of local effects included lungs, trachea, nasal cavity and sinuses. It was stated that representative tissues were examined	mice (B6C3F1) male/female 10 and 40 ppm Exposure: 78-103 weeks, 5 days/week, 6 hours/day. Histopathology of local effects included lungs, trachea, nasal cavity and sinuses. Including special processing was conducted with step

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Subacute study	Subchronic study	Chronic study
	microscopically as described in the section on chronic studies.	cuts from the nostril to the cranial vault to ensure adequate tissue sampling and visualization of the extent of tumour.
	4/10 male mice exposed to 3 ppm died and 1/10 female mice exposed to 75 ppm died. Eye irritation was observed during weeks 12 and 13 at 75 ppm. Megalocytic cells found lining the bronchioles in 3/10 male mice and 9/10 female mice at 75 ppm. No other local effects reported.	Significantly increased incidence of lung tumours in 40 ppm mice. Tumours of the nasal cavity in female mice at 40 ppm. Increase in serous inflammation (males: 0/50, 15/50 and 22/50: females 0/50, 19/50 and 14/50), suppurative inflammation (males: 0/50, 3/50 and 22/50: females 0/50, 4/50 and 20/50) and hyperplasia (females 0/50, 0/50 13/50). $LOEC_{local}$ 10 ppm.
	NTP (1982b)	NTP (1982b)

Local effects:

Data are lacking for sub-acute exposure. A NOEC of 15 ppm with effects at the next highest concentration of 75 ppm was established in a sub-chronic study. In the chronic study, local effects were observed at the lowest concentration (10 ppm). A NOEC was not established. From the prevalence of effects in the chronic study it would have been expected to see local effects in up to 3 animals whereas no local effects were observed other than megalocytic cells in the bronchioles at 75 ppm. This appears to indicate that an AF for study duration of at least 7.5 is appropriate. However, this situation is mirrored in the NTP studies in rats with this chemical. In rats, however, the study by Nitsche and co-workers, using the same protocol and strain of rat as in the NTP study, pointed to the NTP sub-chronic study being insensitive. As these studies were conducted at the same time and in the same laboratory with essentially the same protocol, it must be concluded that uncertainty exists whether the power of the sub-chronic study is sufficient to assess the time dependency of the development of local effects from sub-chronic to chronic exposure in a quantitative way.

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Propylene oxide (CAS 75-56-9)

Summary of rat studies in NTP report 267

Key data extracted from Kalberlah and Schneider (1998), table 1a (figures in ppm)

Subacute study	Subchronic study	Chronic study
$NOEC_{local}$ target: 1433 --	$NOEC_{local}$ target: 500 --	$NOEC_{local}$ target: (200) nose
$NOEC_{systemic}$ target: 487 b.w., u.s.	$NOEC_{systemic}$ target: 500 --	$NOEC_{systemic}$ target: 200 b.w.

values in brackets ( ) represents LOAEL; n.p.= not performed; b.w. = change in body weight;
u.s. = unspecified symptoms; -- = no effects observed

Study details of NTP report 267

Subacute study	Subchronic study	Chronic study
Rats (F344/N) 5 male/ 5 female: 0, 47.2, 98.5, 196, 487 and 1433 ppm Exposure: 6 hours/day, 5 days/week for 2 weeks. Necropsy on all animals; no histopathology.	Rats (F344/N) 10 male/ 10 female: 0, 31, 63, 125, 250 and 500 ppm Exposure: 6 hours/day, 5 days/week for 13 weeks. Necropsy on all animals; histopathology on controls and high dose group plus animals that died prior to final kill.	Rats (F344/N) 50 male/ 50 female: 0, 200 and 400 ppm Exposure: 6 hours/day, 5 days/week for 99 weeks. Necropsy and histopathology on all animals.
One high-dose rat died; severe weight loss at highest dose level in both male and female rats; severe weight loss in highest dose group rats (both males and females) and some weight loss in all. No local effects observed.	Apart from some body weight loss in high dose animals, no effects observed (including nasal turbinates).	No $NOEC_{local}$ identified. Rats: LOAEC: 200 ppm (male/female) Primary target tissue: nasal cavity. Local effects in rats: Increase in suppurative inflammation of the nasal cavity (males: 9/50, 21/50 and 38/50: females 3/50, 5/50 and 23/50) at 0, 200 and 400 ppm, respectively. Increase in epithelial hyperplasia (males: 0/50, 1/50, and 11/50; females 1/50, 0/48 and 5/48). Squamous metaplasia (males:1/50, 3/50, 21/50; females 1/50, 2/48 and 11/48).
NTP (1985)	NTP (1985)	NTP (1985)

Local effects:

In the acute and sub-chronic studies, local effects are not the most sensitive endpoints. No histopathology was done on the acute study and only on the 500 ppm group in the sub-chronic study. 500 ppm appeared to be a NOEC in the sub-chronic study. The concentrations in the chronic study were not selected to develop dose-response for local effects. The NOEC of 200 ppm for local effects, i.e. hyperplasia in the chronic study, is not reliable due to background respiratory infection in these animals as evidenced by suppurative inflammation and squamous metaplasia of the nasal cavity in the test and control animals. Although there is evidence of a

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concentration-response relationship a NOEC/LOEC cannot be reliably determined. Hence, the data cannot be used to quantitatively assess the time dependency of the development of local effects.

Summary of mouse studies in NTP report 267

Key data extracted from Kalberlah and Schneider (1998), table 1a (figures in ppm)

Subacute study	Subchronic study	Chronic study
$NOEC_{local}$ target: 487 --	$NOEC_{local}$ target: 500 --	$NOEC_{local}$ target: (200) nose
$NOECs_{systemic}$ target: 98.5 u.s.	$NOEC_{systemic}$ target: 250 b.w.	$NOEC_{systemic}$ target: 200 b.w.

values in brackets ( ) represents LOAEL; n.p.= not performed; b.w. = change in body weight; u.s. = unspecified symptoms; -- = no effects observed

Study details of NTP report 267

Subacute study	Subchronic study	Chronic study
Mice (B6C3F1) 5 male/ 5 female: 0, 20.1, 47.2, 98.5, 196, and 487 ppm. Exposure: 6 hours/day, 5 days/week for 2 weeks. Necropsy on all animals; no histopathology.	Mice (B6C3F1) 10 male/ 10 female: 0, 31, 63, 125, 250 and 500 ppm. Exposure: 6 hours/day, 5 days/week for 13 weeks. Necropsy on all animals; histopathology on controls and high dose group plus animals that died prior to final kill.	Mice (B6C3F1) 50 male/ 50 female: 0, 200 and 400 ppm. Exposure: 6 hours/day, 5 days/week for 99 weeks. Necropsy and histopathology on all animals.
No exposed mice died, some weight loss in high dose group male mice and all but lowest dose group female mice. No local effects observed.	$NOEC_{local}$ 500 ppm. Apart from some body weight loss in high dose animals, no effects observed (including nasal turbinates).	$LOEC_{local}$: 200 ppm (male/female) no effects observed other than effects on nasal cavity. (Survival statistically significant decreased at 400 ppm. B.W. decreased at 400 ppm (10% for females and 22 % for males). Local effects in mice: • Hyperplasia and metaplasia sporadically observed at 400 ppm; more pronounced in the anterior part of the nasal cavity. • Inflammation of the nasal cavity males : 1/50, 14/50, and 38/50; females 0/50, 14/50 and 18/50) at 0, 200 and 400 ppm respectively.
NTP (1985)	NTP (1985)	NTP (1985)

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Local effects:

In the acute and sub-chronic studies, local effects are not the most sensitive endpoints. No histopathology was done on the acute study and only on the 500 ppm group in the sub-chronic study. 500 ppm appeared to be a NOEC in the sub-chronic study. The concentrations in the chronic study were not selected to develop dose-response for local effects. The NOEC of 200 ppm for local effects in the chronic study was based on inflammation of the nasal cavity. Hence, the data possibly support an AF of at least 2 between sub-chronic and chronic.

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1,3-Butadiene (CAS 106-99-0)

Summary of mouse studies in NTP report 288/434

Key data extracted from Kalberlah and Schneider (1998), table 1a (figures in ppm)

Subacute study	Subchronic study	Chronic study
$NOEC_{local}$ target: 8000 --	$NOEC_{local}$ target: 8000 --	$NOEC_{local}$ target: 625 nose
$NOEC_{systemic}$ target: 2500 b.w.	$NOEC_{systemic}$ target: 1250 b.w.	$NOEC_{systemic}$ target: (6.25) sex organs, heart

values in brackets ( ) represents LOAEL; n.p.= not performed; b.w. = change in body weight;
u.s. = unspecified symptoms; -- = no effects observed

Study details of NTP report 288/434

Subacute study	Subchronic study	Chronic study
mice (B6C3F1) male/female (5/sex/dose) 0, 625, 1250, 2500, 5000, 8000 ppm Exposure: 6 hours/day, 5 days/week, 2 weeks. Histopathology (all animals): trachea, lungs and bronchi, nasal cavity, nasal turbinates.	mice (B6C3F1) male/female (10/sex/group) 0, 625, 1250, 2500, 5000, 8000 ppm Exposure: 6 hours/day, 5 days/week, 64 or 63 exposures. Histopathology (control, 8000 ppm dose, early deaths): trachea, lungs and bronchi, nasal cavity, nasal turbinates.	mice (B6C3F1) male/female 1st study: 50/sex/dose 2nd study: 70/sex/dose; 90/sex/dose (625 ppm). 1st study: 0, 625, 1250 ppm: 50/sex/dose: Exposure: 6 hours/day, 5 days/week, 60 (males) and 61 (females) weeks 2nd study: 0, 6.25, 20, 62.5, 200, 625 ppm 6.25 to 200 ppm gas 70 mice/sex/dose and 625 ppm: 90 mice/sex/dose (10 animals/sex/dose were terminated at 9 and 15 months). Histopathology (all animals): trachea, lungs and bronchi, nasal cavity, nasal turbinates (3 sections).
Survival unaffected. No pathologic effects. Slight decrease at mean body weight at highest dose.	Survival decreased in 5000 and 8000 ppm groups (males). Decreased mean body weight No local effects observed.	1st study: Study duration from 103 $\geq$ 60 and 61 weeks due to rapidly declining survival. Lesions of the nasal cavity occurred in mice exposed at 1,250 ppm: chronic inflammation (male, 35/50; female, 2/49); fibrosis (male, 35/50; female, 2/49); cartilaginous metaplasia (male, 16/50; female, 1/49); osseous metaplasia (male, 11/50; female, 2/49); and atrophy of the sensory epithelium (male, 32/50). No nonneoplastic lesions of the nasal cavity were found in the controls or low-dose animals. 2nd study: Systemic toxicity: Females: No female exposed to 200 or 625 ppm or male exposed to 625 ppm survived to the end of the study. Survival decreased at 20 ppm and above.

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Subacute study	Subchronic study	Chronic study
		Lung toxicity: Alveolar epithelial hyperplasia was increased in males at 625 ppm after 9 and 15 months. Positive trend in 2 years study at 62.5 ppm and higher.
NTP (1984)	NTP (1984)	NTP (1984, 1993)

Local effects:

No local effects were observed in the sub-acute and sub-chronic studies up to the highest concentrations tested, although histopathology was only performed on the animals of the 8000 pm group and there was reduced survival at this concentration. The observation of local effects in the chronic study at concentrations where no effects were observed in the sub-chronic study indicated that a time-extrapolation factor (of at least 10) might be warranted. However, since all animals were dying during the course of the chronic study, the fact that local effects were observed at concentrations 100-fold higher than the NOEC for survival suggests that these animals may have been compromised and that the $NOEC_{local}$ might be unreliable.

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Dichloromethane (CAS 75-09-2)

Summary of rat studies in NTP report 306

Key data extracted from Kalberlah and Schneider (1998), table 1a (figures in ppm)

Subacute study	Subchronic study	Chronic study
$NOEC_{local}$ target: 16000 --	$NOEC_{local}$ target: 2100 --	$NOEC_{local}$ target: 2000 nose
$NOEC_{systemic}$ target: 3250 u.s.	$NOEC_{systemic}$ target: 2100 liver	$NOEC_{systemic}$ target: (1000) liver

values in brackets ( ) represents LOAEL; n.p.= not performed; b.w. = change in body weight; u.s. = unspecified symptoms; -- = no effects observed

Study details of NTP report 306

Subacute study	Subchronic study	Chronic study
rat (Fischer 344) male/female 1625, 3250, 6500, 13000, 16000 ppm Exposure: 11 exposures, 6 hours/day. Complete necropsy performed on all animals; tissues were not examined histologically.	rat (Fischer 344) male/female 525, 1050, 2100, 4200, or 8400 ppm Exposure: 13 weeks (5 days/week, 6 hours/day) Complete histologic exam performed on high dose and controls; lower dose groups examined to determine no-effect level.	rat (Fischer 344) male/female: 1000, 2000, 4000 ppm. Exposure: 2 years, 6 hours/day, 5 days/week. Histopathology (all animals): trachea, lungs and bronchi, nasal cavity, nasal turbinates (3 sections).
No histopathology performed.	Foreign body pneumonia (focal accumulation of mononuclear and multinucleated inflammatory cells) was present in 4/10 males and 6/10 females exposed at 8,400 and in 1/10 females exposed at 4,011 ppm. $NOEC_{local}$ Not established.	Squamous metaplasia was observed at an increased incidence at 4000 ppm. female rats; (male: control, 4/50, 8%; low dose, 5/50, 10%; mid dose, 3/50, 6%; high dose, 3/50, 6%; female: control, 1/50,2%; low dose, 2/50, 4%; mid dose, 3/50,6%; high dose, 9/50,18%). $NOEC_{local}$ 2000 ppm.
NTP (1986a)	NTP (1986a)	NTP (1986a)

Local effects:

In the sub-chronic study foreign body pneumonia was observed at higher doses, rendering them sensitive to local effects. Consequently, this study cannot be used to derive a reliable NOEC. The only local effect observed in the chronic study was a slight increase in incidences of squamous metaplasia in the nasal cavity at 4000 ppm in female rats with a NOEC of 2000 ppm in the two-year studies.

Due to the foreign body pneumonia reported in the sub-chronic study, the NTP studies in rats cannot be used for the assessment of time dependency of the development of local effects in the upper respiratory system.

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Summary of mouse studies in NTP report 306

Key data extracted from Kalberlah and Schneider (1998), table 1a (figures in ppm)

Subacute study	Subchronic study	Chronic study
$NOEC_{local}$ target: 16000 --	$NOEC_{local}$ target: 8400 --	$NOEC_{local}$ target: (2000) lung
$NOEC_{systemic}$ target: (1625) lethality	$NOEC_{systemic}$ target: 2100 liver	$NOEC_{systemic}$ target: 2000 liver

values in brackets ( ) represents LOAEL; n.p.= not performed; b.w. = change in body weight;
u.s. = unspecified symptoms; -- = no effects observed

Study details of NTP report 306

Subacute study	Subchronic study	Chronic study
mice (B6C3F1) male/female 1625, 3250, 6500, 13000, 16000 ppm Exposure: 14 exposures, 6 hours/day. Complete necropsy performed on all animals; tissues were not examined histologically.	mice (B6C3F1) male/female 525, 1050, 2100, 4200, 8400 ppm Exposure: 13 weeks (5 days/week, 6 hours/day) Complete histologic exam performed on high dose and controls; lower dose groups examined to determine no-effect level.	mice (B6C3F1 male/female: 2000, 4000 ppm. Exposure: 2 years, 6 hours/day, 5 days/week. Histopathology (all animals): trachea, lungs and bronchi, nasal cavity, nasal turbinates (3 sections).
No histopathology performed.	No clinical or histopathological findings reported.	Incidences of alveolar/bronchiolar adenomas in both male and female mice. No other histopathological findings.
NTP (1986a)	NTP (1986a)	NTP (1986a)

Local effects:

An increased incidence of alveolar/bronchial adenomas and carcinomas of the lung was observed in both male and female mice. No local effects of the upper respiratory tract were reported. Hence, the NTP studies in mice add little to the assessment of time dependency of the development of local effects in the upper respiratory system.

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Perchloroethylene (CAS 127-18-4)

Summary of rat studies in NTP report 311

Key data extracted from Kalberlah and Schneider (1998), table 1a (figures in ppm)

Subacute study	Subchronic study	Chronic study
$NOEC_{local}$ target: 1750 --	$NOEC_{local}$ target: 800 lung	$NOEC_{local}$ target: 400 --
$NOEC_{systemic}$ target: 875 u.s.	$NOEC_{systemic}$ target: 100 liver	$NOEC_{systemic}$ target: (200) kidney

values in brackets ( ) represents LOAEL; n.p.= not performed; b.w. = change in body weight;
u.s. = unspecified symptoms; -- = no effects observed

Study details of NTP report 311

Subacute study	Subchronic study	Chronic study
rat (Fischer 344) male/female 100, 200, 425, 875, 1750 ppm Exposure: 14 exposures, 6 hours/day. Necropsy performed on all animals; Histopathology of local effects include: lungs and bronchi and nasal cavity.	rat (Fischer 344) male/female 100, 200, 400, 800, or 1600 ppm Exposure: 13 weeks (5 days/week, 6 hours/day). Necropsy performed on all animals; Histopathology was performed on *control and high dose groups*; tissues of local effects include: larynx, trachea, lungs, bronchi, and nasal cavity but it is not clear if they performed serial sections of the nasal cavity and turbinates. 800 ppm lungs and bronchi.	rat (Fischer 344) male/female: 200, 400 ppm. Exposure: 2 years, 6 hours/day, 5 days/week. Necropsy performed on all animals; Histopathology of local effects include: trachea, lungs and mainstem bronchi, nasal cavity and nasal turbinates.
No clinical or histopathological findings reported. $NOEC_{local}$: 1750 ppm	Four of 10 male and 7/10 female rats exposed at 1,600 ppm died before the end of the studies. Lung congestion was observed in rats exposed at 1,600 ppm (Congestion was most severe in animals that died before the end of the studies.) Histopathology was done only at the high does group with high mortality. $NOEC_{local}$ cannot be derived due to the lack of histopathologic data at the lower dose groups.	Increase in the incidence of squamous metaplasia in the nasal cavities in dosed male rats (male: 0/50; 5/50, 5/50; female: 2/50, 4/50, 2/50). $NOEC_{local}$ Not established due to background respiratory infection.
NTP (1986b)	NTP (1986b)	NTP (1986b)

Local effects:

No local effects were reported in the sub-acute study and no histopathology data are mentioned in the result section of the study report. Hence, it is not reliable to assume that 1750 ppm is a NOEC for local effects. In the sub-chronic study, no local effects were reported other than lung congestion at 1600 ppm. Since full histopathology was done only at the high-dose group (4/10 male and 7/10 female rats exposed at 1,600 ppm died before the end of the studies) no reliable information on local effects is available from this study. Hence, no $NOEC_{local}$ can be defined in this study. In the two-year studies, the only local effect observed was a slight increase in incidences of squamous metaplasia in the nasal cavity of the 200 and 400 ppm exposed male rats. Since this effect is not dose-dependent and squamous metaplasia is also observed in control

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females, it is questionable if squamous metaplasia in the nasal cavities in males should be regarded as a compound-related adverse effect. As squamous metaplasia in the nasal cavity is often observed in animals with background respiratory infection, this NOEC may be unreliable.

Squamous metaplasia in the nasal cavities was the only local effect observed in the chronic study. Since the histopathology performed in the sub-chronic study included nasal cavity only in the high-dose group (with high mortality and, consequently, only limited value for investigation of local effects) but not at the next lower dose, no information on the potential target organ nasal cavities can be drawn from the sub-chronic study. Hence, the NTP studies in rats cannot be used for a quantitative assessment of time dependency of the development of local effects in the upper respiratory system.

Summary of mouse studies in NTP report 311

Key data extracted from Kalberlah and Schneider (1998), table 1a (figures in ppm)

Subacute study	Subchronic study	Chronic study
$NOEC_{local}$ target: 1750 --	$NOEC_{local}$ target: 1600 --	$NOEC_{local}$ target: 200 --
$NOEC_{systemic}$ target: 425 liver	$NOEC_{systemic}$ target: 200 kidney	$NOEC_{systemic}$ target: (100) kidney

values in brackets ( ) represents LOAEL; n.p.= not performed; b.w. = change in body weight;
u.s. = unspecified symptoms; -- = no effects observed

Study details of NTP report 311

Subacute study	Subchronic study	Chronic study
mice (B6C3F1) male/female 100, 200, 425,875.1750 ppm Exposure: 14 exposures, 6 hours/day. Necropsy performed on all animals; Histopathology of local effects include: lungs and bronchi and nasal cavity.	mice (B6C3F1) male/female 100, 200, 400, 800, 1600 ppm Exposure: 13 weeks (5 days/week, 6 hours/day) Necropsy performed on all animals; Histopathology was performed on *control and high dose groups*; tissues of local effects include: larynx, trachea, lungs, bronchi, and nasal cavity but it is not clear if they performed serial sections of the nasal cavity and turbinates. Histopathology	mice (B6C3F1 male/female: 100, 200 ppm. Exposure: 2 years, 6 hours/day, 5 days/week. Necropsy performed on all animals; Histopathology of local effects include: trachea, lungs and mainstem bronchi, nasal cavity and nasal turbinates.
No clinical or histopathological findings	No clinical or histopathological findings	Acute passive congestion was observed at increased incidences in dosed mice (male: control, 1/49; low dose, 8/49; high dose, 10/50; female: 1/48; 5/50; 6/50)
NTP (1986b)	NTP (1986b)	NTP (1986b)

Local effects:

No local effects were observed with perchloroethylene. Hence, the NTP studies in mice add little to the assessment of time dependency of the development of local effects in the upper respiratory system.

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Methyl methacrylate (CAS 80-62-6)

Summary of rat studies in NTP report 314

Key data extracted from Kalberlah and Schneider (1998), table 1a (figures in ppm)

Subacute study	Subchronic study	Chronic study
$NOEC_{local}$ target: 5000 --	$NOEC_{local}$ target: 2000 nose	$NOEC_{local}$ target: (250/500) nose
$NOEC_{systemic}$ target: (500) b.w., u.s.	$NOEC_{systemic}$ target: (1000) brain, bone marrow	$NOEC_{systemic}$ target: 250 bone marrow

values in brackets ( ) represents LOAEL; n.p.= not performed; b.w. = change in body weight;
u.s. = unspecified symptoms; -- = no effects observed

Study details of NTP report 314

Subacute study	Subchronic study	Chronic study
rat (Fischer 344) male/female 500, 1000, 2000, 3000 and 5000 ppm corresponding to ca. 2.05, 4.1, 8.2, 12.3 and 20.5 mg/L, respectively). Exposure: 10 exposures (over 11 days), 6 hours/day. No histopathology on rats.	rat (Fischer 344) male/female 500, 1000, 2000, 3000 and 5000 ppm Exposure: 13 weeks (5 days/week, 6 hours/day) equivalent or similar to OECD Guideline 412 (Repeated Conc Inhalation Toxicity: 28/14-days). Histopathology of nasal turbinates (no serial sections), larynx, trachea, lungs. Other 90 day study: 63, 125, 250, 500, 1000 ppm not included as confirmatory.	rat (Fischer 344) male/female: male 500 and 1000 ppm; female 250 and 500 ppm. Exposure: 2 years, 6 hours/day, 5 days/week. Histopathology of local effects included nasal turbinates (no serial sections), larynx, trachea, lungs.
No histopathology NOEC relates to clinical observations only.	$NOEC_{local}$ 1000 ppm $LOEC_{local}$ 2000 ppm	$NOEC_{local}$ Not established Serous and suppurative inflammation of nasal cavity and olfactory degeneration (incidence 39/50) in both male and female rats at the lowest concentrations tested (males: 500 ppm and females; 250 ppm).
NTP (1986c)	NTP (1986c)	NTP (1986c)

Additional key studies not addressed in analysis include:

Acute	Subacute study	Chronic study
$NOEC_{local}$ target	$NOEC_{local}$ target	$NOEC_{local}$ target
First exposure group (6 hours) in subacute study. rat (Fischer 344) male/female subacute (inhalation) 0, 110, or 400 ppm, 6 hours/day, groups of 5 animals for 1, 2, 5, 10, or 28 consecutive days. (36 weeks recovery to assess reversibility of the nasal olfactory lesions.	rat (Fischer 344) male/female subacute (inhalation) 0, 110, or 400 ppm, 6 hours/day, groups of 5 animals for 1, 2, 5, 10, or 28 consecutive days. (36 weeks recovery to assess reversibility of the nasal olfactory lesions.	rat (Fischer 344) male/female chronic (inhalation) (whole body); 25, 100 and 40 Vehicle: unchanged (no vehicle) Exposure: 2 years (104 weeks) (6 hours/day, 5 days /week) equivalent or similar to OECD Guideline 453 (Combined Chronic Toxicity / Carcinogenicity Studies) Histopathology of nasal turbinates (serial sections), larynx, trachea, lungs.
LOEL (local): 110 ppm (male) Minimal degeneration of olfactory epithelium at 110 ppm in animals exposed to a single 6 hours exposure.	$LOEC_{local}$ 110 ppm Minimal degeneration of olfactory epithelium at 110 ppm by 1day recovered by day 5.	$NOEC_{local}$ 25 ppm $LOEC_{local}$ (nasal lesions) 100 ppm Minimal degeneration of neuroepithelium, basal cell

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Acute	Subacute study	Chronic study
	Moderate degeneration at 400 ppm by day 1 regressed to minimal by day 28 recovered after cessation of exposure.	hyperplasia and atrophy of Bowman's glands at 100 ppm. Multifocal degeneration at 400 ppm.
Hext *et al* (2001)		Lomax *et al* (1997), Reno (1979)

Local effects:

The concentration selection in the NTP study was made with the objective of characterising carcinogenicity up to concentrations that neared lethality and not for the development of local effects in the nose. Hence, they are considerably higher and more widely spaced than would be required to characterise the NOEC for local effects. Furthermore, no histopathology was performed in the 11-day study. The histopathology done in the 11- and 90-day studies was very limited, likely only one standard section in the nose was done at this time so it is unlikely that the target tissue (olfactory) for esters was studied. Extensive histopathology in the two-year study, though concentration selection was like in the 11-day study, could also not establish a NOEC for local effects. Hence, the NTP studies in rats add little to the assessment of time dependency of the development of local effects in the upper respiratory system after inhalation of methyl methacrylate.

Further single- and repeated-dose studies have been performed and are essential for the characterisation of the local effects due to inhalation of methyl methacrylate. In the EU ESR on methyl methacrylate, the nasal cavity was identified as the target organ for chronic toxicity in male and female rats exposed to 100 or 400 ppm (Lomax) (EU, 2002). The microscopic nasal cavity changes occurred primarily in the olfactory epithelium lining of the dorsal meatus and consisted of degeneration of neuroepithelium, basal cell hyperplasia and atrophy of Bowman's glands. In the inhalation studies, local degeneration of the olfactory epithelia was observed in acute (6 hours) to sub-acute (28 days) at 110 ppm (Hext) and chronic (2 years) at 100 ppm (LOEC) studies, with marked degeneration at 400 ppm and above. The NOEC for local effects was considered to be 25 ppm.

Summary of mouse studies in NTP report 314

Key data extracted from Kalberlah and Schneider (1998), table 1a (figures in ppm)

Subacute study	Subchronic study	Chronic study
$NOEC_{local}$ target: (500) nose	$NOEC_{local}$ target: 1000 nose	$NOEC_{local}$ target: (500) b.w.
$NOEC_{systemic}$ target: (3000) u.s.	$NOEC_{systemic}$ target: 500 b.w.	$NOEC_{systemic}$ target: (500) b.w.

values in brackets ( ) represents LOAEL; n.p.= not performed; b.w. = change in body weight; u.s. = unspecified symptoms; -- = no effects observed

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Study details of NTP report 314

Subacute study	Subchronic study	Chronic study
mice (B6C63F1) male/female 500, 1000, 2000, 3000 and 5000 ppm corresponding to ca. 2.05, 4.1, 8.2, 12.3 and 20.5 mg/L, respectively) Exposure: 10 exposures (over 11 days), 6 hours/day. Histopathology (lung and nose) on 1 or 2 male mice at 500, 1000, 2000 and 3000 ppm.	IBT study: mice (B6C63F1) male/female 0, 63, 125, 250, 500, 1000 ppm Exposure: 13 weeks (5 days/week, 6 hours/day – 64 exposures) equivalent or similar to OECD Guideline 412 (Repeated Conc. Inhalation Toxicity: 28/14-days). Histopathology (tissues not specified), in 1000 ppm animals only. BNW study: 500, 1000, 2000, 3000 and 5000 ppm. Exposure: 13 weeks (5 days/week, 6 hours/day – 64 exposures) Histopathology of local effects in 2000 ppm animals but not on lower conc. groups.	mice (B6C63F1) male/female: 500 and 1000 ppm; Exposure: 2 years, 6 hours/day, 5 days/week. Histopathology of local effects included nasal turbinates (no serial sections), larynx, trachea, lungs.
Dyspnea, redness and swelling of nasal region observed (conc. not specified so assumed all concentrations. No NOEC established.	IBT: $NOEC_{local}$ 1000 ppm. Inflammation in nasal turbinates and metaplasia not observed in highest conc. studied (1000 ppm) study. BNW study: Inflammation in nasal turbinates and metaplasia observed in all animals at (2000 ppm). $NOEC_{local}$ Not established.	$NOEC_{local}$ Not established. Olfactory degeneration (incidence male: 48/50, female 44/49) in both male and female mice at the lowest conc. tested (500 ppm).
NTP (1986c)	NTP (1986c)	NTP (1986c)

Local effects:

The concentration selection in the NTP study was made with the objective of characterising carcinogenicity up to concentrations that neared lethality and not for the development of local effects in the nose. Hence, they are considerably higher and more widely spaced than would be required to characterise the NOEC for local effects. Only in the 13-week study were lower (relevant) concentrations tested, but in this study histopathology was only performed in mice exposed to 2000 ppm. Furthermore, no histopathology was performed in the 11-day study. The histopathology in these studies was very limited, likely only one standard section in the nose was done at this time, so it is unlikely that the target tissue (olfactory) for esters was studied. Extensive histopathology was done in the two-year study, albeit it is unlikely that the serial sectioning of the nose necessary to characterise olfactory degeneration was included. No NOEC was established in this study. Hence, the NTP studies in mice add little to the assessment of time dependency of the development of local effects in the upper respiratory system after inhalation of methyl methacrylate.

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Ethylene oxide (CAS 75-21-8)

Summary of mouse studies in NTP report 326

Key data extracted from Kalberlah and Schneider (1998), table 1a (figures in ppm)

Subacute study	Subchronic study	Chronic study
$NOEL_{local}$ target: 800 ---	$NOEL_{local}$ target: 100 nose	$NOEL_{local}$ target: 100 lung
$NOEL_{systemic}$ target: 400 u.s.	$NOEL_{systemic}$ target: 50 kidney	$NOEL_{systemic}$ target: 100 ---

Study details of NTP report 326

Subacute study	Subchronic study	Chronic study
Mice B6C3F1 5 male / 5 female 0, 50, 100, 200, 400 or 800 ppm Vehicle: dilution air (vapour delivery) Exposure: 6 hours per day, 5 days per week for 14 days (10 exposures). Necropsy performed on all animals. Tissues from 8 mice that lived to the end of the studies were examined histologically. Tissues examined in 6 exposed mice included larynx, trachea, lungs and bronchi. The eyes of 2 female controls were examined microscopically.	mice (B6C3F1) 10 male / 10 female 0, 50, 100, 200, 400 or 600 ppm Vehicle: dilution air (vapour delivery) Exposure: 14 weeks (5 days/week, 6 hours/day). Necropsy performed on all animals; histologic exam performed on all controls and the 2 highest dose groups. Tissues examined: included lungs, bronchi, and nasal cavity but it is not clear if they performed serial sections of the nasal cavity and turbinates.	mice (B6C3F1) 50 male / 50 female: 0, 50, or 100 ppm Vehicle: dilution air (vapour delivery) Exposure: 102 weeks: 6 hours/day, 5 days/week. Necropsy and histologic exam performed on all animals. Tissues examined: gross lesions and tissue masses, mandibular lymph nodes, mammary gland, skin, salivary glands, sternebrae, thyroid gland, parathyroids, small intestine (3 sections), colon, liver, prostate/testis or ovaries/uterus, gallbladder, lungs, bronchi, heart, oesophagus, stomach, brain (3 sections), thymus, trachea, pancreas, spleen, kidneys, adrenal glands, urinary bladder, pituitary gland, nasal cavity, and nasal turbinates (3 sections).
$NOEC_{Local}$ is equal or higher than 400 ppm (all animals died at 800 ppm). No clinical signs were reported in any group. However, it is not clear which animals were examined histologically for local effects as the report refers to tissues being taken from '8 mice that survived', but 'tissues examined from 6 mice exposed mice'. And, according to the report most animals survived up to and including 400 ppm, i.e. 38/40 but all animals died at 800 ppm. $NOEC_{Systemic}$ established at 400 based on all mice dying at 800 ppm. No other effects observed.	$NOEC_{Local}$ –100 ppm: Rhinitis of the nasal cavity was observed at 200 ppm and above. Loss of polarity of olfactory and respiratory epithelial cells, necrosis of epithelium, loss of cilia, and transmigration of inflammatory cells with accumulation of purulent exudates in some mice were the most frequent alterations found in the nasal portion of the respiratory tract. These dose-related lesions appeared most pronounced in the dorsal turbinate areas. $NOEC_{Systemic}$: 50 ppm based on renal tubular degeneration at 100 ppm.	$NOEC_{Local}$ –100 ppm No compound related clinical signs or non-neoplastic lesions were observed. However the combined incidences of the benign and malignant lung tumours occurred with positive trends. $NOEC_{Systemic}$: 100 ppm based on no compound related clinical signs were observed.
NTP (1986d)	NTP (1986d)	NTP (1986d)

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Results/Effects:

In the case of ethylene oxide, the doses used in longer-term studies were decreased due to lethality observed in exposed animals. In the sub-acute study (10 exposures) no clinical signs were reported for any animal investigated. As all mice died in the 800 ppm group it is safe to assume that the NOEC for local effects should refer to the 400 ppm group in which most animals survived. It should be noted however, that the report contains only limited details. Thus, there is some uncertainty as to which animals were examined histologically for local effects. Consequently, this study cannot be used to derive a rigorous NOEC for local effects after sub-acute exposure. In the sub-chronic study (14 weeks) local effects (rhinitis) was observed at 200 ppm and above. No local effect was reported in the chronic study. Since the highest dose tested (100 ppm) in the chronic study is equal to the local NOEC in the sub-chronic study (100 ppm), these data support an AF of 1 for study duration for local effects.

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1,2-Epoxybutane (CAS 106-88-7)

Summary of rat studies in NTP report 329

Key data extracted from Kalberlah and Schneider (1998), table 1a (figures in ppm)

Subacute study	Subchronic study	Chronic study
$NOEC_{local}$ target: 800 nose, lung	$NOEC_{local}$ target: 400 nose	$NOEC_{local}$ target: (200) nose, lung
$NOEC_{systemic}$ target: 400 b.w., u.s.	$NOEC_{systemic}$ target: 400 b.w.	$NOEC_{systemic}$ target: 400 --

values in brackets ( ) represents LOAEL; n.p.= not performed; b.w. = change in body weight; u.s. = unspecified symptoms; -- = no effects observed

Study details of NTP report 329

Subacute study	Subchronic study	Chronic study
Rats (F344/N): 5 male/ 5 female: 0, 400, 800, 1600, 3200 and 6400 ppm. Exposure: 6 hours/day, 5 days/week for 2 weeks. Necropsy on all animals; histopathology on 1 male rat at 3200 ppm, 2 male and 2 female rats at 1600 ppm and 1 male rat at 800 ppm; tissues not specified.	Rats (F344/N): 5 male/ 5 female: 0, 50, 100, 200, 400, and 800 ppm. Exposure: 6 hours/day, 5 days/week for 13 weeks. Necropsy on all animals; histopathology on controls and high dose groups (400 and 800 ppm); tissues examined for local effects: lungs and mainstem, bronchi,, nasal cavity and nasal turbinates.	Rats (F344/N): 50 male/ 50 female: 0, 200 and 400 ppm. Exposure: 6 hours/day, 5 days/week for 103 (rats) or 102 (mice) weeks. Necropsy and histopathology on all animals. tissues examined for local effects: lungs and mainstem bronchi,, nasal cavity, trachea.
Al rats exposed to 6400 or 3200 ppm died, 2/5 females died at 1600 ppm; weight loss at 800 and 1600 ppm. Acute suppurative rhinitis (moderate severity) in surviving 1600 ppm animals. Multifocal pulmonary haemorrhage (moderate severity) in 2/2 male and ½ surviving females at 1600 ppm.	Rats: Body weight loss in high dose animals (800 ppm), inflammation of nasal cavity in all animals at 800 ppm but not at lower concentrations. $NOEC_{local}$ = 400 ppm	(male/female) Primary target tissue: nasal cavity. $NOEC_{Local}$ not established $LOEC_{Local}$ 200 ppm* Inflammation of the nasal cavity (males: 9/50, 36/50 and 42/50: females 25/50, 32/50 and 43/50 at 0, 200 and 400 ppm, respectively). Increase in epithelial hyperplasia (males: 8/50, 38/50, and 46/50; females 5/50, 29/48 and 40/48 at 0, 200 and 400 ppm, respectively) Squamous metaplasia (males:4/50, 22/50, 40/50; females 1/50, 4/48 and 36/48 at 0, 200 and 400 ppm, respectively. * inflammation observed ion controls indicating background infection hence LOEC should be interpreted with caution.
NTP (1988)	NTP (1988)	NTP (1988)

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Local effects:

Acute suppurative rhinitis (moderate severity) were reported in the surviving animals in the sub-acute study (1600 pm) but there is no indication that respiratory tissues were included in the histopathology. Hence, it is not reliable to assume that 800 ppm is a NOEC for local effects. In the sub-chronic study inflammation of nasal cavity was reported in all animals at 800 ppm but not at 400 ppm. In the two-year studies inflammation of the nasal cavity, hyperplasia and squamous metaplasia was observed in all groups including controls. Hence, no NOEC was established for local effects. Since this effect is often observed in animals with background respiratory infection, this NOEC may be unreliable. Hence, the NTP studies in rats add little to the quantitative assessment of time dependency of the development of local effects in the upper respiratory system.

Summary of mouse studies in NTP report 329

Key data extracted from Kalberlah and Schneider (1998), table 1a (figures in ppm)

Subacute study	Subchronic study	Chronic study
$NOEC_{local}$ target: 6400 --	$NOEC_{local}$ target: 100 nose	$NOEC_{local}$ target: (50) nose
$NOEC_{systemic}$ target: 400 kidney	$NOEC_{systemic}$ target: 400 kidney	$NOEC_{systemic}$ target: (50) b.w.

values in brackets ( ) represents LOAEL; n.p.= not performed; b.w. = change in body weight; u.s. = unspecified symptoms; -- = no effects observed

Study details of NTP report 329

Subacute study	Subchronic study	Chronic study
Mice ($B6C3F_1$): 5 male/ 5 female: 0, 400, 800, 1600, 3200 and 6400 ppm Exposure: 6 hours/day, 5 days/week for 2 weeks. Necropsy on all animals; histopathology on 2 male mice at 1600 ppm, 2 male and 1 female mouse at 800 ppm and 1 male mouse at 400 ppm; tissues not specified.	Mice ($B6C3F_1$): 5 male/ 5 female: 0, 50, 100, 200, 400, and 800 ppm Exposure: 6 hours/day, 5 days/week for 13 weeks. Necropsy on all animals; histopathology on controls and high dose groups (400 and 800 ppm); tissues examined for local effects: lungs and mainstem bronchi, nasal cavity and nasal turbinates.	Mice ($B6C3F_1$): 50 male/ 50 female: 0, 50 or 100 ppm. Exposure: 6 hours/day, 5 days/week for 103 (rats) or 102 (mice) weeks. Necropsy and histopathology on all animals. tissues examined for local effects: lungs and mainstem bronchi, nasal cavity, trachea.
Mice: all mice exposed to 1600 ppm and 1/5 males of the 800 ppm group died. Body weight loss was observed in all exposed mice. No local effects reported.	$NOEC_{Local}$ not established $LOEC_{Local}$ 100 ppm All mice exposed to 800 ppm died; reduced liver weights in 400 ppm females; renal tubular necrosis at 800 ppm (both sexes) but not at lower doses. Inflammation nasal cavity in all mice exposed to 200 ppm and in 0/10 males but 7/10 females exposed to 100 ppm. No data reported on 50 ppm dose groups.	$NOEC_{Local}$ not established LOEC: 50 ppm (male/female) Primary target tissue: nasal cavity. Inflammation of the nasal cavity males: 0/50, 33/50, and 40/50; females 0/50, 39/50 and 44/50 at 0, 50 and 100 ppm, respectively. Increase in epithelial hyperplasia (males: 0/50, 32/50, and 45/50; females 1/50, 3448 and 35/48 at 0, 50 and 100 ppm, respectively.

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Subacute study	Subchronic study	Chronic study
	Animals in 5 ppm group not investigated.	Squamous metaplasia (males: 1/50, 24/50, 41/50; females 0/50, 34/48 and 41/48 at 0, 50 and 100 ppm, respectively. Nasal gland hyperplasia (males: 0/50, 10/50, 24/50; females 0/50, 23/48 and 29/48 at 0, 50 and 100 ppm, respectively. Nasolacrimal duct hyperplasia (males: 0/50, 12/50, 21/50; females 1/50, 18/48 and 21/48 at 0, 50 and 100 ppm, respectively.
NTP (1988)	NTP (1988)	NTP (1988)

Local effects:

No local effects were reported in the sub-acute study but there is no indication that respiratory tissues were included in the histopathology. Hence, it is not reliable to assume that 6400 ppm is a NOEC for local effects. In the sub-chronic study no inflammation of the nasal cavity was observed at 100 ppm and higher. Since no histopathology was conducted on the animals of the 50, 100 and 200 ppm groups, no NOEC for local effects can be attributed in this study. In the two- year studies, inflammation of the nasal cavity, hyperplasia and squamous metaplasia was observed in all groups and only in occasional controls. Hence, 50 ppm can be interpreted as a LOEC for local effects in this study. With LOEC from the sub-chronic and chronic studies, but no NOEC, it is not possible to make a quantitative assessment of time dependency of the development of local effects in the upper respiratory system.

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Chloroethane (CAS 75-00-3)

Summary of rat studies in NTP report 346

Key data extracted from Kalberlah and Schneider (1998), table 1a (figures in ppm)

Subacute study	Subchronic study	Chronic study
$NOEC_{local}$ target: 19000 --	$NOEC_{local}$ target: 19000 --	$NOEC_{local}$ target: 15000 --
$NOEC_{systemic}$ target: 19000 --	$NOEC_{systemic}$ target: 19000 --	(15000) b.w.

values in brackets ( ) represents LOAEL; n.p.= not performed; b.w. = change in body weight;
u.s. = unspecified symptoms; -- = no effects observed

Study details of NTP report 346

Subacute study	Subchronic study	Chronic study
rat (Fischer 344) male/female 19000 ppm. Exposure: 14 exposures, 6 hours/day. Necropsy performed on all animals; histologic exams performed on 1 female rat and 1 male mouse in the control groups and 2 male rats, 1 female rat, 1 male mouse, and 2 female mice in the exposed groups: tissues investigated for local effects: larynx, lungs and bronchi, nasal cavity, trachea.	rat (Fischer 344) male/female 2,500, 5,000, 10,000, or 19,000 ppm. Exposure: 13 weeks (5 days/week, 6 hours/day). Necropsy performed on all animals; histologic exams performed on all control and high dose animals. Tissues investigated for local effects: larynx, lungs and bronchi, trachea and nasal cavity but it is not clear if they performed serial sections of the nasal cavity and turbinates.	rat (Fischer 344) male/female: 15000 ppm. Exposure: 2 years, 6 hours/day, 5 days/week. Necropsy performed on all animals; histologic exams performed on all animals. Tissues investigated for local effects: larynx, lungs and mainstem bronchi, nasal cavity, trachea.
No clinical or histopathological findings. $NOEC_{local}$: only concentration investigated 19000 ppm.	No clinical or histopathological findings. $NOEC_{local}$: 19000 ppm.	No clinical or histopathological findings. $NOEC_{local}$: only concentration investigated 15000 ppm.
NTP (1989a)	NTP (1989a)	NTP (1989a)

Local effects:

No local effects were observed with chloroethane. Hence, the NTP studies in rats add little to the assessment of time dependency of the development of local effects in the upper respiratory system.

Summary of mouse studies in NTP report 346

Key data extracted from Kalberlah and Schneider (1998), table 1a (figures in ppm)

Subacute study	Subchronic study	Chronic study
$NOEC_{local}$ target: 19000 --	$NOEC_{local}$ target: 10000 nose	$NOEC_{local}$ target: 15000 --
$NOEC_{systemic}$ target: 19000 --	$NOEC_{systemic}$ target: 19000 --	$NOEC_{systemic}$ target: (15000) kidney

values in brackets ( ) represents LOAEL; n.p.= not performed; b.w. = change in body weight;
u.s. = unspecified symptoms; -- = no effects observed

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Study details of NTP report 346

Subacute study	Subchronic study	Chronic study
mice (B6C3F1) male/female 19000 ppm Exposure: 14 exposures, 6 hours/day. Necropsy performed on all animals; histologic exams performed on 1 female rat and 1 male mouse in the control groups and 2 male rats, 1 female rat, 1 male mouse, and 2 female mice in the exposed groups: tissues investigated for local effects: larynx, lungs and bronchi, nasal cavity, trachea.	mice (B6C3F1) male/female 2,500, 5,000, 10,000, or 19,000 ppm Exposure: 13 weeks (5 days/week, 6 hours/day). Necropsy performed on all animals; histologic exams performed on all control and high dose animals. Tissues investigated for local effects: larynx, lungs and bronchi, trachea and nasal cavity but it is not clear if they performed serial sections of the nasal cavity and turbinates.	mice (B6C3F1 male/female: 15000 ppm. Exposure: 2 years, 6 hours/day, 5 days/week. Necropsy performed on all animals; histologic exams performed on all animals. Tissues investigated for local effects: larynx, lungs and mainstem bronchi, nasal cavity, trachea.
No clinical or histopathological findings. $NOEC_{local}$: only concentration investigated 19000 ppm.	No clinical or histopathological findings. Nasal cavity haemorrhage of minimal severity was observed grossly in 3/10 male and 6/10 female mice exposed to 19,000 but was considered to be an artefact of necropsy and unrelated to exposure to chloroethane because no microscopic lesions associated with exposure to chloroethane were observed in the nasal mucosa of these animals. $NOEC_{local}$: highest concentration investigated 19000 ppm.	No clinical or histopathological findings $NOEC_{local}$: only concentration investigated 15000 ppm.
NTP (1989a)	NTP (1989a)	NTP (1989a)

Local effects:

No local effects were observed with chloroethane. Hence, the NTP studies in mice add little to the assessment of time dependency of the development of local effects in the upper respiratory system.

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Bromoethane (CAS 74-96-4)

Summary of rat studies in NTP report 363

Key data extracted from Kalberlah and Schneider (1998), table 1a (figures in ppm)

Subacute study	Subchronic study	Chronic study
$NOEC_{local}$ target: 4000 --	$NOEC_{local}$ target: 1600 --	$NOEC_{local}$ target: (100) nose, lung
$NOEC_{systemic}$ target: 1000 mortality	$NOEC_{systemic}$ target: 400 liver	$NOEC_{systemic}$ target: (100) adrenals

values in brackets ( ) represents LOAEL; n.p.= not performed; b.w. = change in body weight;
u.s. = unspecified symptoms; -- = no effects observed

Study details of NTP report 363

Subacute study	Subchronic study	Chronic study
rat (Fischer 344) male/female 250, 500, 1,000, 2,000, or 4,000 ppm Vehicle: unchanged (no vehicle) Exposure: 14 exposures, 6 hours/day. Necropsy performed on all animals; histologic exams performed on 3 animals from the 1,000 and 2,000-ppm groups only. Tissues examined: nasal cavity, trachea, and lungs and mainstem bronchi.	rat (Fischer 344) male/female 0, 0, 0, 100, 200, 400, 800, or 1,600 ppm. Vehicle: unchanged (no vehicle) Exposure: 13 weeks (5 days/week, 6 hours/day). Necropsy performed on all animals; histologic exams performed on all control, 800 and 1600 ppm animals. Tissues investigated for local effects: larynx, lungs and bronchi, trachea and nasal cavity but it is not clear if they performed serial sections of the nasal cavity and turbinates.	rat (Fischer 344) male/female: 0, 100, 200, or 400 ppm. Exposure: 2 years, 6 hours/day, 5 days/week. Necropsy performed on all animals; histologic exams performed on all animals. Tissues investigated for local effects: larynx, lungs and mainstem bronchi, nasal cavity, trachea.
Haemorrhage and/or acute inflammation of the nasal turbinates, trachea, and lung were seen in one rat at 2,000 ppm, minor pulmonary congestion and haemorrhage were seen in one rat at 1,000 ppm, and minimal-to-mild pulmonary congestion was seen in two rats at 2,000 ppm. Due to the limited number of animals investigated histopathologically, no $NOEC_{local}$ can be established.	$NOEC_{local}$: highest concentration investigated 1600 ppm.	Suppurative inflammation of nasal cavity, larynx and lung was seen in all groups, including the controls. No NOEC can be derived due to respiratory infection of the animals.
NTP (1989b)	NTP (1989b)	NTP (1989b)

Local effects:

No consistent local effect was reported in the sub-acute study because of the limited number of animals investigated histopathologically. No local effect was reported in the sub-chronic study up to a concentration of 1600 ppm. In the chronic study suppurative inflammation of nasal cavity, larynx and lung was seen with similar incidence in all groups, including the controls. Background respiratory infection in these animals was suspected and no reliable information on the local irritation potential of the compound can be concluded. Hence, the NTP studies on bromoethane in rats add little to the assessment of time dependency of the development of local effects in the upper respiratory system.

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Summary of mouse studies in NTP report 363

Key data extracted from Kalberlah and Schneider (1998), table 1a (figures in ppm)

Subacute study	Subchronic study	Chronic study
$NOEC_{local}$ target: 4000 --	$NOEC_{local}$ target: 1600 --	$NOEC_{local}$ target: 400 --
$NOEC_{systemic}$ target: 1000 mortality	$NOEC_{systemic}$ target: 800 mortality, u.s., b.w., muscles, sex organs	$NOEC_{systemic}$ target: (100) sex organs.

values in brackets ( ) represents LOAEL; n.p.= not performed; b.w. = change in body weight; u.s. = unspecified symptoms; -- = no effects observed

Study details of NTP report 363

Subacute study	Subchronic study	Chronic study
mice (B6C3F1) male/female 250, 500, 1,000, 2,000 or 4,000 ppm Vehicle: unchanged (no vehicle) Exposure: 14 exposures, 6 hours/day. Necropsy performed on all animals; histologic exams performed on **3** animals of each species from the 1,000 and 2,000-ppm groups. Tissues examined: nasal cavity, trachea, and lungs and mainstem bronchi.	mice (B6C3F1) male/female 0, 0, 100, 200, 400, 800 or 1,600 ppm Vehicle: unchanged (no vehicle) Exposure: 13 weeks (5 days/week, 6 hours/day) Necropsy performed on all animals; histologic exams performed on all control, 800 and 1600 ppm animals. Tissues investigated for local effects: larynx, lungs and bronchi, trachea and nasal cavity but it is not clear if they performed serial sections of the nasal cavity and turbinates.	mice (B6C3F1 male/female: 0, 100, 200 or 400 ppm. Exposure: 2 years, 6 hours/day, 5 days/week. Necropsy performed on all animals; histologic exams performed on all animals. Tissues investigated for local effects: larynx, lungs and mainstem bronchi, nasal cavity, trachea.
Minimal pulmonary congestion was seen in one mouse at 1,000 ppm, and mild pulmonary haemorrhage was seen in another mouse. Due to the limited number of animals investigated histopathologically. $NOEC_{local}$ cannot be established.	No clinical or histopathological findings.	Acute and chronic inflammation was observed at increased incidences in the lungs in female mice at 200 and 400 ppm (male: 2/50; 1/50; 1/50; 1/50; female: 1/50; 1/50; 4/49; 6/49). Alveolar epithelial hyperplasia was increased in rats exposed to 400 ppm. $NOEC_{local}$ cannot be established due to respiratory infection of the animals.
NTP (1989b)	NTP (1989b)	NTP (1989b)

Local effects:

No consistent local effects were observed with bromoethane in sub-acute and sub-chronic studies. In the chronic study, acute/chronic inflammation of the lung was observed at increased incidences in female mice at 200 and 400 ppm. Low level inflammation was reported for all animal groups, including controls, reflecting the presence of a background respiratory infection in these animals and making the distinction of a NOEC unreliable. These findings in mice are consistent with the findings of the study in rats. Hence, the NTP studies on bromoethane in mice add little to the assessment of time dependency of the development of local effects in the upper respiratory system.

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Vinyl toluene (CAS 25013-15-4)

Summary of rat studies in NTP report 375

Key data extracted from Kalberlah and Schneider (1998), table 1a (figures in ppm)

Subacute study	Subchronic study	Chronic study
$NOEL_{local}$ target: 800 lung	$NOEL_{local}$ target: 1000 ---	$NOEL_{local}$ target: (100) nose
$NOEL_{systemic}$ target: 200 b.w.	$NOEL_{systemic}$ target: 60 kidney	$NOEL_{systemic}$ target: (100) b.w.

Study details of NTP report 375

Subacute study	Subchronic study	Chronic study
rat (Fischer 344) male/female 200, 400, 800 and 1300 ppm Vehicle: dilution air (vapour delivery) Exposure: 10 exposures (over 15 days), 6 hours/day. Histopathologic examinations were performed on rats in the 1,300 ppm group only but this did not include the nasal passages and turbinates.	rat (Fischer 344) male/female 0, 25, 60, 160, 400, and 1,000 ppm Vehicle: dilution air (vapour delivery) Exposure: 13 weeks (5 days/week, 6 hours/day). Histological examination of controls and high dose group animals (1000 ppm only). Tissues examined included lungs and nasal cavity but it is not clear if they performed serial sections of the nasal cavity and turbinates.	rat (Fischer 344) male/female: 100 and 300 ppm; Vehicle: dilution air (vapour delivery) Exposure: 2 years: 6 hours/day, 5 days/week for 103 week. Necropsy and histologicical exams performed included lungs and nasal cavity and turbinates.
$NOEC_{Local}$ 800 ppm* $LOEC_{Local}$ 1300 ppm* *Based on dysplasia of the bronchial epithelium, chronic bronchitis, and lymphoid hyperplasia of the lung were observed in all rats exposed to 1,300 ppm. The severity was minimal to slight in males and minimal in females.	$NOEC_{Local}$ 1000 ppm No local effects reported in lungs and nasal passages at 1000 ppm although excessive lacrimation, palpebral closure, and rough hair coats was noted.	$NOEC_{Local}$ 100 ppm Based on lesions in the olfactory and respiratory epithelium at 300 ppm $LOEC_{Local}$ Hyperplasia of the respiratory epithelium was usually diffuse and was characterized by increased numbers of goblet cells and increased height of the epithelium; in some males, slight folding of the epithelium (papillary hyperplasia) was seen. The cysts were small, intraepithelial gland-like structures distended with mucus. Lesions involving the olfactory epithelium occurred primarily in the anterior region along the dorsal meatus. The olfactory epithelium was focally eroded; the underlying Bowman's glands were cystically dilated, and the glandular epithelium was replaced by ciliated columnar cells (olfactory epithelium, cyst). In some exposed male rats, the olfactory epithelium was focally replaced by pseudostratified ciliated columnar epithelium (respiratory epithelial metaplasia). In the olfactory epithelium of exposed female rats, there were increased

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Subacute study	Subchronic study	Chronic study
		numbers of cells with homogeneous eosinophillic cytoplasm or hyaline degeneration (hyperplasia, eosinophil).This degenerative change apparently results from the intracytoplasmic accumulation of secretory material.
NTP (1986e)	NTP (1986e)	NTP (1986e)

Results/Effects:

The nasal passages and turbinates were not assessed in the sub-acute study. Dysplasia of the bronchial epithelium, chronic bronchitis, and lymphoid hyperplasia was noted in the 1300 ppm animals. The lungs and nasal passages were assessed in the sub-chronic study but no effects were reported. Excessive lacrimation and palpebral closure was noted in the 1000 ppm animals. The effects on the nasal passages in the 300 ppm animals in the chronic study were described by NTP as "*degenerative change apparently resulting from the intracytoplasmic accumulation of secretory material*". These effects are not consistent with typical, local, irritant or cytotoxic mechanisms but rather a mechanism unlikely to be relevent to shorter duration studies. The $NOEC_{local}$ of 100 ppm should therefore not be regarded as a true NOEC for local effects in this study. Hence, in the absence of a NOEC in the chronic study little can be concluded from the NTP studies with vinyl toluene in rats as to the time dependency of the development of local effects in the upper respiratory system.

Summary of mouse studies in NTP report 375

Key data extracted from Kalberlah and Schneider (1998), table 1a (figures in ppm)

Subacute study	Subchronic study	Chronic study
$NOEL_{local}$ target: 100 lung	$NOEL_{local}$ target: (10) nose	$NOEL_{local}$ target: (10) nose, lung
$NOEL_{systemic}$ target: 50 liver	$NOEL_{systemic}$ target: 10 b.w.	$NOEL_{systemic}$ target: (10) b.w.

Study details of NTP report 375

Subacute study	Subchronic study	Chronic study
Mice $B6C3F_1$ male/female`0, 10, 25, 50, 100 or 200 ppm Vehicle: dilution air (vapour delivery) Exposure: 10 exposures (over 15 days), 6 hours/day. Histopathologic examinations were performed on mice in the 200 ppm group and 1 male and female from control group. Tissues examined did not include nasal passages.	Mice ($B6C3F_1$) male/female 0, 10, 25, 60 or 160 ppm Vehicle: dilution air (vapour delivery) Exposure: 13 weeks (5 days/week, 6 hours/day). Histopathology on control and high dose group animals. Tissues examined included lungs and nasal cavity but it is not clear if they performed serial sections of the nasal cavity and turbinates.	Mice ($B6C3F_1$) male/female: 10 and 25 ppm; Vehicle: dilution air (vapour delivery) Exposure: 2 years: 6 hours/day, 5 days/week for 103 week. Necropsy and histologicical exams performed included lungs and nasal cavity and turbinates.

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Subacute study	Subchronic study	Chronic study
$LOEC_{Local}$ is 200 ppm Severe hyperaemia and haemorrhage of the pulmonary parenchyma were seen in exposed male mice that died on day 3. Three other exposed male mice had interstitial pneumonia. All five female mice exposed to 200 ppm had hyperplasia of the epithelium of the intrapulmonary bronchi. $NOEC_{Local(lung)}$ 100ppm. $NOEC_{Systemic}$ established at 50 is questioned based on available data.	$LOEC_{Local}$ –10 – based on Inflammation of the lung was observed in 5/10 male and 3/9 female mice exposed to 160 ppm, in 4/9 male and 2/10 female mice exposed to 60 ppm, and in 1/10 female controls. Metaplasia of the respiratory epithelium of the nasal turbinates (hyaline cytoplasmic alteration) was seen in all exposed groups. Acute inflammation and/or metaplasia of the nasal turbinates were seen in 7/10 male and 919 female mice exposed to 160 ppm, 718 male and 10/10 female mice exposed to 60 ppm, 8/9 male and 9/10 female mice exposed to 25 ppm, 3/10 male and 4/10 female mice exposed to 10 ppm, and 1/10 female controls. Lesions of the lungs and nasal turbinates were not seen in the male controls. $NOEC_{Systemic}$: based on bw change (10-23% lower) in mice exposed to 25 ppm.	$LOEC_{Local}$ –10 ppm Increased incidences of chronic active inflammation and hyperplasia of the respiratory epithelium occurred in exposed mice. Lesions were located in the middle and posterior portions of the dorsal meatus. The severity of the lesions was dose related; inflammation and hyperplasia were generally mild and moderate in the 10-ppm males and females, respectively, and moderate and marked in the 25-ppm males and females, respectively. $LOAEL_{Systemic}$: 10 ppm based on body weight changes.
NTP (1986e)	NTP (1986e)	NTP (1986e)

Results/Effects:

Effects on the lungs were observed in the sub-acute study. But the nasal passages, i.e. the more sensitive target in longer duration studies, were not investigated. Hence, it is not possible to derive a comparable NOEC for local effects. In the sub-chronic and chronic studies metaplasia in the nasal passage was the lead local effect. In both studies effects were observed at the lowest concentration studied (LOEC of 10 ppm), so the data do not allow a comparison of NOECs. The available information is insufficient to make any assessment of time dependency of the development of local effects in the upper respiratory system.

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Toluene (CAS 108-88-3)

Summary of rat studies in NTP report 371

Key data extracted from Kalberlah and Schneider (1998), table 1a (figures in ppm)

Subacute study	Subchronic study	Chronic study
$NOEL_{local}$ target	$NOEL_{local}$ target: 3000 ---	$NOEL_{local}$ target: (600) nose
$NOEL_{systemic}$ target	$NOEL_{systemic}$ target: (100) b.w. , u.s.	$NOEL_{systemic}$ target: (600) kidney, stomach.

Study details of NTP report 371

Subacute study	Subchronic study	Chronic study
	rat (Fischer 344) male/female; 10 per group: 0, 100, 625, 1250, 2500 and 3000 ppm Vehicle: dilution air (vapour delivery) Exposure: 15 weeks (5 days/week, 6.5 hours/day) Necropsy and histological exams performed on animals in 2,500- and 3.000- ppm. Tissues examined included lungs, bronchi, aorta and nasal cavity but it is not clear if they performed serial sections of the nasal cavity and turbinates.	rat (Fischer 344) male/female: 60 per group: 600 and 1200 ppm; Vehicle: dilution air (vapour delivery) Exposure: 2 years: 6 hours/day, 5 days/week for 103 week. Necropsy and histologicical exams performed included nasal cavity and turbinates.
	Eight of 10 male rats exposed at 3,000 ppm died during week 2. Changes were observed in the relative lung weights at 2500 ppm and above but there were no local effects such as inflammation or hyperplasia reported hence effects on lung weight are not considered to be local effects. $NOEC_{Local}$ 3000 ppm	$LOEC_{Local}$ 600 ppm. $NOEC_{Local}$ not established 15 month: degeneration of olfactory and respiratory epithelium and goblet cell hyperplasia; In the nasal cavity, mild-to-moderate degeneration of the olfactory and respiratory epithelium (male: control, 5/10; 600 ppm, 10/10; 1,200 ppm, 10/10; female: 2/10; 10/10; 9/10] and goblet cell hyperplasia was somewhat increased (male: 3/10; 8/10; 5/10; female: 2/10; 5/10; 6/10). 2 year: erosion of olfactory epithelium and degeneration of respiratory epithelium and (females only) inflammation of nasal mucosa and metaplasia of olfactory epithelium.
	NTP (1986f)	NTP (1986f)

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Results/Effects:

In the sub-chronic study changes were only observed in the relative lung weights at 2500 and 3000 ppm and no local effects were observed. Although nasal tissue was investigated in the list of tissues reported as being examined histologically, it is not stated if the serial sectioning used in the chronic study was employed. Hence, some effects may have been missed particularly in the olfactory and respiratory tissues. In the chronic studies (15 months and 2 years) local effects including degeneration of the olfactory and respiratory epithelium and hyperplasia were observed at 600 and 1200 ppm and also at lower levels in controls. No NOEC for this effect was established and the presence of background infection makes the assertion of 600 ppm as a LOEC unreliable. Furthermore, as the serial sectioning of the nasal passages performed in the chronic study appeared not to be evaluated in the sub-chronic study, it is not possible to make a direct comparison between the two studies. Hence, the NTP studies in rats cannot be used for the assessment of time dependency of the development of local effects in the upper respiratory system.

Summary of mouse studies in NTP report 371

Key data extracted from Kalberlah and Schneider (1998), table 1a (figures in ppm)

Subacute study	Subchronic study	Chronic study
$NOEL_{local}$ target	$NOEL_{local}$ target: 3000 ---	$NOEL_{local}$ target: 1200 ---
$NOEL_{systemic}$ target	$NOEL_{systemic}$ target: (100) b.w., liver	$NOEL_{systemic}$ target: 120 spleen

Study details of NTP report 371

Subacute study	Subchronic study	Chronic study
	Mice (B6C3F1) male/female 0, 100, 625, 1250, 2500 and 3000 ppm Vehicle: dilution air (vapour delivery) Exposure: 14 weeks (5 days/week, 6.5 hours/day) Necropsy performed on all animals; histologic exams performed on all controls and the 2,500 and 3.000 ppm groups, and all animals dying before the end of the studies. Tissues examined included lungs and bronchi, but not nasal cavity and turbinates.	Mice (B6C3F1) male/female: 120, 600 and 1200 ppm; Vehicle: dilution air (vapour delivery) Exposure: 15 months and 2 years: 6 hours/day, 5 days/week for 103 week. Necropsy and histologic exams performed on all animals except 3 high dose female mice. Tissues examined included lungs and bronchi, nasal cavity and turbinates.
	Changes were observed in the relative lung weights at 1250 ppm and above but there were no local effects such as inflammation or hyperplasia reported hence effects on lung weight are not considered to be local effects. $NOEC_{Local}$ –3000 ppm $LOEC_{Systemic}$: [100 ppm cited based on bw changes although 625 ppm may be more appropriate.	No local effects observed. $NOEC_{Local}$ – 1200 ppm which is based on no effects observed. $NOEC_{Systemic}$: 120 ppm is based on increased spleen pigmentation in exposed mice.
	NTP (1986f)	NTP (1986f)

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Results/Effects:

In the sub-chronic study no local effects were observed at the highest concentration studied (3000 ppm). As in the rat study, no histological examination of the nasal cavity and turbinates tissues was reported. In the chronic study no local effects were observed in any respiratory tissue, thus the highest concentration studied (1200 ppm) is being regarded as a NOEC for local effects. As toluene does not consistently appear to produce local effects upon repeated exposure, the NTP studies on toluene in mice cannot be used for the assessment of time dependency of the development of local effects in the upper respiratory system.

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Allyl glycidyl ether (CAS 106-92-3)

Summary of rat studies in NTP report 376

Key data extracted from Kalberlah and Schneider (1998), table 1a (figures in ppm)

Subacute study	Subchronic study	Chronic study
$NOEC_{local}$ target: 25 nose	$NOEC_{local}$ target: (4) larynx, lung, trachea	$NOEC_{local}$ target: (5) nose
$NOEC_{systemic}$ target: 200 mortality	$NOEC_{systemic}$ target: 30 b.w.	$NOEC_{systemic}$ target: 10 --

values in brackets ( ) represents LOAEL; n.p.= not performed; b.w. = change in body weight; u.s. = unspecified symptoms; -- = no effects observed

Study details of NTP report 376

Subacute study	Subchronic study	Chronic study
Rats (Osborne-Mendel) 5 male/ 5 female: 0, 25, 50, 100, 200, 500 ppm Exposure: 6 hours/day, 5 days/week for 2 weeks. Necropsy on all animals; histopathology on 1 or 2 from the higher dose groups.	Rats (Osborne-Mendel) 10 male/ 10 female: 0, 4, 10, 30, 100, 200 ppm Exposure: 6 hours/day, 5 days/week for 13 weeks. Full histopathology on controls and high dose group; histopathology of oesophagus, larynx, bronchi, lungs, nasal cavity, thyroid and trachea. Results description suggests serial sectioning of the nasal tissues.	Rats (Osborne-Mendel) 50 male/ 50 female: 0, 5, 10 ppm Exposure: 6 hours/day, 5 days/week for 103 weeks (rats) or 102 weeks (mice). Full histopathology on all rats and on controls and high dose mice; nasal cavity for low dose mice.
All rats exposed to 500 ppm died, rats exposed to 200 ppm or less survived; $NOEC_{local}$ Not established. Acute inflammation of the nasal passages and major airways was observed.	$NOEC_{local}$ Not established $LOEC_{local}$: 4 ppm Histologic lesions included squamous metaplasia of the nasal passage in all exposure groups (4 ppm, lowest concentration) and involved both the respiratory epithelium and the olfactory epithelium. The lesions were more severe anteriorly and dorsally and with increasing concentration. At 30 ppm and higher, erosion was seen in the nasal passage and squamous metaplasia was seen in the upper airways.	$NOEC_{local}$ Not established $LOEC_{local}$: 5 ppm Inflammation, squamous metaplasia, respiratory metaplasia (replacement of olfactory epithelium by ciliated epithelium), hyperplasia of the respiratory epithelium, and degeneration of the olfactory epithelium observed at 5 ppm.
NTP (1990a)	NTP (1990a)	NTP (1990a)

Local effects:

Probably due to the epoxy moiety and the fact that rodents are obligatory nasal breathers, local effects (irritation of the nasal passages) were observed at all concentrations tested. Due to the absence of NOEC and differences in histopathology, the data cannot be used in assessing time dependency in the development of local effects in the upper respiratory system.

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Summary of mouse studies in NTP report 376

Key data extracted from Kalberlah and Schneider (1998), table 1a (figures in ppm)

Subacute study	Subchronic study	Chronic study
$NOEC_{local}$ target: (25) nose	$NOEC_{local}$ target: (1) nose	$NOEC_{local}$ target: (5) nose
$NOEC_{systemic}$ target: 25 mortality	$NOEC_{systemic}$ target: 30 --	$NOEC_{systemic}$ target: (5) b.w.

values in brackets ( ) represents LOAEL; n.p.= not performed; b.w. = change in body weight;
u.s. = unspecified symptoms; -- = no effects observed

Study details of NTP report 376

Subacute study	Subchronic study	Chronic study
Mice ($B6C3F_1$) 5 male/ 5 female: 0, 25, 50, 100 ppm. Exposure: 6 hours/day, 5 days/week for 2 weeks. Necropsy on all animals; histopathology on 1 or 2 from the higher dose groups.	Mice ($B6C3F_1$) 10 male/ 10 female: 0, 1, 4, 10, 30 ppm. Exposure: 6 hours/day, 5 days/week for 13 weeks. Full histopathology on controls and high dose group; including larynx, nasal cavity and trachea.	Mice ($B6C3F_1$) 50 male/ 50 female: 0, 5, 10 ppm. Exposure: 6 hours/day, 5 days/week for 103 weeks (rats) or 102 weeks (mice). Full histopathology on all rats and on controls and high dose mice; nasal cavity for low dose mice.
All male mice and 3/5 female died at 100 and 2/5 males and 1/5 females died at 50 ppm; acute inflammation of the nasal passages and major airways was observed.	$NOEC_{local}$ Not established $LOEC_{local}$ 1 ppm (nasal lesions) Squamous metaplasia of the nasal passage, involving both the respiratory epithelium and the olfactory epithelium, which tended to be more severe in the anterior and dorsal portions of the nasal passage at 10 and 30 ppm. In mice exposed to 30 ppm, epithelial erosions were also observed.	$NOEC_{local}$ Not established. Suppurative inflammation of nasal cavity; degeneration and metaplasia of olfactory epithelium in mice at the lowest concentrations tested (5 ppm).
NTP (1990a)	NTP (1990a)	NTP (1990a)

Local effects:

Probably due to the epoxy moiety and the fact that rodents are obligatory nasal breathers, local effects (irritation of the nasal passages) were observed at all concentrations tested. Due to the absence of NOEC and differences in histopathology, the data cannot be used for the assessment of time dependency of the development of local effects in the upper respiratory system.

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o-Chlorobenzal-malonitrile (CAS 2698-41-1)

Summary of rat studies in NTP report 377

Key data extracted from Kalberlah and Schneider (1998), table 1a (figures in ppm)

Subacute study	Subchronic study	Chronic study
$NOEC_{local}$ target: 3 nose	$NOEC_{local}$ target: (0.4) nose, larynx[1], trachea[1]	$NOEC_{local}$ target: (0.075) nose
$NOEC_{systemic}$ target: (1) u.s.	$NOEC_{systemic}$ target: 0.75 b.w.	$NOEC_{systemic}$ target: 0.25 b.w.

1) Adequacy of the shorter examination not judgeable on the basis of the description of the test design
values in brackets ( ) represents LOAEL; n.p.= not performed; b.w. = change in body weight;
u.s. = unspecified symptoms; -- = no effects observed

Study details of NTP report 377

Subacute study	Subchronic study	Chronic study
rats (F344/N) male/female 1, 3, 10, 30, 100 mg/m^3 Exposure: 6 hours/day, 5 days/week, 2 weeks. Histopathology (not specified): on selected rats and mice exposed at concentrations up to 30 mg/m^3.	rats (F344/N) male/female 0.4, 0.75, 1.5, 3, 6 mg/m^3 Exposure: 6 hours/day, 5 days/week, 13 weeks. Histopathology: - control and 3 and 6 mg/m^3: larynx, lungs, bronchi, trachea. - all groups: nasal passage.	rats (F344/N) male/female 0.075, 0.25, 075 mg/m^3 Exposure: 6 hours/day, 5 days/week, 105 weeks. Histopathology: - control and high dose: larynx, lungs, mainstem bronchi, nasal passage and turbinates, trachea. - lower dose groups: lungs (only males), nasal passage (both sexes). *Dose Selection Rationale:* Exposure concentrations were selected based on body weight gain and deaths observed at higher concentrations. Even though the exposure at highest concentration selected (0.75 mg/ m^3) resulted in nasal lesions, their severity was minimal and they were not considered to be life threatening.
30 and 100 mg/m^3: all animals died. Nasal discharge, dacryorrhea and mouth breathing observed only in 10 mg/m^3.	No NOEC established. Compound-related lesions: nasal passage, larynx, and trachea. At higher concentrations: more frequent and/or more severe. Focal erosions with regenerative hyperplasia and focal squamous metaplasia of the respiratory Epithelium; proliferation of the periosteum and new bone formation (hyperostosis) were associated with the inflammation in the nasal turbinates; inflammation and hyperplasia of the respiratory epithelium of the larynx and trachea in a few animals at the higher concentrations (minimal in severity compared with those in the nasal passage); minimal focal squamous metaplasia in the larynx of a few exposed rats.	No NOEC established. Nasal Passage; hyperplasia and focal squamous metaplasia of the respiratory epithelium occurred at increased incidences in rats exposed to 0.75 mg/m^3; inflammation, characterized by focal accumulations of mononuclear inflammatory cells in the submucosa, and proliferation of the periosteum of the turbinate bones at increased incidences in rats at the top concentration.
NTP (1990b)	NTP (1990b)	NTP (1990b)

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Local effects:
Although the effects on the nasal passage are seen in both the sub-chronic and chronic study, due to the absence of a defined NOEC the data cannot be used for the assessment of time dependency of the development of local effects in the upper respiratory system.

Summary of mouse studies in NTP report 377

Key data extracted from Kalberlah and Schneider (1998), table 1a (figures in ppm)

Subacute study	Subchronic study	Chronic study
$NOEC_{local}$ target: 3 nose	$NOEC_{local}$ target: 0.75 nose	$NOEC_{local}$ target: (0.75) nose
$NOEC_{systemic}$ target: (1) u.s.	$NOEC_{systemic}$ target: 1.5 b.w.	$NOEC_{systemic}$ target: (0.75) b.w.

values in brackets ( ) represents LOAEL; n.p.= not performed; b.w. = change in body weight;
u.s. = unspecified symptoms; -- = no effects observed

Study details of NTP report 377

Subacute study	Subchronic study	Chronic study
mice (B6C3F1) male/female 1, 3, 10, 30, 100 mg/m^3 Exposure: 6 hours/day, 5 days/week, 2 weeks. Histopathology (not specified) on selected rats and mice exposed at concentrations up to 30 mg/m^3	mice (B6C3F1) male/female 0.4, 0.75, 1.5, 3, 6 mg/m^3 Exposure: 6 hours/day, 5 days/week, 13 weeks. Histopathology: - control and 3 and 6 mg/m^3: larynx, lungs, bronchi, trachea - all groups: nasal passage.	mice (B6C3F1) male/female 0.75, 1.5 mg/m^3 Exposure: 6 hours/day, 5 days/week, 105 weeks. Histopathology: - control and high dose: larynx, lungs, mainstem bronchi, nasal passage and turbinates, trachea - lower dose groups: lungs (only males), nasal passage (both sexes).
All animals died in the 10, 30 and 100 mg/m^3 groups. Dacryorrhea and nasal discharge observed in 30 mg/m^3.	All animals died in the 6 mg/m^3 group. $NOEC_{local}$ 0.75 mg/m^3 In 1.5 mg/m^3 and higher: compound-related lesions in the nasal passage (focal inflammation and squamous metaplasia, primarily in the nasal turbinates, and inflammation in the vomeronasal organ).	$NOEC_{local}$ not established. $LOEC_{local}$ 0.75 mg/m^3. Main affected site: respiratory epithelium, nasal passage.
NTP (1990b)	NTP (1990b)	NTP (1990b)

Local effects:
The nose is one of the target organs that are affected by exposure to o-chlorobenzal-malonitrile. The histopathology in the two-week study was limited compared to the sub-chronic and chronic study. In the two-year study it was not possible to determine a NOEC.

These studies can be used for the assessment of time dependency of the development of local effects from sub-acute to sub-chronic exposure and they suggest an AF of 2.

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2-Chloro-acetophenone (CAS 532-27-4)

Summary of rat studies in NTP report 314

Key data extracted from Kalberlah and Schneider (1998), table 1a (figures in ppm)

Subacute study	Subchronic study	Chronic study
$NOEC_{local}$ target: 64 --	$NOEC_{local}$ target: 4 --	$NOEC_{local}$ target: (1) nose[1]
$NOEC_{systemic}$ target: (4.8) b.w., u.s.	$NOEC_{systemic}$ target: 2 b.w.	$NOEC_{systemic}$ target: (1) stomach[1]

1) Adequacy of the shorter examination not judgeable on the basis of the description of the test design values in brackets ( ) represents LOAEL; n.p.= not performed; b.w. = change in body weight; u.s. = unspecified symptoms; -- = no effects observed

Study details of NTP report 314

Subacute study	Subchronic study	Chronic study
rat (F344/N) male/female (5 animals/sex) 4.8, 10, 19, 43, 64 mg/m^3 Exposure: 6 hours/day, 5 days/week, 2 weeks. Histopathologic examinations were performed on two rats and one male and one female rat exposed to 10 mg/m^3. Tissues not specified.	rat (F344/N) male/female (10 animals/sex) 0.25, 0.5, 4 mg m^3 Exposure: 13 weeks. Histopathologic examinations were performed on all controls and animals exposed to 4 mg/m^3 and all animals dying before the end of the studies Tissues not specified.	rat (F344/N) male/female (60 animals/sex) 1, 2 mg/m^3 Exposure: 6 hours/day, 5 days/week, 15 month and 2 years. Histopathology: all males, females 2 mg/m^3 larynx, lungs, mainstem bronchi, nasal passage and turbinates, trachea and tracheobronchial lymph nodes.
All rats exposed to 19, 43, or 64 mg/m^3 and 1/5 male rats exposed to 10 mg/m^3 died before the end of the study. No local effects reported.	Eye irritation during exposure observed in animals exposed to 0.5 mg/m^3 or higher. No local effects reported.	$NOEC_{local}$ 1 mg/m^3 15 month: Minimal-to-mild focal squamous metaplasia and hyperplasia of the respiratory epithelium were seen at increased incidences in rats exposed to 2 mg/m^3 (metaplasia--male: control, 0/10; 1 mg/m^3, 0110; 2 mg/m^3, 2/10; female: 0/10; 0/10; 3/10; hyperplasia- male: 0/10; 1/10; 5/10; female: 1/10; 1/10; 9/10). 2 years: Squamous metaplasia of the respiratory epithelium was seen in 4/49 female and 2/48 male mice exposed to 4 mg/m^3 The irritant effects on the nasal mucosa may have been exacerbated by viral infection.
NTP (1990c)	NTP (1990c)	NTP (1990c)

Local effects:

The concentrations selected for the sub-acute study produced a marked lethality at 10 mg/m^3 and above. Furthermore, as it is not clear whether histopathology of the nasal passages was performed in either this or the sub-chronic study, it is not reliable to assume that the highest concentration studied in either study is a NOEL for local effects. This is further justified by the observation of eye irritation at 0.5 mg/m^3 or higher indicating that local effects would have been likely in the sub-chronic study. Local effects were observed in the two-year study with an apparent NOEC of 1 mg/m^3. In the study report it is recognised, however, that these effects may

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have been exacerbated by infection which was commonly observed in both control and test animals that were used in studies with other chemicals during that time. Therefore, the NTP data on 2-chloro-acetophenone in rats cannot be used for the assessment of time dependency of the development of local effects in the upper respiratory system.

Summary of mouse studies in NTP report 314

Key data extracted from Kalberlah and Schneider (1998), table 1a (figures in ppm)

Subacute study	Subchronic study	Chronic study
$NOEC_{local}$ target: 64 --	$NOEC_{local}$ target: 4 --	$NOEC_{local}$ target: 4 --
$NOEC_{systemic}$ target: (4.8) u.s.	$NOEC_{systemic}$ target: (0.25) b.w.	$NOEC_{systemic}$ target: 2 b.w.

values in brackets ( ) represents LOAEL; n.p.= not performed; b.w. = change in body weight;
u.s. = unspecified symptoms; -- = no effects observed

Study details of NTP report 314

Subacute study	Subchronic study	Chronic study
mice (B6C3F1) male/female (5 animals/sex) 4.8, 10, 19, 43, 64 mg/m^3 Exposure: 6 hours/day, 5 days/week, 2 weeks. Histopathologic examinations were performed on three mice of each sex exposed to 4.8 mg/m^3. Tissues not specified.	mice (B6C3F1) male/female (10 animals/sex) 0.25, 0.5, 4 mg/m^3 Exposure: 13 weeks. Histopathologic examinations were performed on all controls and animals exposed to 4 mg/m3 and all animals dying before the end of the studies Tissues not specified.	mice (B6C3F1) male/female 2, 4 mg/m^3 Exposure: 6 hours/day, 5 days/week, 2 years. Histopathology (all animals): larynx, lungs, mainstem bronchi, nasal passage and turbinates, trachea, tracheobronchial lymph nodes.
All mice exposed to 10 mg/m^3 or more died before the end of the studies. No compound- related lesions were seen in mice exposed to 4.8 mg/m^3. No local effects reported.	No compound-related lesions included eye irritation during exposure to 0.5 mg/m^3 or higher were observed.	$NOEC_{local}$ 2 mg/m$^{3.}$ 15 month: No local effects. 2 yr: Squamous metaplasia of the respiratory epithelium of the nasal passage was seen in four females and two males exposed to 4 mg/m^3.
NTP (1990c)	NTP (1990c)	NTP (1990c)

Local effects:

Very similar effects were seen in mice and in rats. The concentrations selected for the sub-acute study produced a marked lethality at 10 mg/m^3 and above. Furthermore, as it is not clear whether histopathology of the nasal passages was performed in this or the sub-chronic study, it is not reliable to assume that the highest concentration studied in either study is a NOEL for local effects. Local effects were observed in the two-year study with an apparent NOEC of 2 mg/m^3. Therefore, the NTP data on 2-chloro-acetophenone in rats cannot be used for the assessment of time dependency of the development of local effects in the upper respiratory system.

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1-Epinephrine hydrochloride (CAS 55-31-2)

Summary of rat studies in NTP report 380

Key data extracted from Kalberlah and Schneider (1998), table 1a (figures in ppm)

Subacute study	Subchronic study	Chronic study
$NOEC_{local}$ target: 200 --	$NOEC_{local}$ target: 10 larynx, nose	$NOEC_{local}$ target: (1.5) nose
$NOEC_{systemic}$ target: (12.5) mortality	$NOEC_{systemic}$ target: 20 u.s., heart, adrenals	$NOEC_{systemic}$ target: 5 --

Concentrations in mg/m^3 values in brackets ( ) represents LOAEL; n.p.= not performed; b.w. = change in body weight; u.s. = unspecified symptoms; -- = no effects observed

Study details of NTP report 380

Subacute study	Subchronic study	Chronic study
rat (Fischer 344) male/female 12.5, 25, 50, 100 and 200 mg/m^3. Exposure: 2 weeks, 5 days/week, 6 hours/day. Exposure to acidic aerosol in dilute hydrochloric acid solution (pH 2.8). Histopathology on 12.5, 25, 50 mg/m^3 groups. Histological examination of 1-2 animals from each of the 12.5, 25, and 50 mg/m^{3}groups but it does not indicate whether nasal passage were sectioned.	rat (Fischer 344) male/female 2.5, 5, 10, 20 and 40 mg/m^3 Exposure: 13 weeks, 5 days/week, 6 hours/day. Exposure to acidic aerosol in dilute hydrochloric acid solution (pH 2.8). Histological examination of nasal passage of control and 40 mg/m^3 animals and all animals dying before the end of the studies as well as anterior nasal passage on 20 mg/m^3 animals.	rat (Fischer 344) male/female: 1.5 and 5 mg/m^3 Exposure: 103 weeks, 5 days/week, 6 hours/day. Exposure to acidic aerosol in dilute hydrochloric acid solution (pH 2.8). Histopathology of local effects included nasal passage and larynx. High dose ¼ of the MTD; studies were considered inadequate for detecting carcinogenic activity.
All male rats exposed to 50 mg/m^3 epinephrine or greater and all females exposed to 100 mg/m^3 or greater died before the end of the studies. 3/5 female rats exposed to 50 mg/m^{3,} 4/5 male rats and 1/5 female rats exposed to 25 mg/m^3, and 3/5 male rats exposed to 12.5 mg/m^3 died before the end of the studies. No local effects reported but not clear if nasal passages were sectioned.	$LOEC_{local}$ 20 mg/m^3 $NOEC_{local}$ not established. Degenerative lesions of the laryngeal muscle at 20 or 40 mg/m^3. Squamous metaplasia in respiratory epithelium of the nasal mucosa at 40 mg/m^3. 10 mg/m^3 animals not examined.	$NOEC_{local}$ not established. $LOEC_{local}$ 1.5 mg/m^3 Suppurative inflammation of nasal passage, dilatation of nasal gland, hyperplasia of respiratory epithelium.
NTP (1990d)	NTP (1990d)	NTP (1990d)

Local effects:

In the sub-acute study it is not clear whether the lack of reporting of local effects was due to an absence of effects or due to the absence of histological examination of the nasal passages. Hence, no NOEC can be established. In the sub-chronic study only animals in the 20 and 40 mg/m^3 groups were subject to histological examination of the nasal passages. Hence, 20 mg/m^3 was the LOEC for this effect and no NOEC could be established. A LOEC of 1.5 mg/m^3 was established in the chronic study, but this was the lowest concentration investigated and no NOEC could be established. The data cannot be used for the assessment of the time dependency of the development of local effects in the nasal passages from sub-chronic to chronic exposure.

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Summary of mouse studies in NTP report 380

Key data extracted from Kalberlah and Schneider (1998), table 1a (figures in ppm)

Subacute study	Subchronic study	Chronic study
$NOEC_{local}$ target: 200 --	$NOEC_{local}$ target: 20 nose	$NOEC_{local}$ target: (1,5) nose
$NOEC_{systemic}$ target: (12,5) u.s.	$NOEC_{systemic}$ target: 5 stomach	$NOEC_{systemic}$ target: 3 --

Concentrations in mg/m^3 values in brackets ( ) represents LOAEL; n.p.= not performed; b.w. = change in body weight; u.s. = unspecified symptoms; -- = no effects observed

Study details of NTP report 380

Subacute study	Subchronic study	Chronic study
mice (B6C3F1) male/female 12.5, 25, 50, 100 and 200 mg/ Exposure: 2 weeks, 5 days/week, 6 hours/day. Exposure to acidic aerosol in dilute hydrochloric acid solution (pH 2.8). Histopathology on 12.5, 25, 50 mg/m^3 groups. Histological examination of 1-2 animals from each of the 12.5, 25, and 50 mg/m^3 groups but it does not indicate whether nasal passage were sectioned.	mice (B6C3F1) male/female 2.5, 5, 10, 20 and 40 mg/m^3 Exposure: 13 weeks, 5 days/week, 6 hours/day. Exposure to acidic aerosol in dilute hydrochloric acid solution (pH 2.8). Histological examination of nasal passage of control and 40 mg/m^3 animals and all animals dying before the end of the studies as well as anterior nasal passage on 20 mg/m^3 animals.	mice (B6C3F1) male/female 1.5 and 3 mg/m^3 Exposure: 104 weeks, 5 days/week, 6 hours/day. Exposure to acidic aerosol in dilute hydrochloric acid solution (pH 2.8). Histopathology of local effects included nasal passage and larynx. High dose is 1/8 of the MTD; studies were considered inadequate for detecting carcinogenic activity.
All mice exposed to 100 or 200 mg/m^3 and 2/5 male mice and 1/5 female mice exposed to 50 mg/m^3 died before the end of the studies. No local effects reported but not clear if nasal passages were sectioned.	$LOEC_{local}$ 20 mg/m^3 $NOEC_{local}$ not established. Squamous metaplasia in respiratory epithelium of the nasal mucosa at 40 mg/m^3. 10 mg/m^3 animals not examined.	$NOEC_{local}$ not established. $LOEC_{local}$ 1.5 mg/m^3 Suppurative inflammation of nasal passage, hyaline degeneration of olfactory and respiratory epithelium.
NTP (1990d)	NTP (1990d)	NTP (1990d)

Local effects:

In the sub-acute study it is not clear whether the lack of reporting of local effects was due to an absence of effects or due to the absence of histological examination of the nasal passages. Hence, no NOEC can be established. In the sub-chronic study only animals in the 20 and 40 mg/m^3 groups were subject to histological examination of the nasal passages. Hence, 20 mg/m^3 was the LOEC for this effect and no NOEC could be established. A LOEC of 1.5 mg/m^3 was established in the chronic study, but this was the lowest concentration investigated and no NOEC could be established. The data cannot be used for the assessment of the time dependency of the development of local effects in the nasal passages from sub-chronic to chronic exposure.

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Methyl bromide (CAS 74-83-9)

Summary of mouse studies in NTP report 385

Key data extracted from Kalberlah and Schneider (1998), table 1a (figures in ppm)

Subacute study	Subchronic study	Chronic study
$NOEC_{local}$ target: 100 lung	$NOEC_{local}$ target: 120 --	$NOEC_{local}$ target: 10 nose
$NOEC_{systemic}$ target: (12) u.s.	$NOEC_{systemic}$ target: 20 blood [1)]	$NOEC_{systemic}$ target: (10) heart

[1)]Target organ not adequately examined in the shorter study values in brackets ( ) represents LOAEL;
n.p.= not performed; b.w. = change in body weight; u.s. = unspecified symptoms; -- = no effects observed

Study details of NTP report 385

Subacute study	Subchronic study	Chronic study
B6C3F1 mice Doses: 0, 12, 25, 50, 100 or 200 ppm Duration of dosing: 6 hours/day; 10 exposures over 14 days. group size: 5 animals per sex. Histopathology on control, 100 and 200 ppm groups only. Organs investigated included lung with main steam bronchi as well as nasal cavity and turbinates.	B6C3F1 mice 0, 10, 20, 40, 80, 120 ppm 6 hours/day; 5 days/week for 13 weeks. 10 animals per sex. All animals including lung with main steam bronchi as well as nasal cavity and turbinates.	B6C3F1 mice 0, 10, 33, 100 ppm 10/33 ppm group: 6 hours/day; 5 days/week for 103 weeks <u>100 ppm: 6 hours/day; 5 days/week for 20 weeks followed by 84 weeks of observation.</u> Interim sacrifice after 6 and 15 months 70 animals per sex All animals including : - lung with main steam bronchi - nasal cavity and turbinates.
Results with respect to local effects: -minimal hyperemia of the lung at 200 ppm.	No effects reported.	Treatment related increased incidence of non-neoplastic lesions in the nose: 0; 10; 33 and 100 ppm. Olfactory epithelium: Metaplasia Males: 0/50; 0/50; 1*/50; 2*/69 Females: 0/50; 0/50; 0/50; 5*/60 *terminal sacrifice Necrosis Males: 0/50; 0/50; 0/50; 6**/69 Females: 0/50; 0/50; 0/50; 1**/60 **Animals that died during day 4 and 138.
NTP (1992)	NTP (1992)	NTP (1992)

No local effects were reported in the sub-acute or sub-chronic study. Local effects were observed in the 'chronic' study but the animals determining the LOEC (100 ppm) were exposed only for 20 weeks, because exposure was terminated after 20 weeks due to debilitating neurotoxicity and mortalities. These animals were subsequently exposed to untreated air for the remainder of the two-year study period. Necrosis was observed only in animals that died during day 4 and 138. In conclusion, the local effects observed at 100 ppm in the 'chronic' study were due to sub-chronic exposure. These data cannot be used for the assessment of the time dependency of the development of local effects.

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Tetranitromethane (CAS 509-14-8)

Summary of rat studies in NTP report 386

Key data extracted from Kalberlah and Schneider (1998), table 1a (figures in ppm)

Subacute study	Subchronic study	Chronic study
$NOEC_{local}$ target: 10 lung	$NOEC_{local}$ target: 5 lung	$NOEC_{local}$ target: (2) lung
$NOEC_{systemic}$ target: 5 b.w.	$NOEC_{systemic}$ target: (0.2) liver	$NOEC_{systemic}$ target: 2 b.w.

[1)] Target organ not adequately examined in the shorter study values in brackets ( ) represents LOAEL; n.p.= not performed; b.w. = change in body weight; u.s. = unspecified symptoms; -- = no effects observed

Study details of NTP report 386

Subacute study	Subchronic study	Chronic study
SD rats (Male/Female; 5 animals per sex): 0, 2, 5, 10, 25 ppm; 6 hours/day; 10 exposures over 14 days. Histopathology (2 males /females in control); 1 male/female in dose groups. Tissues examined not specified.	SD rats (Male/Female; 10 animals per sex) 0, 0.2, 0.7, 2, 5, 10 ppm: 6 hours/day; 5 days/week for 13 weeks (65 exposures). Necropsy performed on all animals; histologic exams performed on all controls and the 5 and 10 ppm groups. Tissues examined included lungs, bronchi, trachea and nasal cavity but it is not clear if they performed serial sections of the nasal cavity and turbinates.	SD rats (Male/Female; 50 animals per sex; additional 6-10 animals for interim sacrifice) 0, 2, 5 ppm; 6 hours/day; 5 days/week for 52 or 103 weeks. Necropsy and histologic exams performed on all animals. Tissues examined included lungs, bronchi, trachea and nasal cavity but it is not clear if they performed serial sections of the nasal cavity and turbinates.
$NOEC_{local}$ Not established The two rats exposed to 25 ppm and examined microscopically had mild-to-moderate pulmonary oedema characterized by the accumulation of proteinaceous eosinophilic material in alveoli and in interstitial spaces surrounding bronchioles. All rats exposed to 25 ppm and 50 ppm died by day 2; reduced survival (4/5) in rats exposed to 10 ppm.	$NOEC_{local}$ 5ppm $LOEC_{local}$ 10ppm Serous exudates in the nasal passage in 9/10 (male) and 8/10 (female) rats at 10 ppm. Focal squamous metaplasia of the respiratory epithelium of mild to moderate severity was observed in 4/10 (female) rats at 10 ppm. Minimal-to-moderate chronic inflammation of the lung in 10/10 (males) and 7/10 (females) at 10 ppm.	$NOEC_{local}$ 2ppm $LOEC_{local}$ 5ppm Hyperplasia of the respiratory epithelium in male and female rats: (7/50), (15/50) and (29/50) in males and (5/50), (3/50) and (2/50) in females. Squamous metaplasia of the respiratory epithelium in males (0/50), (1/50) and (13/50) in males, and inflammation of the nasal mucosa in 5 ppm males and females (12/50), (20/50) and (37/50) in males and (13/50), (9/50) and (31/50) in females.
NTP (1990e)	NTP (1990e)	NTP (1990e)

No local effect was reported in the sub-acute study but this was probably due to the fact that all animals died at the top two concentrations and no histopathology was performed on the lower concentrations. Local effects in the nasal cavity were observed in the sub-chronic and chronic studies. Histopathology of the nasal cavity in the sub-chronic study was more limited than in the chronic study. When combined with the presence of background infection in the chronic study, which may have contributed to the prevalence and severity of effects observed, the NOEC appears less reliable. The available information is insufficient to make any assessment of time dependency of the development of local effects in the upper respiratory system.

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Summary of mouse studies in NTP report 386

Key data extracted from Kalberlah and Schneider (1998), table 1a (figures in ppm)

Subacute study	Subchronic study	Chronic study
$NOEC_{local}$ target: 10 lung	$NOEC_{local}$ target: 0.2 nose, lung	$NOEC_{local}$ target: (0.5) nose, lung
$NOEC_{systemic}$ target: 5 b.w.	$NOEC_{systemic}$ target: 5 b.w.; unspecific symptoms	$NOEC_{systemic}$ target: 0.5 b.w.

values in brackets ( ) represents LOAEL; n.p.= not performed; b.w. = change in body weight; u.s. = unspecified symptoms; -- = no effects observed

Study details of NTP report 386

Subacute study	Subchronic study	Chronic study
B6C3F mice (male/female: 5 per sex): 0, 2, 5, 10, 25, 50 ppm: 6 hours/day; 10 exposures over 14 days. Histopathology (2 males /females in control); 1 male/female in dose groups. Tissues examined not specified.	B6C3F mice (male/female: 10 per sex): 0, 0.2, 0.7, 2, 5, 10 ppm: 6 hours/day; 5 days/week for 13 weeks (65 exposures). Necropsy performed on all animals; histologic exams performed on all controls and the 5 and 10 ppm groups. Tissues examined included lungs, bronchi, trachea and nasal cavity but it is not clear if they performed serial sections of the nasal cavity and turbinates.	B6C3F mice (male/female: 50 per sex; additional 6-10 animals for interim sacrifice): 0, 0.5, 2.0 ppm: 6 hours/day; 5 days/week for 52 or 103 weeks. Necropsy and histologic exams performed on all animals. Tissues examined included lungs, bronchi, trachea and nasal cavity but it is not clear if they performed serial sections of the nasal cavity and turbinates.
$NOEC_{local}$ Not established Reddened lungs were seen in exposed mice at necropsy (conc. not stated). Inflammation was observed in the lungs of the three mice exposed to 10 or 25 ppm which lived to the end of the studies and were examined microscopically.	$NOEC_{local}$ 0.7 ppm $LOEC_{local}$ 2 ppm Histopathology nose and lung; most sensitive endpoint. No data given for 0.2 ppm gp. Brochiolar epithelium hyperplasia: Control; 0.7; 2; 5; 10 ppm males: 0/10; 0/10; 2/10; 5*/19; 10*/10 females: 0/10; 1/10; 5*/10; 10*/10; 10*/10	1 year: Alveolar hyperplasia in 5/50, and bronchiolar hyperplasia in 2/50 mice at 2 ppm. Hyperplasia of the respiratory epithelium was seen in the nasal passage of one mouse exposed to 0.5 ppm. 2 years: $NOEC_{local}$ 0.5 ppm nasal effects $LOEC_{local}$ 0.5 ppm bronchiolar and lungs effects Chronic inflammation (11/50; 11/50; 23/50) of the nasal mucosa and hyperplasia (2/50; 5/50; 17/50) and squamous metaplasia (0/50; 2/50; 8/50) of the respiratory epithelium in female mice. Alveolar hyperplasia and bronchiolar hyperplasia was observed at increased levels above controls at 0.5 and 2 ppm.
NTP (1990e)	NTP (1990e)	NTP (1990e)

No local effect was reported in the sub-acute study but this was probably due to the fact that all animals died at the top two concentrations and no histopathology was performed on the lower concentrations. In sub-chronic and chronic studies, tetranitromethane produced more marked local effects in bronchioles and lungs than the nasal passages. The NOEC for local irritation

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effects in the nasal passages was 0.7 ppm in the sub-chronic and 0.5 ppm in the chronic study. Bronchiolar effects were more prevalent in the chronic study than in the one-year and sub-chronic study. The available information is insufficient to make any assessment of time dependency of the development of local effects in the upper respiratory system.

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Appendix C

Quantitative assessment of the time dependency of the development of local effects in the upper respiratory tract (from SCOEL, AGS, EU ESR evaluations)

This appendix contains a few examples on chemicals for which reliable and comparable inhalation studies with different exposure duration are available. They were identified by a quick, non-comprehensive, search of recent SCOEL summary documents, German AGS documentation, EU ESR reports and some personal knowledge.

Overall, this admittedly limited dataset indicates that an AF>1 for time extrapolation starting from sub-acute or sub-chronic studies might not be appropriate.

2-(2-Butoxyethoxy)ethanol – (DEGBE) (CAS 112-34-5)

Studies in rats

Data from SCOEL SUM 10, 2002

Subacute study	**Subchronic study**	**Chronic study**
NOELlocal: --- LOELlocal: 100 mg/m^3 1st study: Wistar rats, groups of 5 males and 5 females received 0, 100 (vapour), 350 (aerosol), and 1000 mg/m^3 DEGBE 6 hours/day, 5 days/week for 2 week (BASF, 1991a). Only 1 animal /group investigated. 2nd study 10 female rats were exposed over 14 days (6 hours/day, 5 days/week) to 350 mg/m³ (BASF, 1991b).	NOELlocal: 94 mg/m^3 LOELlocal: --- Wistar rats, groups of 10 males and 10 females received 0, 2, 6, and 14 ppm (corresponding to 0, 13, 40, and 94 mg/m^3) DEGBE as vapour 6 hours/day, 5 days/week for 90 days followed by a 4 week recovery period (BASF, 1992).	
As regards effects in the respiratory tract, perivascular and peribronchial infiltrate in the only male and female animal investigated and increased lung weight were observed at the two highest doses for males and females (1st study). Due to the indication of lung infection the 2nd study was performed. Lung weight was not affected, but again perivascular and peribronchial infiltrates were found with bronchiolisation. Target for local effects: lung.	No effects were recorded. NOAEL was 94 mg/m³.	
SCOEL SUM 10	SCOEL SUM 10	No study mentioned in SCOEL SUM 10

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SCOEL indicates that 94 mg/m^3 is the highest vapour concentration achievable at room temperature and higher concentrations *"lead to aerosol formation, which might explain the lung effects seen in the sub-acute studies"*. The available data indicate that the NOAEL for vapour did not decrease from sub-acute to sub-chronic exposure, while the LOEL for a vapour/aerosol mixture was not tested in the sub-chronic study. No chronic study was reported. It is concluded that the $NOAEC_{local}$ for lung toxicity (sub-acute, 14 days) at 100 mg/m³ corresponds to the $NOAEC_{sub\text{-}chronic}$. Lung toxicity was observeD at the next higher concentration in the sub-acute study at an aerosol concentration of 350 mg/m³. These data suggest that in the case of DEGBE, no additional AF is required for time extrapolation between sub-acute and sub-chronic exposure for local effects.

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Formaldehyde (CAS 50-00-0)

Studies in rats

Data from Kerns et al, 1983

Rat, squamous metaplasia (% incidence):
The % incidence of squamous metaplasia is given in the table and was estimated from a figure given in the publication. Apart from squamous metaplasia, purulent rhinitis and dysplasia were observed, but no quantitative data are given.

Nasal level	Conc. (ppm)	Effects observed after (months)			
		6	**12**	**18**	**24**
I	0*	15*?	15*?	15*?	15*?
	2	10	35	60	100
	5.6	50	60	85	100
	14.3	100(?)	100(?)	100	100
II	2	0	0	0	0
	5.6	50	40	60	60
	14.3	?	?	100	100
III	2	0	0	0	0
	5.6	0	0	0	10
	14.3	30	50	100	95
IV	2	0	0	0	0
	5.6	0	0	0	0
	14.3	0(?)	0(?)0	35	80
V	2	0	0	0	0
	5.6	0	0	0	0
	14.3	0(?)	0(?)	30	70

* For the 0 ppm exposure group an incidence of less than 15% is described for level I only, but it is unclear at what time point (possibly versus the end of exposure time?).
(?): no data given, but plausible extrapolation due to the other concentrations/time points.
(?): no data given; no plausible extrapolation possible.

Interpretation:
There is insufficient information about the time point when the effects at level I were observed in control animals. Therefore, it is unclear whether at level I the NOAEC was <2 ppm already after 6 months or later after 12 months. But the NOAEC was clearly <2 ppm at level I after 12 months and the incidence at 2 ppm clearly increased from 12 to 24 months. These isolated findings at level I may justify a time extrapolation AF of >1.

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On the other hand, for level II the NOAEC was 2 ppm for all time points. For level III, there was an indication that the NOAEC decreased from 5.6 to 2 ppm between month 18 and 24, and the NOAEC might decrease at level IV and V from 14.3 to 5.6 between month 12 and 18.

Overall, these data may indicate a time-extrapolation AF>1. But these data only represent squamous metaplasia and no quantitative information is available for other alterations of the nasal tissue.

Data from Monticello et al, 1991

Male Fischer 344 rats, exposed at 0, 0.7, 2, 6, 10 ppm; histopathology and cell proliferation at sites of the nasal passages most susceptible to neoplasia (nose at levels I – V) after 1, 4, 9 days and 6 weeks.

Nasal level*	**Conc. (ppm)**	**Histopath. after 1-9 days**	**6 weeks ****
II	0	--	--
	0.7	--	--
	2	--	--
	6	+ // +/--	+ // +/--
	10	++ // +	++
	15	+++ // ++	+++
III	0	--	--
	0.7	--	--
	2	--	--
	6	--	--
	10	+	+
	15	++	++

* different sites were investigated at level II and III
** the results for the different sites are here summarised
(lesions absent: --; minimal: +/--; mild: +; moderate: ++; marked: +++)

Histopathology (light microscopy):
At no time point formaldehyde induced lesions were observed at 0.7 and 2 ppm.
Lesions at predilection sites at level II and III:
Day 1: lesions after 10 and 15 ppm, which became more severe and extensive with prolongation of exposure. NOAEC 6 ppm.
Day 4: progression to erosion and local ulceration at 10 and 15 ppm. NOAEC 6 ppm.
Day 9: hyperplasia and metaplasia. Lesions extended posteriorly and occasionally reached level IV. Only after day 9 less severe lesions already occurred at 6 ppm. NOAEC 2 ppm.

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Week 6: at 10 and 15 ppm hyperplasia and metaplasia with neutrophilic infiltration at level II and III and extending to the nasopharynx. At 6 ppm mild lesions only at level II. NOAEC 2 ppm.

Cell proliferation:
No increase of cell proliferation at 0.7 and 2 ppm.
Predilection sites similar to those for histopathology but at some locations increased cell proliferation occurred without histopathological lesions.
Day 1: statistically significant increase at 6, 10, 15 ppm. NOAEC: 2 ppm.
Day 4, 9, week 6: qualitatively similar to day 1, but more pronounced at the more posterior regions at 6, 10, 15 ppm. NOAEC: 2 ppm.

Data from Monticello et al, 1996

This study is an extension of Monticello *et al* (1991) for up to two years with interim sacrifices after 3, 6, 12, and 18 months.

Histopathology:
At all time points investigated treatment related effects were confined to the anterior nasal passages. They were most severe at 10 and 15 ppm (hypertrophy, hyperplasia, metaplasia, inflammatory cell infiltrate), while lesions at 6 ppm were minimal. An additional olfactory degeneration was found at 10 and 15 ppm. NOAEC: 2 ppm.

Cell proliferation:
Statistically significant increase only at 10 and 15 ppm with the magnitude generally being greater at 15 ppm. The magnitude of increased cell proliferation decreased with time but still remained statistically significant at some locations at 18 months. NOAEC: 6 ppm.

Interpretation of Monticello et al (1991, 1996):
Progression of histopathological lesions from day 1 to day 9 with a decrease of NOAEC from 6 to 2 ppm. Thereafter no further change up to month 18. For cell proliferation there was no increase from day 1 to week 6 and the NOAEC was 2 ppm at all time points up to week 6. Thereafter the magnitude of cell proliferation decreased and the NOAEC was 6 ppm; further decrease of cell proliferation until month 18, but NOAEC remained at 6 ppm.

The data of Monticello *et al* (1991, 1996) were confirmed by an independent experiment of Casanova *et al* (1994), see below.

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Data from Casanova et al, 1994

Male Fischer 344 rats were exposed to 0, 0.7, 2, 6, and 15 ppm over 11 weeks.

Histopathology:
Lesions corresponded to those described by Monticello *et al* (1991). NOAEC: 2 ppm.

Cell proliferation:
Statistically significant increase of cell proliferation at 6 ppm only for one specific location, more pronounced and extended cell proliferation at 15 ppm. NOAEC: 2 ppm.

Overall conclusion from the rat studies:
The histopathological findings of Kerns *et al* (1983) and Monticello *et al* (1991, 1996) are somewhat conflicting with regard to time dependency. More weight must be given to the more recent investigations of Monticello and co-workers that were specifically designed to investigate time and dose dependency of histopathological lesions and cell proliferation using more and more closely spaced exposure concentrations. Furthermore, the findings of Monticello and co-workers were confirmed by an independent investigation (Casanova *et al*, 1994). Histopathological lesions increased from 1 to 9 days with a decreasing NOAEC from 6 to 2 ppm. Thereafter, up to 18 months no exposure time- related trends were observed for histopathological effects.

Cell proliferation was increased already from day 1 onwards to week 6 with a NOAEC of 2 ppm. Thereafter the magnitude of cell proliferation decreased and the NOAEC was 6 ppm from month 3 throughout to month 18.

Overall, these data justify an AF of 1 for time extrapolation of local effects from sub-acute to chronic exposure duration. But for very short exposure periods of up to 9 days the NOAEC for nasal lesions may decrease with time.

Studies in mice

Data from Kerns et al, 1983

The same exposure concentrations and time points for interim sacrifices as in the rat study: 0. 2, 5.6, and 14.3 ppm; 6, 12, 18, and 24 months.

NOAEC after: (months)			
6	**12**	**18**	**24**
14.3 ppm	5.6 ppm	2 ppm	2 ppm

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The findings of Kerns and co-workers are quantitatively in contrast to those reported by Maronpot *et al* (1986), see below.

Data from Maronpot et al, 1986

B6C3F1 mice (male + female) were exposed to 0, 2, 4, 10, 20, and 40 ppm over 13 weeks. Histopathological lesions (metaplasia, inflammation) were observed in the nasal cavity at 10 ppm and above. The NOAEC was around 4 ppm.

Effect	**Incidences (male + female) at (ppm)**					
Nasal cavity	0	2	4	10	20	40
Metaplasia	0/20	0/20	1/20	20/20	20/20	20/20
Inflammation	0/20	0/20	0/20	4/20	18/20	20/20

Overall conclusion from the mouse studies:

There was a large discrepancy between both studies, i.e. the NOAEC after 6 months was 14.3 ppm in the study by Kerns and co-workers, but around 4 ppm after 3 months in the one by Maronpot and co-workers. Therefore the studies in mice do not allow any conclusion for the time-extrapolation factor.

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Morpholine (CAS 110-91-8)

Studies in rats

Data from Conaway et al, 1984

Exposure at 25, 100, and 250 ppm over 13 weeks with interim sacrifice after 7 weeks.

Data from Harbison et al, 1989

Exposure at 10, 50, and 150 ppm over 105 weeks.

Effect	**Conc. (ppm)**	**Incidence (male; female) observed after (weeks)**		
		7	**13**	**105**
Erosion, squamous metaplasia (focal)	250	6/10; 2/10	10/10; 8/10	NI
Neutrophile infiltrate Squamous metaplasia Necrosis of turbinates	150	NI	NI	27/57; 41/60 46/57; 42/60 20/57; 35/60
Focal necrosis, cell debris	100	0/10; 0/10	0/10; 2/10	NI
Neutrophile infiltrate Squamous metaplasia Necrosis of turbinates	50	NI	NI	6/60; 10/60 7/60; 2/60 6/60; 2/60
Focal necrosis, cell debris	25	0/10; 0/10	0/10; 0/10	NI
Neutrophile infiltrate Squamous metaplasia Necrosis of turbinates	10	NI	NI	5/60; 8/60 1/60; 0/60 0/60; 0/60
Neutrophile infiltrate Squamous metaplasia Necrosis of turbinates	0	NI	NI	5/59; 6/60 3/59; 3/60 0/59; 1/60
NOAEC		100 ppm	25 ppm, slightly <100 ppm	10 ppm, slightly <50 ppm

NI = not investigated

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Overall conclusion:

The NOAEC slightly decreased from week 7 (100 ppm) to week 13. A further slight decrease was noticed by prolongation of exposure to two years with a NOAEC of slightly below 50 ppm. This decrease of the NOAEC after two years was governed by necrosis of the nasal turbinates in male animals, an effect not observed after 7 or 13 weeks of exposure. On the other hand, the NOAEC for squamous metaplasia that was the predominant effect after 7 and 13 weeks and for neutrophile infiltration was 50 ppm after 105 weeks.

These data indicate that the NOAEC decreases by a factor being slightly higher that 2-fold up to 10-fold when the duration of exposure to morpholine is increased from 7 to 105 weeks. The LOAEC in the chronic study was higher than the NOAEC in the sub-chronic study. This might indicate that different dose levels rather than different exposure times have to be taken into account. Overall, this example shows that different dose levels as well as exposure durations must be considered when comparing different studies but a clear distinction between these two effects is not possible in this case.

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2-(2-(2-Hydroxyethoxy)-ethyl)-2-aza-bicyclo[2.2.1]heptane (CAS 116230-20-7)

Studies in rats

Evaluated by the German AGS (2010b)

In a 2-week pilot study rats (5 animals/sex/dose) were exposed by inhalation to 11 (vapour), 44 (vapour), 191 (aerosol) and 1019 (aerosol) mg/m³. Due to toxicity, the exposure had to be terminated after 4 days at the highest concentration. In the main 13-week study in rats (10 animals/sex/dose), the exposure concentrations were 10 (vapour), 60 (vapour) and 153 (aerosol) mg/m³. The toxicological profile was determined by local irritation in the nasal tract (hyperplasia of respiratory and transitional epithelium) and at the high concentrations also of the larynx. According to the TRGS 900 (AGS, 2010b) a time-extrapolation factor is not necessary.

NOAEC after (weeks)	
2	**13**
11 mg/m³	10 mg/m³

Overall conclusion:
The local NOAEC (2 weeks) corresponds to the NOAEC (sub-chronic). This supports that no additional AF is needed for time extrapolation (sub-acute to sub-chronic exposure) for local effects.

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Naphthalene (CAS 91-20-3)

Studies in rats

Evaluated in the EU Risk Assessment Report (ECB, 2003b)

On p. 146/147 two inhalation studies are described.

4-week study (Huntingdon Research Centre): rats (5/sex/dose) were exposed to 0, 5, 15, 50, 150 and 370 mg/m³. Local effects were observed with signs of proliferative repair in the nasal olfactory epithelium at all doses down to 5 mg/m³. A NOAEC was not identified. Results were similar to those in the 13-week study.

13-week study (Huntingdon Research Centre): rats (10/sex/dose) were exposed to 0, 10, 50, and 300 mg/m³. Local effects were observed in the nasal olfactory epithelium at all doses down to 10 mg/m³. A NOAEC was not identified. Results were similar to those in the 13-week study. At the lowest exposure concentration the following effects were described for the olfactory epithelium: slight disorganisation, mild erosion (in one rat), minimal atrophy, rosette formation (as attempt for proliferative repair), occasional degenerated cells, loss of Bowmans' glands, minimal hyperplasia.

Overall conclusion:
Although no NOAECs were established neither in the sub-acute nor in the sub-chronic study it should be taken into consideration that the lowest dose level in the 4-week study was lower than the lowest one in the 13-week study. At both exposure durations only minimal effects were found at the same target location. Therefore, these data may be taken as an indication that prolongation of exposure to naphthalene beyond 4 weeks will not lead to a decrease of the local NOAEC. Therefore, a time extrapolation AF of 1 might be appropriate.

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Styrene (CAS 100-42-5)

Studies in rats

Data from Cruzan et al, 1997

Exposure at 0, 200, 500, 1000, and 1500 ppm over 13 weeks.

Data from Cruzan et al, 1998

Exposure at 0, 50, 200, 500, and 1000 ppm over 104 weeks with interim sacrifice after 52 weeks.

Target tissue was the olfactory epithelium. After 13 weeks of exposure focal disorganisation and hyperplasia and rosette formation were observed at 500 ppm and above. After 104 weeks atrophic and degenerative changes and effects on the Bowman's glands were observed starting at 50 ppm. The affected areas extended and the lesions became more severe with higher concentrations. After 52 weeks slight effects were already detected at 50 ppm.

NOAEC after (weeks)		
13	**52**	**104**
200 ppm	<50 ppm	<50 ppm

There was a clear reduction of the NOAEC when exposure extended from 13 to 52 weeks. Although the NOAEC could not be defined at week 52 and 104, the NOAEC might decrease when the exposure duration increases from 52 to 104 weeks since the lesions became more severe at 50 ppm.

Studies in mice

Data from Cruzan et al, 1997

Exposure at 0, 50, 100, 150, and 200 ppm over 13 weeks.

Data from Cruzan et al, 1998

Exposure at 0, 20, 40, 80, and 160 ppm over 98 (females) and 104 (males) weeks with interim sacrifice after 52 and 78 weeks.

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In addition, a sub-chronic follow up study at 40 and 80 ppm was carried out with interim sacrifices after 1, 2, 4, 7, 10, 20, 40, and 65 exposures.

Target tissue was again the olfactory epithelium. Slight effects were detected already after 1 day at 80 ppm. Exposure to 40 ppm over 13 weeks only led to minimal changes in the olfactory epithelium. Exposure to 20 ppm led to alterations in all exposure groups at all intervals. Severity increased with increasing exposure duration and exposure concentration.

NOAEC after:				
1 day	**13 weeks**	**52 weeks**	**78 weeks**	**98/104 weeks**
40 ppm	Slightly <40 ppm	<20 ppm	<20 ppm	<20 ppm

Similar to the rat data these findings indicate that the NOAEC for the adverse olfactory effects decrease with exposure duration.

Mechanistic considerations: Concerning nasal toxicity, mice are more sensitive than rats. It has been shown that the cytochrome P450-mediated metabolism of styrene to the reactive metabolite styrene oxide (Cruzan *et al*, 2009) and to other reactive metabolites (e.g. the downstream metabolites of 4-vinylphenol) is a crucial factor in the expression of nasal epithelium toxicity. The difference in species sensitivity could be explained by the metabolism of styrene in either species. Metabolism studies have further shown that humans are much less sensitive to the specific nasal lesions than the rodent species studied. The nasal effects observed in rats and mice are not elicited by local irritation but are due to specific toxifying metabolic pathways.

Overall conclusion:
As the effects observed after inhalative exposure to styrene are not related to local irritation, these findings cannot be used to define an AF for time extrapolation.
The time-effect relationship observed with vinyltoluene (NTP TR 375, 1986e) strongly resembles that of styrene.

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GLOSSARY [9]

Adverse effect: Change in the morphology, physiology, growth, development, reproduction or life span of an organism, system, or (sub)population that results in an impairment of functional capacity, in an impairment of the capacity to compensate for additional stress, or in an increase in susceptibility to other influences.

Allometry: The relationship between growth rates of different parts of an organism or the study of the change in proportions with increase in size.

Assessment factor: Numerical adjustment used to extrapolate from experimentally determined (dose-response) relationships to estimate the agent exposure below which an adverse effect is not likely to occur (see also uncertainty factor).

Benchmark dose: The statistical lower confidence limit of the dose corresponding to a small increase in effect over the background level. Typically, a 1% or 10% response level above the background is selected.

Derived minimal-effect level: An exposure level corresponding to a low, possibly theoretical risk, which should be seen as a tolerable risk (for non-threshold effects).

Derived no-effect level: An exposure level above which humans should not be exposed.

Dose: Total amount of an agent administered to, taken up by, or absorbed by an organism, system, or (sub) population.

Dose descriptor: A value obtained from a toxicity test or from other relevant data, usually the dose needed to induce a specified adverse effect (e.g. 50% lethality) or the highest dose not causing adverse effects (e.g. NOAEL).

Dose-response: Relationship between the amount of an agent administered to, taken up by, or absorbed by an organism, system, or (sub) population and the change developed in that organism, system, or (sub) population in reaction to the agent.

Exposure: Concentration or amount of a particular agent that reaches a target organism, system, or (sub) population in a specific frequency for a defined duration.

[9] These definitions were mainly taken from ECB, 2003; ECHA, 2008; Greim and Snyder, 2008; IPCS, 2004; van Leeuwen and Vermeire, 2007.

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Hazard: Inherent property of an agent or situation having the potential to cause adverse effects when an organism, system, or (sub) population is exposed to that agent.

Hazard assessment: A process designed to determine the possible adverse effects of an agent or situation to which an organism, system, or (sub) population could be exposed. The process includes hazard identification and hazard characterisation. The process focuses on the hazard, in contrast to risk assessment, where exposure assessment is a distinct additional step.

Local effect: Adverse effect at the site of first contact (e.g. skin, eye, mucous membrane/gastro-intestinal tract, or mucous membrane/respiratory tract).

Mode of action: Processes by which a chemical induces toxicity. A MOA can inform about relevance of observed effects in laboratory animals to humans and the variability of response within the human population.

No (observed, adverse) effect concentration / level: The highest concentration / level of a test substance, to which organisms are exposed, that does not cause any observed and statistically significant adverse effects on the organism compared with the controls. For example, the NOEC/L might be the highest tested concentration / level at which an observed variable, such as growth, did not differ significantly from growth in the control. The NOEC/L customarily refers to sub-lethal effects and to the most sensitive effect unless otherwise specified. NEL, NEC and NOEC are equivalent terms.

Occupational exposure limit: Maximum acceptable air concentrations that are used as reference parameters for the protection of workers from overexposure to chemical substances by inhalation.

Point of departure: The dose-response point that marks the beginning of a low-dose extrapolation. This point is most often the upper bound on an observed incidence or on an estimated incidence from a dose-response model.

Potency: The magnitude, with respect to dose, of the toxic activity of a substance in the species under investigation.

Reference dose: An estimate of a daily exposure to a chemical that is unlikely to cause harmful effects during a lifetime.

Risk assessment: A process intended to calculate or estimate the risk to a given target organism, system, or (sub) population, including the identification of attendant uncertainties, following exposure to a particular agent, taking into account the inherent characteristics of the agent of

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concern as well as the characteristics of the specific target system. The risk assessment process includes four steps: hazard identification, hazard characterisation, exposure assessment, and risk characterisation. It is the first component in a risk analysis process.

Route-to-route extrapolation: The prediction of an equivalent dose and dosing regime that produces the same toxic endpoint or response as that obtained for a given dose and dosing regime by another route.

Systemic effect: A toxicological effect that affects the entire body or many organs.

Toxicity: Inherent property of an agent to cause an adverse biological effect.

Toxicodynamics: Processes of interaction of toxicologically active substances with target sites, and the biochemical and physiological consequences leading to adverse effects.

Toxicokinetics: Time-dependent processes related to toxicants as they interact with a living organism. It encompasses absorption, distribution, storage, biotransformation and elimination.

Threshold: Dose or exposure concentration of an agent below which a stated effect is not observed or expected to occur.

Uncertainty factor: A reductive factor by which an observed or estimated no observed adverse effect level is divided to arrive at the criteria or standard that is considered safe or without appreciable risk (see also assessment factor).

Weight of evidence: A weight-of-evidence approach considers multiple endpoints like *in vitro*, *in vivo* or human data, as they relate to an overall assessment of whether significant risk of harm exists.

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ABBREVIATIONS

ACGIH	American Conference of Industrial Hygienists
ACTS	(UK) Advisory Committee on Toxic Substances
AF	Assessment factor
AGS	(German) Ausschuss für Gefahrstoffe (expert group on dangerous substances)
AIHA	American Industrial Hygiene Association
ANOVA	Analysis of variance
AUC	Area under curve
BAuA	(German) Bundesanstalt fur Arbeitsschutz- und Arbeitsmedizin (Federal Institute for Occupational Safety and Health)
BMC	Benchmark dose concentration
BMCL	Benchmark dose concentration lower confidence limit
BMD	Benchmark dose
BMDL	Benchmark dose lower confidence limit
BOELV	(EU) Binding occupational exposure limit value
C.I.	Confidence interval
CSA	Chemical safety assessment
CT	Computed tomography
DECOS	Dutch Expert Committee on Occupational Standards
DEHP	Di(2-ethylhexyl) phthalate
DIDP	Diisodecyl phthalate
DINP	Di-isononyl phthalate
DMEL	Derived minimal-effect level
DNEL	Derived no-effect level
ECHA	European Chemicals Agency
EDTA	Ethylenediaminetetraacetic acid
EEC	European Economic Community
ERASM	Environmental Risk Assessment and Management (research partnership of the detergents and surfactants industries in Europe
ERP	Emergency Response Planning (committee of the AIHA)
ESR	(EU) Existing Substances Risk Assessment
ES	Exposure scenario
ESIS	European Chemical Substances Information System
EU	European Union
GM	Geometric mean
GSD	Geometric standard deviation
HWE	Healthy worker effect
HSE	(United Kingdom) Health and Safety Executive

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IOELV	(EU) Indicative occupational exposure limit value
i.p.	intraperitoneal
i.v.	intravenous
LD	Lethal dose
L(O)(A)EL	Lowest (observed) (adverse) effect level
MAK	Maximale Arbeitsplatzkonzentration (maximum exposure level at the workplace)
MTD	Maximum tolerated dose
MTD_A	Maximum tolerated dose in animals
MTD_H	Maximum tolerated dose in humans
MOA	Mode of action
NEG	Nordic Expert Group
N(O)(A)EC	No (observed) (adverse) effect concentration
N(O)(A)EL	No (observed) (adverse) effect level
NTP	(US) National Toxicology Program
OECD	Organisation for Economic Co-operation and Development
OEL	Occupational exposure limit
POD	Point of departure
QSAR	Quantitative structure-activity relationship
RDT	Repeated-dose toxicity
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
SCOEL	Scientific Committee on Occupational Exposure Limits
sMCS	self-reported multiple chemical sensitivity
SUM	(SCOEL) Summary
STEL	Short-term exposure limit
TCDD	2,3,7,8-Tetrachlorodibenzodioxin
TDL	Toxic dose low
TG	(OECD) Test guideline
TGD	Technical guidance document
TR	Technical report
TLV	Threshold limit value
TWA	Time-weighted average
UF	Uncertainty factor
UK	United Kingdom
US	United States
VCI	Verband der Chemischen Industrie (German chemical industry association)
WATCH	(UK) Health and Safety Commission's Working Group on the Assessment of Toxic Chemicals

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MEMBERS OF THE TASK FORCE

M. Pemberton	Lucite International UK - Wilmslow
H.J. Wiegand	Evonik Degussa D - Essen
D. Beyer	Bayer Schering Pharma D - Wuppertal
M. Binaglia	Solvay SA B - Brussels
P. Bingham	Rhodia UK UK - Oldbury
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R. McKee	ExxonMobil USA – Annandale, NJ
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G. Rusch	Honeywell USA - Morristown

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E. Rushton — ExxonMobil, B - Machelen

A. Wilschut — DSM, NL - Heerlen

C. Hennes — ECETOC, B - Brussels

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MEMBERS OF THE SCIENTIFIC COMMITTEE

F. Lewis (Chairman) Head of Environmental Safety	Syngenta UK - Bracknell
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D. Salvito Vice President, Environmental Scientist	RIFM USA - Woodcliff Lake
G. Swaen Senior Epidemiologist	Dow Europe NL - Terneuzen
J. Tolls Director, Environmental Safety Assessment	Henkel KGaA D - Düsseldorf
S. van der Vies Professor of Biochemistry	Vrije Universiteit Amsterdam NL - Amsterdam
B. van Ravenzwaay Director, Experimental Toxicology and Ecology	BASF D - Ludwigshafen
H.-J. Wiegand* Head, Product Safety Department	Evonik Degussa D - Essen

* Steward responsible for primary peer review

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No. 3	Risk Assessment of Occupational Chemical Carcinogens (Published May 1985)
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No. 5	Identification and Assessment of the Effects of Chemicals on Reproduction and Development (Reproductive Toxicology) (Published December 1983)
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No. 7	Recommendations for the Harmonisation of International Guidelines for Toxicity Studies (Published December 1985)
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www.sciencedirect.com/science/journal/13835718

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Toxicology Letters, Volume 172, Nos. 1-2
www.sciencedirect.com/science/journal/03784274

No. 38 Toxicity of Engineered Nanomaterials (published May 2009)
Toxicology Letters, Volume 186, Issue 3
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No. 4	The Toxicology of Ethylene Glycol Monoalkyl Ethers and its Relevance to Man (Published June 1982, updated by TR No. 17)
No. 5	Toxicity of Ethylene Oxide and its Relevance to Man (Published September 1982)
No. 6	Formaldehyde Toxicology: An Up-Dating of ECETOC Technical Reports 1 and 2 (Published September 1982)
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No. 16	A Review of Recent Literature on the Toxicology of Benzene (Published December 1984)
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No. 18	Harmonisation of Ready Biodegradability Tests (Published April 1985)
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Joint Assessment of Commodity Chemicals (JACC) Reports

No.	Title
No. 1	Melamine (Published February 1983)
No. 2	1,4-Dioxane (Published February 1983)
No. 3	Methyl Ethyl Ketone (Published February 1983)
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No. 12	1-Chloro-1,2,2,2-tetrafluoroethane (HFA-124) (Published May 1990) (Updated by JACC No. 25)
No. 13	1,1-Dichloro-2,2,2-trifluoroethane (HFA-123) (Published May 1990) (Updated by JACC No. 33)
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No. 25	1-Chloro-1,2,2,2-tetrafluoroethane (HCFC 124) (CAS No. 2837-89-0) (Second Edition) (Published July 1994) (Updated by JACC 46)
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No. 27	*n*-Butyl Acrylate (CAS No. 141-32-2) (Published August 1994)
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No. 30	Methyl Methacrylate (CAS No. 80-62-6) (Published February 1995)
No. 31	1,1,1,2-Tetrafluoroethane (HFC-134a) (CAS No. 811-97-2) (Published February 1995) (Updated by JACC No. 50)
No. 32	Difluoromethane (HFC-32) (CAS No. 75-10-5) (Published May 1995) (Updated by JACC No. 54)
No. 33	1,1-Dichloro-2,2,2-trifluoroethane (HCFC-123) (CAS No. 306-83-2) (Published February 1996) (Updated by JACC No. 47)
No. 34	Acrylic Acid (CAS No. 79-10-7) (Published September 1995)
No. 35	Methacrylic Acid (CAS No. 79-41-4) (Published May 1996)
No. 36	*n*-Butyl Methacrylate; Isobutyl Methacrylate (CAS No. 97-88-1) (CAS No. 97-86-9) (Published December 1996)
No. 37	Methyl Acrylate (CAS No. 96-33-3) (Published September 1998)
No. 38	Monochloroacetic Acid (CAS No. 79-11-8) and its Sodium Salt (CAS No. 3926-62-3) (Published June 1999)
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