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GUIDELINE ON THE LIMITS OF GENOTOXIC IMPURITIES

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7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 13
E-mail: mail@emea.eu.int http://www.emea.eu.int

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TABLE OF CONTENTS

EXECUTIVE SUMMARY 3
1. INTRODUCTION 3
2. SCOPE 3
3. LEGAL BASIS 3
4. TOXICOLOGICAL BACKGROUND 4
5. RECOMMENDATIONS 4
5.1 Genotoxic Compounds With Sufficient Evidence for a Threshold-Related Mechanism 4
5.2 Genotoxic Compounds Without Sufficient Evidence for a Threshold-Related Mechanism 5
5.2.1 Pharmaceutical Assessment 5
5.2.2 Toxicological Assessment 5
5.2.3 Application of a Threshold of Toxicological Concern 5
5.3 Decision Tree for Assessment of Acceptability of Genotoxic Impurities 7
REFERENCES 8

Superseded

EXECUTIVE SUMMARY

The toxicological assessment of genotoxic impurities and the determination of acceptable limits for such impurities in active substances is a difficult issue and not addressed in sufficient detail in the existing ICH Q3X guidances. The data set usually available for genotoxic impurities is quite variable and is the main factor that dictates the process used for the assessment of acceptable limits. In the absence of data usually needed for the application of one of the established risk assessment methods, i.e. data from carcinogenicity long-term studies or data providing evidence for a threshold mechanism of genotoxicity, implementation of a generally applicable approach as defined by the Threshold of Toxicological Concern (TTC) is proposed. A TTC value of 1.5 µg/day intake of a genotoxic impurity is considered to be associated with an acceptable risk (excess cancer risk of <1 in 100,000 over a lifetime) for most pharmaceuticals. From this threshold value, a permitted level in the active substance can be calculated based on the expected daily dose. Higher limits may be justified under certain conditions such as short-term exposure periods.

1. INTRODUCTION

A general concept of qualification of impurities is described in the guidelines for active substances (Q3A, Impurities in New Active Substances) or medicinal products (Q3B, Impurities in New Medicinal Products), whereby qualification is defined as the process of acquiring and evaluating data that establishes the biological safety of an individual impurity or a given impurity profile at the level(s) specified. In the case of impurities with a genotoxic potential, determination of acceptable dose levels is generally considered as a particularly critical issue, which is not specifically covered by the existing guidelines.

2. SCOPE

This Guideline describes a general framework and practical approaches on how to deal with genotoxic impurities in new active substances. It also relates to new applications for existing active substances, where assessment of the route of synthesis, process control and impurity profile does not provide reasonable assurance that no new or higher levels of genotoxic impurities are introduced as compared to products currently authorised in the EU containing the same active substance. The same also applies to variations to existing Marketing Authorisations pertaining to the synthesis. The guideline does, however, not need to be applied retrospectively to authorised products unless there is a specific cause for concern.

In the current context the classification of a compound (impurity) as genotoxic in general means that there are positive findings in established in vitro or in vivo genotoxicity tests with the main focus on DNA reactive substances that have a potential for direct DNA damage. Isolated in vitro findings may be assessed for in vivo relevance in adequate follow-up testing. In the absence of such information in vitro genotoxicants are usually considered as presumptive in vivo mutagens and carcinogens.

3. LEGAL BASIS

This guideline has to be read in conjunction with Directive 2001/83/EC (as amended) and all relevant CHMP Guidance documents with special emphasis on:

Impurities Testing Guideline: Impurities in New Drug Substances (CPMP/ICH/2737/99, ICHQ3A(R))
Note for Guidance on Impurities in New Drug Products (CPMP/ICH/2738/99, ICHQ3B (R))
Note for Guidance on Impurities: Residual Solvents (CPMP/ICH/283/95)
Note for Guidance on Genotoxicity: Guidance on Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals (CPMP/ICH/141/95, ICHS2A)
Note for Guidance on Genotoxicity: A Standard Battery for Genotoxicity Testing of Pharmaceuticals (CPMP/ICH/174/95, ICHS2B)

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4. TOXICOLOGICAL BACKGROUND

According to current regulatory practice it is assumed that (in vivo) genotoxic compounds have the potential to damage DNA at any level of exposure and that such damage may lead/contribute to tumour development. Thus for genotoxic carcinogens it is prudent to assume that there is no discernible threshold and that any level of exposure carries a risk.

However, the existence of mechanisms leading to biologically meaningful threshold effects is increasingly acknowledged also for genotoxic events. This holds true in particular for compounds interacting with non-DNA targets and also for potential mutagens, which are rapidly detoxified before coming into contact with critical targets. The regulatory approach to such chemicals can be based on the identification of a critical no-observed-effect level (NOEL) and use of uncertainty factors.

Even for compounds which are able to react with the DNA molecule, extrapolation in a linear manner from effects in high-dose studies to very low level (human) exposure may not be justified due to several protective mechanisms operating effectively at low doses. However, at present it is extremely difficult to experimentally prove the existence of threshold for the genotoxicity of a given mutagen. Thus, in the absence of appropriate evidence supporting the existence of a threshold for a genotoxic compound making it difficult to define a safe dose it is necessary to adopt a concept of a level of exposure that carries an acceptable risk.

5. RECOMMENDATIONS

As stated in the Q3A guideline, actual and potential impurities most likely to arise during synthesis, purification and storage of the new drug substance should be identified, based on a sound scientific appraisal of the chemical reactions involved in the synthesis, impurities associated with raw materials that could contribute to the impurity profile of the new drug substance, and possible degradation products. This discussion can be limited to those impurities that might reasonably be expected based on knowledge of the chemical reactions and conditions involved. Guided by existing genotoxicity data or the presence of structural alerts, potential genotoxic impurities should be identified. When a potential impurity contains structural alerts, additional genotoxicity testing of the impurity, typically in a bacterial reverse mutation assay, should be considered (Dobo et al. 2006, Müller et al. 2006). While according to the Q3A guideline such studies can usually be conducted on the drug substance containing the impurity to be controlled, studies using isolated impurities are much more appropriate for this purpose and highly recommended.

For determination of acceptable levels of exposure to genotoxic carcinogens considerations of possible mechanisms of action and of the dose-response relationship are important components. Based on the above considerations genotoxic impurities may be distinguished into the following two classes:

- Genotoxic compounds with sufficient (experimental) evidence for a threshold-related mechanism
- Genotoxic compounds without sufficient (experimental) evidence for a threshold-related mechanism

5.1 Genotoxic Compounds With Sufficient Evidence for a Threshold-Related Mechanism

Examples of mechanisms of genotoxicity that may be demonstrated to lead to non-linear or thresholded dose-response relationships include interaction with the spindle apparatus of cell division leading to aneuploidy, topoisomerase inhibition, inhibition of DNA synthesis, overloading of defence mechanisms, metabolic overload and physiological perturbations (e.g. induction of erythropoeisis, hyper- or hypothermia).

For (classes of) compounds with clear evidence for a thresholded genotoxicity, exposure levels which are without appreciable risk of genotoxicity can be established according to the procedure as outlined for class 2 solvents in the Q3C Note for Guidance on Impurities: Residual Solvents. This approach calculates a “Permitted Daily Exposure” (PDE), which is derived from the NOEL, or the lowest-observed effect level (LOEL) in the most relevant (animal) study using “uncertainty factors” (UF).

Superseded

5.2 Genotoxic Compounds Without Sufficient Evidence for a Threshold-Related Mechanism

The assessment of acceptability of genotoxic impurities for which no threshold mechanisms are identified should include both pharmaceutical and toxicological evaluations. In general, pharmaceutical measurements should be guided by a policy of controlling levels to "as low as reasonably practicable" (ALARP principle), where avoiding is not possible. Levels considered being consistent with the ALARP principle following pharmaceutical assessment should be assessed for acceptability from a toxicological point of view (see decision tree & following sections).

5.2.1 Pharmaceutical Assessment

A specific discussion – as part of the overall discussion on impurities (see Q3A(R)) – should be provided in the application with regard to impurities with potential genotoxicity.

A rationale of the proposed formulation/manufacturing strategy should be provided based on available formulation options and technologies. The applicant should highlight, within the chemical process and impurity profile of active substance, all chemical substances, used as reagents or present as intermediates, or side-products, known as genotoxic and/or carcinogenic (e.g. alkylating agents). More generally, reacting substances and substances which show "alerting structure" in terms of genotoxicity which are not shared with the active substance should be considered (see e.g. Dobo et al. 2006). Potential alternatives which do not lead to genotoxic residues in the final product, should be used if available.

A justification needs to be provided that no viable alternative exists, including alternative routes of synthesis or formulations, different starting materials. This might for instance include cases where the structure, which is responsible for the genotoxic and/or carcinogenic potential is equivalent to that needed in chemical synthesis (e.g. alkylation reactions).

If a genotoxic impurity is considered to be unavoidable in a drug substance, technical efforts (e.g. purification steps) should be undertaken to reduce the content of the genotoxic residues in the final product in compliance with safety needs or to a level as low as reasonably practicable (see safety assessment). Data on chemical stability of reactive intermediates, reactants, and other components should be included in this assessment.

Detection and/or quantification of these residues should be done by state-of-the-art analytical techniques.

5.2.2 Toxicological Assessment

The impossibility of defining a safe exposure level (zero risk concept) for genotoxic carcinogens without a threshold and the realization that complete elimination of genotoxic impurities from drug substances is often unachievable, requires implementation of a concept of an acceptable risk level, i.e. an estimate of daily human exposure at and below which there is a negligible risk to human health. Procedures for the derivation of acceptable risk levels are considered in the Appendix 3 of the Q3C Note for Guidance on Impurities: Residual Solvents for Class 1 solvents. However, these approaches require availability of adequate data from long-term carcinogenicity studies.

In most cases of toxicological assessment of genotoxic impurities only limited data from in vitro studies with the impurity (e.g. Ames test, chromosomal aberration test) are available and thus established approaches to determine acceptable intake levels cannot be applied. Calculation of "safety multiples" from in vitro data (e.g. Ames test) are considered inappropriate for justification of acceptable limits. Moreover, negative carcinogenicity and genotoxicity data with the drug substance containing the impurity at low ppm levels do not provide sufficient assurance for setting acceptable limits for the impurity due to the lack of sensitivity of this testing approach. Even potent mutagens and carcinogens are most likely to remain undetected when tested as part of the drug substance, i.e. at very low exposure levels. A pragmatic approach is therefore needed which recognises that the presence of very low levels of genotoxic impurities is not associated with an unacceptable risk.

5.2.3 Application of a Threshold of Toxicological Concern

A threshold of toxicological concern (TTC) has been developed to define a common exposure level for any unstudied chemical that will not pose a risk of significant carcinogenicity or other toxic effects

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(Munro et al. 1999, Kroes and Kozianowski 2002). This TTC value was estimated to be 1.5 µg/person/day. The TTC, originally developed as a "threshold of regulation" at the FDA for food-contact materials (Rulis 1989, FDA 1995) was established based on the analysis of 343 carcinogens from a carcinogenic potency database (Gold et al. 1984) and was repeatedly confirmed by evaluations expanding the database to more than 700 carcinogens (Munro 1990, Cheeseman et al. 1999, Kroes et al. 2004). The probability distribution of carcinogenic potencies has been used to derive an estimate of a daily exposure level (µg/person) of most carcinogens which would give rise to less than a one in a million (1×10^{-6}) upper bound lifetime risk of cancer ("virtually safe dose"). Further analysis of subsets of high potency carcinogens led to the suggestion of a 10-fold lower TTC (0.15 µg/day) for chemicals with structural alerts that raise concern for potential genotoxicity (Kroes et al. 2004). However, for application of a TTC in the assessment of acceptable limits of genotoxic impurities in drug substances a value of 1.5 µg/day, corresponding to a 10^{-5} lifetime risk of cancer can be justified as for pharmaceuticals a benefit exists. It should be recognized in this context that the methods on which the TTC value is based, are generally considered very conservative since they involved a simple linear extrapolation from the dose giving a 50% tumour incidence (TD50) to a 1 in 10^6 incidence, using TD50 data for the most sensitive species and most sensitive site (several "worst case" assumptions) (Munro et al. 1999).

Some structural groups were identified to be of such high potency that intakes even below the TTC would be associated with a high probability of a significant carcinogenic risk (Cheeseman et al. 1999, Kroes et al. 2004). This group of high potency genotoxic carcinogens comprises aflatoxin-like-, N-nitroso-, and azoxy-compounds that have to be excluded from the TTC approach. Risk assessment of members of such groups requires compound-specific toxicity data.

There may be reasons to deviate from the TTC value based on the profile of genotoxicity results. Positive result from in vitro studies only may allow to exempt an impurity from limitation at TTC level if lack of in vivo relevance of the findings is convincingly demonstrated based on a weight-of-evidence approach (see ICH S2 guidelines). This approach will usually need negative results with the impurity from some additional in vitro and/or appropriate in vivo testing.

A TTC value higher than 1.5 µg/day may be acceptable under certain conditions, e.g. short-term exposure, for treatment of a life-threatening condition, when life expectancy is less than 5 years, or where the impurity is a known substance and human exposure will be much greater from other sources (e.g. food). Genotoxic impurities that are also significant metabolites may be assessed based on the acceptability of the metabolites.

The concentration limits in ppm of genotoxic impurity in drug substance derived from the TTC can be calculated based on the expected daily dose to the patient using equation (1).

$$\text{(1) Concentration limit (ppm)} = \frac{\text{TTC [µg/day]}}{\text{dose (g/day]}}$$

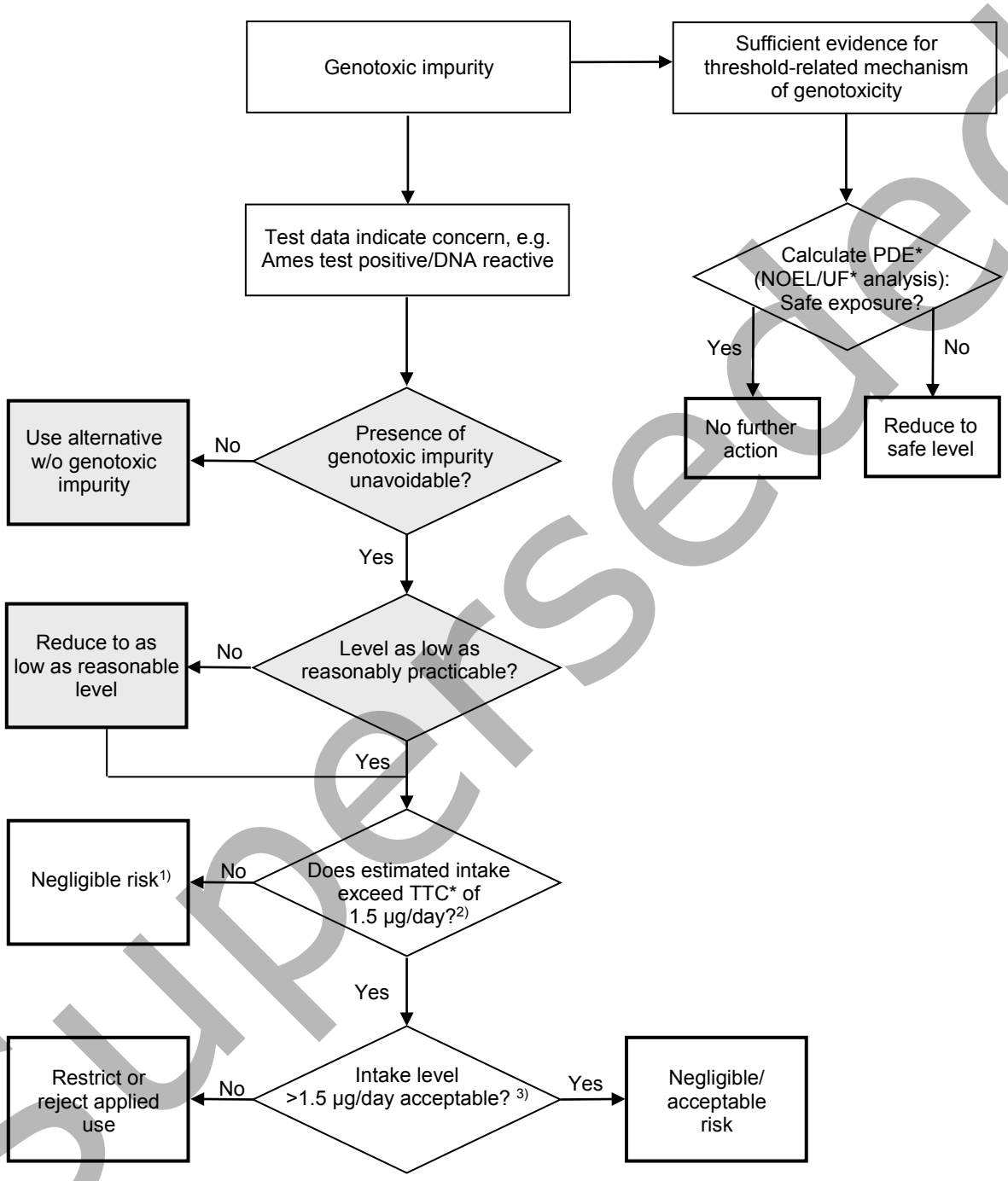
The TTC concept should not be applied to carcinogens where adequate toxicity data (long-term studies) are available and allow for a compound-specific risk assessment.

It has to be emphasized that the TTC is a pragmatic risk management tool using a probabilistic methodology, i.e. there is a high probability that a 10^{-5} lifetime cancer risk will not be exceeded if the daily intake of a genotoxic impurity with unknown carcinogenic potential/potency is below the TTC value. The TTC concept should not be interpreted as providing absolute certainty of no risk.

Superseded

5.3 Decision Tree for Assessment of Acceptability of Genotoxic Impurities

(shaded boxes = pharmaceutical assessment, white boxes = toxicological assessment)



1) Impurities with structural relationship to high potency carcinogens (see text) are to be excluded from the TTC approach
2) If carcinogenicity data available: Does intake exceed calculated 10^{-5} cancer lifetime risk?
3) Case-by-case assessment should include duration of treatment, indication, patient population etc (see text)

*) Abbreviations: NOEL/UF – No Observed Effect Level/Uncertainty Factor,
PDE – Permitted Daily Exposure, TTC – Threshold of Toxicological Concern

Superseded

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