

Output for Risk assessment/characterisation purposes – specific guidance for the individual endpoints – to be inserted under:

1.5.2 Concluding on suitability for Chemical Safety Assessment in the detailed end-point guidance on mutagenicity (RIP 3.3-2)

MUTAGENICITY

BACKGROUND

Mutagenicity - threshold and non-threshold effects

The default assumption for chemicals with mutagenic activity is that they have linear, non-thresholded dose-response relationships. However, both direct and indirect mechanisms of mutagenicity/genotoxicity can be non-linear (i.e. supra-linear or sub-linear) and occasionally even truly thresholded. Thus, sometimes the default assumption of linear dose-response for genotoxicity and mutagenicity may not be warranted.

Examples of mechanisms of mutagenicity/genotoxicity that may be demonstrated to lead to non-linear or thresholded dose-response relationships include inhibition of DNA synthesis, alterations in DNA repair, overloading of defence mechanisms, interaction with microtubule assembly leading to aneuploidy, topoisomerase inhibition, high cytotoxicity, metabolic overload, low dose/high dose metabolic shift and some physiological perturbations.

For mutagenic/genotoxic substances, where the default assumption of linear, non-thresholded dose-response relationships applies, a true NOAEL do not exist and consequently no DNEL can be calculated. For such cases, the general provisions for chemical safety assessment in REACH (Annex I, point 6.5) foresee a “qualitative” approach to be applied. Thus, a qualitative assessment of the likelihood that effects are avoided when implementing the exposure scenario shall be carried out.

The concept of “adequate control” (i.e. exposure < DNEL) do thus not seem to apply for non-threshold mutagens/genotoxicants. Meanwhile, the general provisions to ensure that such substances do not adversely affect human health (REACH Article 1.3) would implicitly call for a low risk [i.e. a {*qualitatively?*} high likelihood that risks are avoided should be shown for each exposure scenario].

Some proposals for the application of alternative, proxy data methods for (semi)qualitative risk characterisation of non-threshold mutagens are found below under section 1.2 *Considerations on the use of alternative data for hazard assessment purposes*.

For the purpose of the discussions in the DNEL Drafting group it is anticipated in this paper that a quantitative DMEL-approach for risk characterisation of non-threshold mutagens will be allowed for in REACH.

1 DERIVATION OF TYPICAL DOSE DESCRIPTORS – [STEP 1 GENERAL DNEL CHAPTER]

1.1 Typical dose descriptors

The task – according to Dinant’s paper [Proposed structure DNEL part endpoint chapters.doc](#) :

- *Derivation of typical dose descriptors (e.g. NOAELs, BMD, LD50, T25, TD50....) from all available studies*

The data available for hazard assessment of mutagenicity/genotoxicity are normally results from single dose/short term *in vitro* and *in vivo* studies.

1.1.1 Threshold mutagens

The task:

- *Describe the most frequently used dose descriptor(s) for risk assessment purposes for this end-point.*
- *If it is sometimes (or always) not possible to identify a dose descriptor for this endpoint: describe other ways than the dose-response for this end-point is normally addressed in a risk assessment*

In case a threshold mode of action has been reliably established it may be possible to determine a relevant NOAEL for the underlying toxic effect from other studies available, e.g. repeated dose toxicity and special mechanistic studies. Appropriate DNEL(s) may then be derived after correction of the starting point and application of appropriate assessments factors in a fashion that is similar to the procedures used for the endpoint Repeated Dose Toxicity (c.f. Section XX).

However, the potentially high degree of severity of the effects in question must be recognised.

1.1.2 Non-threshold mutagens

The task:

- *Describe how the dose-response is normally reflected quantitatively (e.g. T25 or BMDL10 for non-threshold carcinogens), semi-quantitatively (e.g. high, medium, low c.f. potency group for specific conc. limits <1 ; 1-100; >100 mg/kg/d) or qualitatively*

Conventional dose descriptors adequately characterising the mutagenic potency/activity of non-threshold mutagens are seldom or never available. This is due to the fact that the available *in vitro* and *in vivo* test methods for hazard assessment of potential genotoxicity/mutagenicity generally provide *qualitative* evidence of mutagenicity only.

1.2 Considerations on the use of alternative data for hazard assessment purposes

The task:

- *Describe any considerations about which alternative data could be used for risk assessment purposes.*
- *This is a key interface to RIP 3.3 end-point groups, which in a next step should reflect and/or add to this.*

This part of the guidance remains to be elaborated further.....

1.2.1 *Threshold mutagens*

1.2.1.1 **Animal data**

N/A

1.2.1.2 ***In vitro* data**

N/A

1.2.1.3 **Non-testing data**

SAR, QSAR, chemical categories, read across etc.....

1.2.2 *Non-threshold mutagens*

1.2.2.1 **Use of carcinogenicity data as proxies for mutagenicity**

When reliable carcinogenicity data for a non-threshold genotoxic/mutagenic substance is available and a conservative risk characterisation for this endpoint can be undertaken this assessment may be considered to cover also mutagenic effects including heritable damage. This position may be argued based on the assertion that genotoxicity is a main driving force in chemical carcinogenesis. However, it is commonly recognised that carcinogenicity may be a much more complex process than mutagenesis. Proxy assessments of mutagenicity based on cancer data may thus be burdened with very high uncertainty.

1.2.2.2 **Mutagenic/carcinogenic potency predicted from repeated dose toxicity data**

For hazard assessment and risk characterisation of a mutagenic substance for which no cancer data are available, a rough (order of magnitude) estimate of the BMD10, T25 or TD50 values for carcinogenicity can be calculated based on data on repeated dose toxicity. Carcinogenic potency has been convincingly shown to correlate with various measures of toxicity. Furthermore, the MTD (maximum tolerated dose) for rats has been shown to be correlated with MTD for mice, for carcinogens that are effective in both species, thereby implying a correlation between cancer potency values for these species. In addition, limited studies suggest that rodent potency estimates correlate with the potency recorded for some recognised human carcinogens. For a review of these issues a report from US National Research Council should be consulted: "Issues in Risk Assessment", National Academy Press, Washington DC, 1993 [available at: <http://www.nap.edu/catalog/2078.html>].

Based on this review and also other publications [e.g. Gold et al.; Regulatory Toxicology and Pharmacology 37 (2003), 45-53] "safe" exposure levels might be calculated by dividing a MTD or minimally toxic dose from sub-chronic studies in rodents with a default, large assessment factor.

Alternatively, the MTD might be adopted as a proxy measure of a T25 or BMD10 cancer potency value. Subsequently, any one of the three quantitative approaches suggested for the derivation of cancer DMELs could be applied.

This way DMELs for mutagenicity/carcinogenicity of genotoxic/mutagenic substances would become available even if end-point specific data suitable for hazard assessment and risk characterisation is lacking. Such an approach would be very useful since the data/test requirements in REACH will presumably reveal a substantial number of “new” mutagenic substances that will have to be risk assessed adequately. This also goes for all the presently recognised mutagens.

The TTC approach

It could also been proposed that the Threshold of Toxicological Concern (TTC) value for non-threshold genotoxicants (mutagens and thus potential carcinogens) should be adopted as a pragmatic DMELs carrying a finite but very low risk (Kroes et al., 2004). According to these authors a TTC of 0.15 µg/person/day (= 0.002 µg/kg/day) would for most substances imply a risk level of less than 1 in 1,000,000 (10^{-6}). Corresponding doses for risk levels of 10^{-5} and 10^{-4} would (by linear extrapolation or *regula de tri*) be 1.5 and 15 µg/person/day, respectively (= 0.02 and 0.2 µg/kg/day).

2 MODIFICATION OF THE STARTING POINT – [STEP 2 GENERAL DNEL CHAPTER]

2.1 Issues relevant for modification of the starting point

The task:

- *When necessary, modification of the dose descriptor to the correct starting point*
- *NB! only fill in specific issues for this end-point, i.e. no need to repeat issues from the general DNEL chapter*
- *Describe any particular issues to take into account for this end-point in relation to modification of the starting point (only relevant if there is a quantitative dose-descriptor).*

2.1.1 Specific guidance

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3 ASSESSMENT FACTORS – APPLICATION OF ASSESSMENT FACTORS TO THE CORRECTED STARTING POINT TO OBTAIN THE ACCEPTABLE DAILY LEVEL (ADL) – [STEP 3 GENERAL DNEL CHAPTER]

The task:

- *NB! only fill in specific issues for this end-point, i.e. no need to repeat issues from the general DNEL chapter*
- *Describe any particular issues to take into account for this end-point in relation to the use of assessment factors and particular uncertainties to be aware of for this end-point.*
- *For end-points to be assessed qualitatively (no quantitative dose descriptor): describe particular issues (e.g. in relation to uncertainties and potency) that should be reflected in a discussion on the dose-response for that end-point.*

3.1 Application of assessment factors to the dose descriptor for threshold mutagenicity

3.1.1 General assessment factors

Traditional assessment factors are only applicable for hazard assessment of systemically and/or locally active thresholded mutagenic and/or carcinogenic effects. If a threshold dose-response can be reliably shown, the hazard assessment is concluded based on an identified NOAEL. Appropriate DNEL(s) may be derived after correction of the starting point and application of appropriate assessments factors in a fashion that is similar to the procedures used for the endpoint Repeated Dose Toxicity (c.f. Section XX above).

3.1.2 Specific assessment factors

The potentially high degree of severity of the mutagenic effects must be recognised. This should be reflected in the choice of assessment factors for dose-response and normally an AF >> 1 would be warranted to cater for endpoint-severity.

3.2 Application of assessment factors to the dose descriptor for non-threshold mutagenicity

N/A

4 IDENTIFICATION OF THE CRITICAL MEASURE FOR DOSE-RESPONSE (DNEL(s), DMEL(s) OR “QUANTITATIVE” – [STEP 4 GENERAL DNEL CHAPTER]

Remains to be elaborated ...

Above some instances have been described where a NOAEL, LOAEL or a measure of mutagenic/carcinogenic potency (e.g. T25) can be calculated for mutagenic substances. For the derivation of the corresponding DNEL(s) and DMEL(s) for mutagenic effects, in principle all available hazard information (in accordance with Annexes V-IX) needs to be evaluated. In order to select the leading health effect and thus the most relevant DNEL/DMEL for a given exposure pattern/route the lowest DNEL/DMEL for a given route, exposure pattern and population is to be used for risk characterisation for each exposure scenario. This value shall also be communicated down the supply chain via the SDS.