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## WATCH COMMITTEE

### Technical Guidance for derivation of DNELs and risk characterisation of non-threshold effects in the context of REACH

#### Issue

1. Methodology for the development of "Derived No Effect Levels" (DNELs) and risk characterisation of non-threshold effects in the context of REACH.

#### Timing Considerations

2. The development of the REACH Technical Guidance Document on setting DNELs is in progress. HSE is involved in the Expert Drafting Group. Views from WATCH are invited in order to influence the final stages of this process.

#### Recommendation

3. WATCH is invited to consider the issues noted in this cover paper and to respond to the actions in paragraph 21.

#### Background

4. According to the legal text of REACH, DNELs represent a level of exposure above which humans should not be exposed (Common Position, Annex I, 1.0.1). REACH legal text also states that, taking into account the available information and the exposure scenario(s) it may be necessary to identify different DNELs for each relevant human population (e.g. workers, consumers and humans via the environment) and possibly for certain vulnerable sub-populations (e.g. children, pregnant women) and for different routes of exposure (Common Position, Annex I, 1.4.1). The purpose of DNELs is to act as a benchmark for determining adequate control of exposure for specified scenarios (Common Position, Annex I, 6.4). The draft Technical Guidance Document (TGD) that sets out the general methodology for setting DNELs is attached as Annex 1 to this Cover Paper. It should be noted that the draft TGD for REACH is based to a large extent on the recently revised TGD that was produced for the purposes of the Existing Substances Regulation (ESR).

5. According to REACH legal text, DNELs should be derived for all substances subject to registration that are manufactured/imported/used in quantities of 10 tonnes or more per year as part of the chemical safety assessment (CSA). DNELs should be documented in the chemical safety report (CSR). DNELs are subsequently to be used in the risk characterisation part of the CSA and for hazard communication, via extended SDS.

6. The Draft TGD for the derivation of DNELs and risk characterisation of non-threshold effects is being developed by an Expert Drafting Group (EDG) within the REACH Implementation Project (RIP) 3.2. RIP 3.2 is aimed at developing guidance for industry on how to produce the CSA. The EDG includes representatives from EU Member States regulatory bodies, the Commission, industry and NGOs. It is envisaged that further development of this draft guidance will continue through 2007.

7. HSE wishes to take advice from WATCH to help formulate its comments and suggestions for these final changes. HSE is aware that there are a number of contentious issues surrounding the DNEL methodology, not least those concerning the use of uncertainty/assessment factors. While the systematic application of uncertainty/assessment

factors has a well established history of use in relation to setting standards for food contaminants, air and water quality and pesticide approvals, there has been no such tradition in relation to the derivation of OELs. Hence the systematic use of formal assessment factors in deriving DNELs for workers is an important area of debate. It is hoped that this issue can be discussed at WATCH in the coming month, but for the purposes of this WATCH meeting HSE wishes to focus particularly on issues relating to mutagens and genotoxic carcinogens as this is an area that is currently under development and intense discussion at EU level.

8. For toxicological endpoints that exhibit a threshold of effect, the methodology for deriving DNELs involves the application of “assessment factors” (uncertainty factors) to a toxicological reference point such as a NOAEL or LOAEL (Annex 1). For toxicological endpoints such as mutagenicity and also carcinogenicity arising or assumed to arise from a genotoxic mechanism, although a biological threshold for these effects may exist, from the scientific information usually available, neither the existence of a threshold can be confirmed nor can the location of a threshold on the dose-response curve be identified. Therefore, without evidence for a threshold, the application of assessment factors to a NOAEL or LOAEL is not appropriate.

9. For mutagens and for genotoxic carcinogens, REACH requires that a qualitative risk assessment be performed (Common Position, Annex I, 6.5). REACH also states that for substances classified as mutagens or carcinogens category 1 or 2 for which it is not possible to identify a threshold, an authorisation may be granted if it is shown that socio-economic benefits outweigh the risk to human health arising from the use of the substance and if there are no suitable alternative substances or technologies (Art 59.4). Although the legal text refers to a qualitative assessment, no further elaboration on how this should be performed is provided. This lack of clarity has led some members of the RIP 3.2 EDG to propose that (data permitting) quantitative reference levels should be established to aid the risk characterisation of these effects and to assist risk managers to focus on the areas of greatest concern. It has been suggested that such levels could be referred to as “Derived Minimal Effect Levels” (DMELs) (see Annexes 2 and 3 to this cover paper). HSE has various concerns about the proposed approaches for deriving DMELs and has produced a short paper recommending alternative approaches for carcinogens (Annex 4), which has been recently submitted to the EDG for consideration.

## Argument

10. *Genotoxic carcinogens*: The proposed methodology for deriving DMELs for genotoxic carcinogens is largely based on linear extrapolation from animal carcinogenicity dose-response data to predict a level of exposure that would be associated with a defined low level of risk in humans (e.g. an increased lifetime risk of cancer of  $10^{-5}$  or  $10^{-6}$ ). This approach to cancer risk assessment is already utilised in certain EU Member States as a starting point for setting OELs. HSE, in line with the Committee on Carcinogenicity (CoC) guidelines, does not support methods based on extensive extrapolation from relatively high dose animal carcinogenicity data to predict specified low levels of risk in humans at exposure levels orders of magnitude below the observed range of data. HSE considers that the risk predictions so derived would be of unknown accuracy and could never be validated by empirical observations. The HSE concerns about this approach are set out in Annex 4. Do WATCH members have any additional comments that they feel should be fed into the further development of the TGD? What are the views of WATCH on the alternative approaches recommended by HSE?

11. *Somatic cell mutagens with no cancer data*: This group of substances comprises chemicals that have been shown to be *in vivo* somatic cell mutagens in standard tests (e.g. bone marrow micronucleus or chromosome aberrations, liver UDS), but for which there are no carcinogenicity data. The presumption must be for such substances that they might have the potential to cause cancer. In general, it is not possible to identify a threshold level of exposure for *in vivo* mutagenicity. Dose-response data for somatic cell mutagenicity might be available for some substances, which implies that quantitative modelling of these data might be possible. However, largely due to the methodological limitations of the detection systems employed (single high dose levels, one single tissue examined, microscopically visible

evidence of genotoxic change represents gross genetic damage), using such data to assess the risk of developing cancer would be fraught with uncertainties. Hence, there is no reliable basis for a quantitative cancer risk assessment based directly on *in vivo* somatic cell mutagenicity data. Two indirect approaches have been proposed for setting DMELs in such circumstances (Annex 2). It can be seen that the draft Guidance on setting DMELs for such chemicals is still at a very early stage and is in need of considerable further work. One proposed approach is based on a suggested relationship between the Maximum Tolerated Dose (MTD) and carcinogenic potency in repeated-dose studies in experimental animals, and the other approach is based on the concept of the “Threshold of Toxicological Concern” (TTC) for carcinogens (which might be regarded as an extreme form of “read-across” approach).

12. *The MTD approach to setting DMELs for somatic cell mutagens with no cancer data:* The MTD represents a dose that does not cause overt toxicity or more than a 10% reduction in body weight gain in a sub-chronic (90-day) study. Identification of the MTD from a sub-chronic study is meant to provide the basis for selecting the highest dose in a chronic (2-year) study, as a dose that should not reduce longevity compared to controls. An analysis of 139 rodent carcinogens concluded that the MTD obtained from 90-day studies was related to carcinogenic potency (Gold et al 2003, paper attached as Annex 5). Carcinogenic potency was based on the LTD10 values obtained in cancer bioassays (the LTD10 equates to the lower 95<sup>th</sup> confidence interval limit on the dose estimated to cause a 10% increased risk of cancer). The draft TGD proposes that the MTD be taken as the starting point for derivation of a DMEL for somatic cell mutagens with no cancer data, perhaps by application of a large assessment factor (AF). HSE does not support this proposed approach because it seems to lack any credible underlying biological basis; there seems to be no reason why the mutagenic or carcinogenic potency of a mutagen should relate to non-specific health effects such as body weight gain.

13. *The TTC approach to setting DMELs for somatic cell mutagens with no cancer data:* A published paper setting out the TTC methodology is attached for reference (Annex 6). In brief, the TTC methodology was developed as an approach for human health risk assessment for chemicals in food. The philosophy is based on the *de minimus* concept; this acknowledges that there will be a practical human threshold value for chemicals below which there will be no significant risk to health. This threshold is referred to as the “threshold of toxicological concern” (TTC). Exposures below the TTC would be regarded as not posing any grounds for concern for human health.

14. The TTC for genotoxic carcinogens is based on a carcinogen potency database containing 730 compounds (this was developed from an earlier database developed by Gold). For the chemicals in this database, TD50 values were derived (doses estimated to cause a 50% excess risk of developing cancer following exposure over a lifetime when tested in animals). Linear extrapolation from the TD50 values was undertaken to calculate the dose giving a risk of 10<sup>-6</sup> of developing cancer. From the distribution of doses estimated to cause a 10<sup>-6</sup> risk of developing cancer, a “threshold” of 0.15 µg per person/day was determined. It was concluded that there was an extremely low probability of exceeding a risk of 10<sup>-6</sup> of developing cancer with exposures below 0.15 µg per person/day (0.0025 µg/kg/day, assuming 60 kg bodyweight).

15. HSE does not support the use of the TTC approach for setting DMELs for somatic cell mutagens with no cancer data, although it does appear to offer a simple and pragmatic answer to this issue. The key reason for not supporting this approach is based on a matter of principle; the approach is based on linear extrapolation and purports to lead to a specified numerical level of risk (10<sup>-6</sup> increased lifetime risk of cancer). This apparently precise level of risk does not convey the very large uncertainties involved, and HSE feels that no credibility can be attached to such a risk estimate. Also, there is a concern that the numerical risk estimate could be perceived as “real”.

16. *How to deal with somatic cell mutagens with no cancer data under REACH:* HSE does not support the TTC or the MTD approaches to setting DMELs in such circumstances. One option might be to argue that it is not possible to set DMELs for somatic cell mutagens with no cancer data, and to maintain that a qualitative assessment and reliance on ALARA (as-low-

as-reasonably-achievable) is the only way forward. Another option might be to consider that a quantitative DMEL may be an inevitable outcome and that there is therefore a need to propose an alternative acceptable basis for setting DMELs in such circumstances. An arbitrary approach may be acceptable as long as it did not infringe scientific principles. The views of WATCH are sought.

17. *Other DNEL issues:* As indicated in paragraph 5 of this Cover Paper, there are a number of issues relating to DNELs that possibly merit further consideration. There is unlikely to be time at the November meeting of WATCH to discuss all of these issues but they could be followed up at the next meeting of WATCH. For example: HSE would wish further consideration of: -

- a) the selection of Assessment Factors (AFs) in particular circumstances for workers and the general public;
- b) the implicit reliance on allometric scaling that underlies the use of certain AFs;
- c) the use of AFs to deal with uncertainties relating to animal/human differences where the effect is local inflammation in the respiratory tract
- d) how to deal with data gaps for sensory irritation.

WATCH members may also identify additional issues that they would wish to comment on in writing.

### **Link to HSC Strategy**

18. These issues are linked to HSE mandatory responsibilities in relation to chemicals.

### **Consultation**

19. HSE has sent a copy of the draft TGD to the Department of Health and the Committee on Toxicity and the Committee on Carcinogenicity will be receiving various sections of the draft TGD for information and comment in the near future.

### **European Context**

20. This work is framed completely in a European context and the outputs from this meeting will feed into the further development of the TGD.

### **Action**

21. WATCH is asked to consider the issues described in this paper and to: -
- i) Provide views on the approaches to developing DMELs for genotoxic carcinogens and for somatic cell mutagens with no cancer data.
  - ii) Offer suggestions on any other suitable approaches to developing DMELs for such chemicals.
  - iii) Comment on any other specific aspect of DNEL derivation and/or identify priority issues for consideration.

### **Contact:**

Nicola Gregg  
WATCH Secretariat

### **References / Attachments**

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|---------|---|
| Annex 1 | Reference preliminary Technical Guidance Document (reference p-TGD). Chapter 3, Human health hazard assessment. |
| Annex 2 | Specific guidance on mutagens (RIP3.2-2_TGD_DNEL_Muta)  |
| Annex 3 | Specific guidance on carcinogens (RIP3.2-2_TGD_DNEL_Carc)   |
| Annex 4 | HSE paper on genotoxic carcinogens submitted to EU EDG, Sept. 2006  |

- Annex 5 Gold LS, Gaylor DW and Slone TH (2003) *Comparison of cancer risk estimates based on a variety of risk assessment methodologies*. Reg Toxicol and Pharmacol 37: 45-53
- Annex 6 Kroes et al (2004) *Structure-based threshold of toxicological concern (TTC): guidance for application to substances present at low levels in the diet*. Food and Chemical Toxicology 42:65-83