

**Joint Task Force**

**ECHA Committee for Risk Assessment (RAC)**

**and**

**Scientific Committee on Occupational Exposure  
Limits (SCOEL)**

**on**

**Scientific aspects and methodologies related to  
the exposure of chemicals at the workplace**

**TASK 2**

**6 December 2017**

***Final report***

**EUROPEAN COMMISSION**

Directorate-General for Employment, Social Affairs and Inclusion  
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**EUROPEAN CHEMICALS AGENCY**

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## Foreword

This report concerns the third task in the Commission's mandate to the Joint Task Force (JTF) set up between the ECHA Committee for Risk Assessment (RAC) and DG-EMPL's Scientific Committee on Occupational Exposure Limits (SCOEL).

This joint report is a reflection of the discussions of the JTF at its meetings held on 15 June, 23 August and 26 October 2017. The report reflects the discussion and the views and opinions of the two Committees on the concept of a "practical threshold", which it was agreed was more appropriately described as a "mode of action based threshold". It was also noted that the term 'non-threshold substances' in the mandate in the underlying joint report is interpreted as 'non-threshold carcinogens'.

Scientifically, the investigation of carcinogenic modes of action as a tool in developing occupational exposure limits is a challenging one, as each chemical provides a different toxicological and carcinogenic profile. As a result, the discussions in the JTF were challenging but always stimulating and carried out in a spirit of collegiality and openness. The pioneering work of Prof. Hermann Bolt, former Chairman of SCOEL, in developing the 'practical threshold' for use in a regulatory context and who provided some initial pointers to the JTF discussions is gratefully acknowledged.

There was a positive collaborative working environment within the JTF and the two Committees specifically focused on improving mutual understanding of the different scientific approaches to agree on the commonalities of their scientific procedures and principles which could form the basis of a common approach in assessing non-threshold substances in relation to workers' exposure to chemicals. It was noted that since the report for Tasks 1 and 3 was published in February 2017, and the further development of the SCOEL methodology there has already been convergence of a number of points raised in the report.

### **Co-Chairpersons of the JTF**

Andrea Hartwig and Tim Bowmer

## 1. Introduction

The European Chemicals Agency (ECHA) and the Scientific Committee on Occupational Exposure Limits (SCOEL) were requested by the European Commission on 6 July 2015 by way of an Article 95(3) of the REACH Regulation request and an Article 2(9) of Commission Decision 2014/113/EU<sup>1</sup>, to create a Joint Task Force (JTF), composed of members from each of the ECHA Committee for Risk Assessment (RAC) and SCOEL, including representatives from the Secretariats.

The terms of reference for the JTF included three tasks: Tasks 1 and 3 have been reported and published on the RAC website<sup>2</sup>; this report addresses Task 2. The task as described in the Commission mandate is as follows:

### **Mandate Task 2**

Comparative critical assessment of ECHA and SCOEL methodologies in relation to non-threshold substances.

- Outline the present methodologies used by SCOEL and under REACH in estimating risks from non-threshold agents relevant for worker protection.
- Assess in particular the SCOEL methodology for deriving a “practical threshold” and its link to the DNEL and DMEL concepts.
- If the existing SCOEL methodology is deemed not appropriate for use under REACH, assess whether it could be adapted in order to make such use appropriate:
  - If such adaptation is appropriate and possible, describe and scientifically justify the necessary modifications;
  - ECHA should also consider the appropriateness of its guidance by comparison with SCOEL methodology.
- Compare and assess the methodology used by SCOEL to establish ‘risk calculations’ for non-threshold substances with the methodologies used under REACH to establish reference dose/response curves and DMELs with a view to adapting/improving these in order to align them:
  - Justify any opinion that convergence of a given aspect of the methodologies is not scientifically appropriate.

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<sup>1</sup> Commission Decision 2014/113/EU of 3 March 2014 on setting up a Scientific Committee on Occupational Exposure Limits for Chemical Agents and repealing Decision 95/320/EC

<sup>2</sup> [https://echa.europa.eu/documents/10162/13579/rac\\_joint\\_scoel\\_opinion\\_en.pdf/58265b74-7177-caf7-2937-c7c520768216](https://echa.europa.eu/documents/10162/13579/rac_joint_scoel_opinion_en.pdf/58265b74-7177-caf7-2937-c7c520768216)

One of the objectives of each of the REACH Regulation<sup>3</sup>, the Chemical Agents Directive<sup>4</sup> (CAD) and the Carcinogens or Mutagens Directive<sup>5</sup> (CMD), is to improve the protection of workers' health. A key means of achieving this objective is by enhancing the quality of scientific evaluations related to human health and exposure to chemical substances, to support delivery of relevant policies and to improve standards of worker protection in Europe. This report specifically focuses on worker protection.

The report is the product of the JTF and was agreed by them on 24 November 2017. The report has been endorsed by the European Chemicals Agency's Committee for Risk Assessment (RAC) and by the Scientific Committee on Occupational Exposure Limits (SCOEL) at their plenary meetings in December 2017 (RAC-43 and SCOEL-103).

## 2. Responses by the JTF to the mandate points

1. *Outline present methodologies used by SCOEL and under REACH in estimating risks from non-threshold agents relevant for worker protection.*

This point is addressed by the descriptions drafted in sections 3 and 4 of this report.

2. *Assess in particular the SCOEL methodology for deriving a "practical threshold" and its link to the DNEL and DMEL concepts.*

This point is addressed in section 5 of this report where the concept of a "practical threshold" is considered to be more appropriately described as a "mode of action (MoA) based threshold": the latter term is used throughout this document.

There is no direct link between the SCOEL methodology and the DNEL and DMEL concepts. If data allows, SCOEL either proposes a health-based OEL derived from an "MoA-based threshold" or for non-threshold substances, provides numerical cancer risk estimates corresponding to defined exposure levels; if data are insufficient, no exposure limits (OELs) or risk estimates will be proposed.

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<sup>3</sup> Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC (OJ L 396 of 30 December 2006, p. 1; corrected by OJ L 136, 29.5.2007, p. 3)

<sup>4</sup> Council Directive 98/24/EC of 7 April 1998 on the protection of the health and safety of workers from the risks related to chemical agents at work (fourteenth individual Directive within the meaning of Article 16(1) of Directive 89/391/EEC), (OJ L 131, 5.5.1998, p.11), as amended by Directive 2014/27/EU of the European Parliament and of the Council of 26 February 2014 amending Council Directives 92/58/EEC, 92/85/EEC, 94/33/EC, 98/24/EC and Directive 2004/37/EC of the European Parliament and of the Council, in order to align them to Regulation (EC) No 1272/2008 on classification, labelling and packaging of substances and mixtures ), (OJ L 65, 5.3.2014, p.1).

<sup>5</sup> Directive 2004/37/EC of the European Parliament and of the Council of 29 April 2004 on the protection of workers from the risks related to exposure to carcinogens or mutagens at work (Sixth individual Directive within the meaning of Article 16(1) of Council Directive 89/391/EEC) (OJ L 158, 30.4.2004, p. 50).

3. *If SCOEL methodology is not appropriate for use under REACH, can it be adapted?*

In general, the JTF considered that the SCOEL methodology and underlying principles are appropriate and feasible for use under REACH but with some adaptation.

4. *If adaptation (under REACH) is possible, describe and justify adaptations/modifications.*

Adaptation under REACH would be possible, provided that the focus remains on the scientific basis of determining an MoA-based threshold. Such adaptations could include:

- the requirement to explain transparently the remaining uncertainty; this is needed to clearly indicate to the legislator that the limit/level proposed may contain some uncertainties as to a possible residual risk;
- omission of the SCOEL grouping system as it is not considered a necessary step in the procedure;
- use of a transparent approach for correcting the point of departure (PoD) and the application of assessment factors;
- use of allometric scaling and other adjustment factors as described in the recently revised SCOEL methodology are applied in the same way as described in the ECHA guidance<sup>6</sup>. However, uncertainty factors used by SCOEL may differ from the assessment factors applied by ECHA.

5. *Consider appropriateness of [current] ECHA guidance in comparison to the [current/revised] SCOEL methodology.*

In light of the current RAC work programme in relation to worker protection and the experience being gained from REACH Authorisations and CMD, it is too early to conclude whether the (relevant) ECHA guidance is appropriate for the MoA-based threshold approach or whether this should be reviewed. It is considered appropriate for RAC to revisit this issue after the Committee has completed opinions on the currently mandated CMD substances (arsenic acid and its inorganic salts, 4,4'-methylene-bis-[2-chloroaniline] (MOCA), benzene, nickel and its compounds and acrylonitrile).

It should be noted that there is ongoing further development of the SCOEL methodology.

6. *Compare SCOEL methodology to establish 'risk calculations' for non-threshold substances with ECHA/RAC dose-response curves and DMELs.*

This point is addressed in section 5 of this report.

7. *Justify any aspect that is not considered appropriate to converge.*

This point is addressed by points 3 and 4 above.

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<sup>6</sup> Guidance on IR & CSA: Chapter R8.

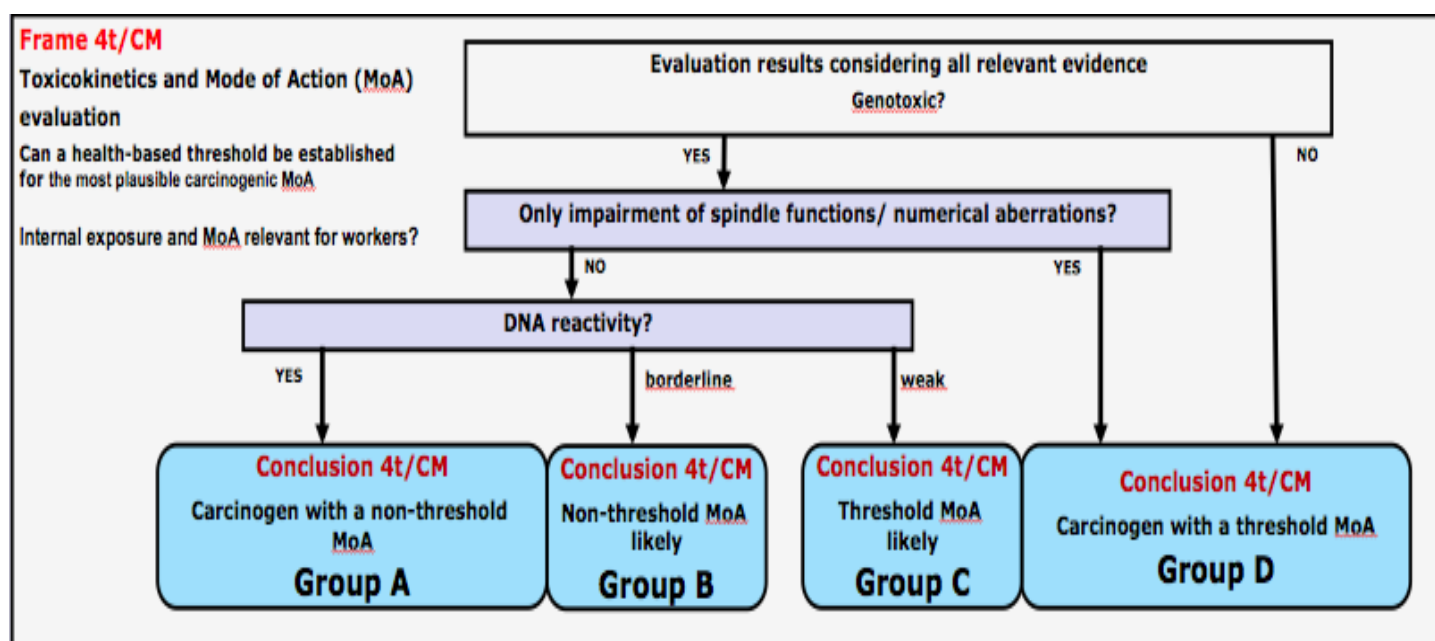
[https://echa.europa.eu/documents/10162/13632/information\\_requirements\\_r8\\_en.pdf/e153243a-03f0-44c5-8808-88af66223258](https://echa.europa.eu/documents/10162/13632/information_requirements_r8_en.pdf/e153243a-03f0-44c5-8808-88af66223258)

### 3. SCOEL Methodology for the evaluation of chemical carcinogens and mutagens

Within the legal framework of Directive 98/24/EC (Chemical Agents Directive, CAD) and Directive 2004/37/EC (on the protection of workers from the risks related to the exposure to carcinogens or mutagens at work, CMD), SCOEL makes substance-specific recommendations to be used as the scientific basis for policy discussion at EU level for OELs under CAD/CMD. In doing so, SCOEL distinguishes between carcinogens acting via a threshold or believed to act via a non-threshold mechanism, the latter often direct DNA-damaging mutagens.

There is growing recognition that carcinogenic risk extrapolation to low doses (and standard setting) must consider the mode of action (MoA) of a given chemical. So far, there is agreement to distinguish between genotoxic and non-genotoxic chemicals, yet further differentiations seem appropriate. To account for differences in the MoA of chemical carcinogens, SCOEL has established the following approach, based on Bolt and Huici-Montagud, 2008<sup>7</sup>, and modified within the revised SCOEL methodology. It should be noted that the groupings (A-D) are not intended to be a *de facto* classification of carcinogenicity *per se*, but simply a useful discussion tool to examine and make transparent the available data on the MoA in relation to the likely presence, or absence, of a threshold.

**Figure 1: Grouping of carcinogens based on the MoA.**



**Key - Figure 1:**

**Group A:** Carcinogens with an MoA for which no threshold is assumed, due to direct DNA reactivity of the carcinogen or its metabolites.

**Group B:** Carcinogens that are likely to act by an MoA for which no threshold is assumed, either because direct DNA reactivity cannot be excluded or the evidence for genotoxicity due to non-DNA reactive mechanisms is insufficient.

<sup>7</sup> Bolt HM, Huici-Montagud A (2008). Strategy of the scientific committee on occupational exposure limits (SCOEL) in the derivation of occupational carcinogens and mutagens

**Group C:** Carcinogens for which a genotoxic threshold MoA is likely. These include carcinogens that are weakly DNA-reactive when compared with other toxicities they exert and their carcinogenicity appears to be driven by other mechanism(s) that secondarily induce(s) genotoxicity (genotoxic by indirect mechanisms).

**Group D:** Carcinogens with a threshold MoA. The SCOEL assigns non-genotoxic carcinogens (such as tumour promoters) and non-DNA reactive genotoxic carcinogens leading to numerical chromosomal aberrations but not increasing the frequency of gene mutations, into this group.

**Genotoxic carcinogens** will be considered on a case-by-case basis, taking into account all available evidence (epidemiological data, animal experimental data, MoA data).

For **DNA-reactive genotoxic carcinogens**, the possibility to establish a health-based threshold has to be evaluated based on the following considerations:

- A health-based threshold cannot be established, if the chemical agent is clearly DNA-reactive and / or it has the potential to initiate DNA reactivity leading to mutagenic and carcinogenic effects. Depending on the degree of evidence, substances are grouped in A or B.
- A practical threshold can be established for those DNA-reactive genotoxic carcinogens which are only weakly genotoxic and their carcinogenicity is not primarily driven by the DNA reactivity, but appears to arise from other mechanisms, such as sustained local tissue damage and associated increased cell proliferation (Group C).

The SCOEL distinguishes between the following types of **non-DNA reactive genotoxic carcinogens**:

- Chemical agents that increase the background level of oxidative DNA damage, e.g. by catalysing Fenton-type reactions and exceeding the anti-oxidative defence, or by interfering with the anti-oxidative defence or due to chronic inflammation (Group C).
- Chemical agents that interact with the cellular response to DNA damage, e.g. by inactivating DNA repair mechanisms, or by epigenetic effects. Thereby, genomic stability is reduced and the mutation frequency increases. The SCOEL assumes that such chemical agents elicit effects only above a certain threshold (Group C).
- Chemical agents that act on the chromosomal level alone, i.e. in the absence of gene mutations. Non-DNA reactive genotoxic MoA include the induction of numerical chromosomal aberrations (Group D).

As the decision framework to assign carcinogens or mutagens into one of the four carcinogen groups reveals (Figure 1), the respective assignment determines how the SCOEL further evaluates the evidence that is available for the given chemical agent and whether or not a health based OEL can be recommended:

- **In case of Group A or B chemical agents**, no health-based OEL will be recommended. If sufficient data are available, SCOEL may provide a numerical risk calculation, indicating assumed cancer risk at different exposure levels; this will be based on linear extrapolation from epidemiological or experimental animal data. In such cases, the corresponding SCOEL document (recommendation) will clearly state that a carcinogenic risk assessment has been carried out. It will contain a table summarising the concentrations explored and the associated risks calculated at these concentrations. However it may be noted that the establishment of a reference cancer risk level is not within the mandate of SCOEL as this is of societal concern and needs policy guidance. SCOEL will not provide a



specific recommended OEL as in the case for health-based values. In case of insufficient data, no values or risk estimates will be provided.

- **In case of Group C or D chemical agents**, a health-based OEL will be recommended. Where appropriate, also a biological limit value may be proposed in those cases, where an air concentration alone may not provide sufficient protection of workers.

In each case, the rationale for grouping of a chemical agent into one of the four groups will be clearly described in the respective recommendation. The group assigned by SCOEL will appear in the frame of the table on the front page of the recommendation as "SCOEL carcinogen group: X", (of the SCOEL recommendation).

## 4. REACH Methodology for risk assessment of chemical carcinogens and mutagens

Within the legal framework of REACH, registrants are obliged to demonstrate that the risks arising from the manufacture, import or use of their chemical substances are adequately controlled. To that aim, REACH has defined the DNEL. DNELs need to be derived for all human health effects, in order to identify the most critical effect. Under REACH the risk to humans can be considered to be controlled if the estimated exposure levels do not exceed the derived DNELs.

For human health effects for which no DNEL can be derived, (e.g. non-threshold carcinogens), REACH requires a qualitative or semi-quantitative approach for risk assessment. In ECHA guidance on REACH the DMEL is suggested as a semi-quantitative approach for non-threshold carcinogens. A DMEL is a cancer risk value considered to be of very low concern and exposures at the workplace should be controlled to at least this level. The derivation of a DMEL is described in detail in the ECHA guidance<sup>8</sup> (see Section R.8.5 and Appendix R.8-7), but in brief the process involves four main steps (adapted from Section R.8.1.3 of ECHA Guidance):

- Step 1: Gather typical dose descriptors (e.g. N(L)OAEL, BMD, LD50, LC50, T25, BMD(L)10) from all available and relevant studies on the different human health endpoints and/or other information of the potency when no dose descriptor is available.
- Step 2: Decide on mode of action (threshold or non-threshold).
- Step 3: If possible, derive DMEL(s) for non-threshold endpoints by:
  - a) selection of relevant dose-descriptor(s) for the endpoint concerned;
  - b) modification, when necessary, of relevant dose descriptor(s) per endpoint to the correct starting point (i.e., correct the unit of exposure);
  - c) application, when necessary, of assessment factors/high to low dose risk extrapolation factor<sup>9</sup> to the correct starting point to obtain endpoint-specific DMEL(s) for the relevant exposure pattern (duration, frequency, route and exposed human population).
- Step 4: Select the leading health effect(s) and the corresponding DNEL, DMEL or other qualitative/semi-quantitative description.

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<sup>8</sup> Guidance on IR & CSA: Chapter R8.

[https://echa.europa.eu/documents/10162/13632/information\\_requirements\\_r8\\_en.pdf/e153243a-03f0-44c5-8808-88af66223258](https://echa.europa.eu/documents/10162/13632/information_requirements_r8_en.pdf/e153243a-03f0-44c5-8808-88af66223258)

<sup>9</sup> The term assessment factor is used because of it being a neutral term. However, these factors can in the DMEL-approach also be viewed as 'correction factors' and 'uncertainty factors'.

It should be noted that a DMEL is not equivalent to a DNEL. A DNEL expresses a derived value which is a "safe" level below which exposures should be controlled – with the underlying assumption that such an exposure level would be below a no-effect-level. For non-threshold effects, the underlying assumption is that a no-effect-level cannot be established and a DMEL therefore expresses an exposure level corresponding to a low, possibly theoretical, risk.

Identical to SCOEL, the establishment of a reference cancer risk level for the DMEL is not within the remit of ECHA/RAC, as this is of societal concern and needs policy guidance. The ECHA guidance therefore only presents examples of cancer risk levels that have been set and used in different contexts (it is for instance mentioned that  $1 \times 10^{-5}$  and  $1 \times 10^{-6}$  could be seen as an indicative tolerable risk level when setting a DMEL for workers).

The ECHA guidance document describes two methodologies for deriving a DMEL, of which the one most commonly used is based on linear extrapolation. There is no clear distinction made in the approach to be followed for genotoxic carcinogens acting via a direct or an indirect MoA, although it is recognised that this is important to consider.

The default assumption for genotoxic substances has for a long time been that they have a linear dose (concentration)-response relationship. However, this assumption has recently been challenged by experimental evidence showing that both direct and indirect acting genotoxins can possess non-linear or threshold dose (concentration)-response curves.

For genotoxic carcinogens exhibiting direct interaction with DNA, it is not generally possible to infer the position of the threshold from the NOEL on a dose-response curve, even though a biological threshold below which cancer is not induced may exist.

For non-genotoxic carcinogens, no-effect thresholds are assumed to exist. The same may be the case for certain carcinogens that cause genetic alterations via indirect effects on DNA. However the scientific evidence needed to convincingly underpin such an indirect mode of genotoxic action may be more difficult to achieve. Examples of non-DNA reactive mechanisms that may lead to genotoxicity via non-linear or threshold dose (concentration)-response relationships include inhibition of DNA synthesis, alterations in DNA repair, overloading of defence mechanisms (anti-oxidants or metal homeostatic controls), interaction with microtubule assembly leading to aneuploidy, topoisomerase inhibition, high cytotoxicity, metabolic overload and physiological perturbations (e.g. induction of erythropoiesis). The mechanisms underlying non-linear or threshold dose (concentration)-response relationships for some DNA reactive genotoxic substances like alkylating agents seem linked to DNA repair capacity.

Assessment of the significance to be assigned to genotoxic responses mediated by such mechanisms would include an assessment of whether the underlying mechanism can be induced at substance concentrations that can be expected to occur under relevant *in vivo* conditions.

## 5. Exploring the concept of an MoA-based threshold

### 5.1 General points

#### 5.1.1 Similarity of methods & approaches

With regard to direct acting genotoxic carcinogens, the risk assessment methodologies used by RAC and SCOEL are relatively similar. In the absence of adequate information about the potential carcinogenic response at relevant human exposure levels, both

Committees use the T25 and/or BMD(L)<sub>10</sub> as a starting point for extrapolation from higher exposure levels and apply by default, a linear relationship.

SCOEL prefers BMDL as a starting point for linear extrapolation in the case of animal data whereas ECHA guidance does not give clear preference. Similarly, both Committees may use human epidemiological data for the dose-response assessment when available. In the case of epidemiological data, SCOEL prefers the use of life-table analysis, which gives a more accurate estimate of lifetime risk whereas ECHA/RAC does not make a clear choice between conditional and unconditional risk calculations. SCOEL does not propose an OEL but provides numerical risk estimates for defined exposure levels if sufficient data are available.

In order to effectively use the methods, policy advice on “acceptable” risk levels needs to be provided by the Commission, which can then be integrated into risk characterisation and used in cases where an MoA-based threshold cannot be set.

When considering other carcinogens, it is necessary to assess whether the mechanism of action is essentially non-genotoxic, or involves early (i.e. induced by the compound (or its metabolite(s) under consideration) genotoxic events that are induced by indirect mechanisms. There is broad agreement on the science, scientific principles and assessment of carcinogens in considering an MoA-based threshold: the differences arise when applied in the different regulatory contexts. However, the quality and clarity of the supporting information is especially important. In the case of genotoxic carcinogens, in the absence of such robust information, the default position is to assume they are direct-acting *in vivo* at relevant doses.

### 5.1.2 Scope of the approach

The starting point, once it is established that a substance is potentially carcinogenic based on epidemiological, laboratory *in vivo* data or both, and that the substance may be genotoxic, is to address the way in which genotoxicity may be expressed in target tissues. The genotoxicity may be either direct or indirect (see section 5.2). The focus should be on events considered critical for the induction of a carcinogenic response. In some cases, consideration is needed separately for each type of cancer induced by the substance. Some chemical carcinogens may have potential to induce cancer by both genotoxic and non-genotoxic modes of action.

The critical endpoint is cancer and thus the MoA-based threshold should refer to a threshold for cancer and not just one for mutation. The significance of the threshold event in the induction of cancer is also critical, i.e. in general, the threshold should apply to the step that is the driving force of the carcinogenesis.

It is generally agreed that with respect to occupational carcinogens, the scope for using the MoA-based methodology applies most likely to a limited number of substances. At the same time it is also recognised that the individual substances for which a MoA-based threshold may be considered relevant are very important from a workers' health protection perspective, (e.g. formaldehyde). In some cases the MoA toxicological information may be complemented by recent informative epidemiological studies. These studies may have detailed exposure information for the individual worker which allows more refined analysis of the shape of the exposure response relationship at relatively low levels. In general, all available information is used to decide on and to quantify an MoA-based threshold.

## 5.2 Genotoxicity

Genotoxicity is the initiating event in carcinogenesis and the question whether or not a threshold based on the underlying mechanism of genotoxicity can be anticipated is of critical importance.

Genotoxicity can be evoked either by direct interaction with DNA or, via indirect events/interactions, such as the genotoxic effect results from the interaction with a physiological process. There are therefore, two main groups of genotoxic carcinogens:

- i. where genotoxicity is caused by direct interaction of the respective substance or its metabolite with the DNA, and the risks are assessed using the dose response relationship which is mostly anticipated to be linear;
- ii. where genotoxicity may occur through indirect mechanisms that cause damage to DNA or chromosomes, frequently by interactions with proteins and there is sufficient evidence that a threshold can be identified, then an occupational exposure limit may be derived.

The two carcinogenicity groups above partly correspond to the SCOEL methodology of grouping carcinogens into the categories A to D: group (i) above would cover SCOEL groups A and B, while group (ii) above would cover groups C and D. Members agreed that the more simplified "two groups" was acceptable for distinguishing the potential substances for an MoA-based threshold and the grouping into the A, B, C or D Groups was not a necessity for considerations by RAC under REACH.

### 5.2.1 Genotoxic MoA

The potential genotoxic modes of action encountered in assessing the risks of chemicals in the workplace are numerous. Substances may cause cancer involving several mechanisms, some assumed with and others without, thresholds.

The most important point of agreement was on the diverse genotoxic modes of action and that in certain cases a threshold could be established, which could subsequently be defined and explained.

There are potentially three broad categories of MoA for indirect genotoxicity:

- i. substances that are toxic to non-DNA targets: such as those which interact with proteins; this group includes aneugens;
- ii. substances that overload the system/change metabolism and exceed natural protective mechanisms in the body, such as stimulation of cell proliferation due to irritation, chronic inflammation or change in homeostasis; this group would include ROS (reactive oxygen species);
- iii. substances that are directly genotoxic but for which DNA repair mechanisms protect from the induction of mutations at low exposure levels. This category is rarely seen.

For the purpose of this task, a review of such mechanisms was not required and further experience in evaluating substances with MoA-based thresholds should be accumulated first. It was acknowledged that such risk assessments require a significant amount of specific *in vivo* and mechanistic data, significantly more than the standard data requirements under REACH and that in many cases, considerable expert judgement would be required in the analysis of the data. It was highlighted that the current concerns to avoid animal testing (under REACH) could have a negative impact on the generation of such data for use in worker protection in the future as neither CAD or CMD contain provisions for generating data.

When evaluating genotoxicity from *in vivo* studies, the test data used in support of a risk assessment should be carefully evaluated with regards to the doses applied, to ensure that laboratory data at unrealistically high-doses or unrealistically low-doses, are appropriately weighed.

The interaction between other modes of action such as irritation leading to cytotoxicity and inflammation/cell proliferation and the resulting genotoxicity, need to be clearly described.

From the totality of evidence on the genotoxic and other modes of action it should be clear which is the driving force behind the carcinogenicity.

In the case of MoA-based threshold substances, simple linear extrapolation from high to low levels of exposure can lead to an overestimation of the risk. This may make the use of the REACH DMEL approach impractical for such substances. For example, the DMEL may be well below natural physiological or background levels for a substance or its metabolites.

### 5.3 MoA-based threshold

Substances that are genotoxic and for which there is robust evidence for an indirect mode of action, can follow a "threshold approach". These substances are described as having an 'MoA-based threshold' rather than a 'practical threshold' as described by Bolt et al, (2002, 2004, 2008). Where it is possible to identify such a threshold, it is then used to derive an OEL. However, if the evidence on the dose-response is insufficient or for borderline cases which are likely to have a threshold but where it might be difficult to decide on the level with some certainty, then the non-threshold approach should be followed by default.

In identifying the threshold, account should also be taken of possible other, non-genotoxic modes of action, such as irritation leading to cytotoxicity and inflammation/cell proliferation. The threshold should be set on the MoA that is the driving force of the carcinogenicity.

Where a MoA-based threshold can be confidently established, the resulting recommendation for an OEL sets a level of exposure where it is assumed that there will be no expectation of a significant residual risk and that the remaining uncertainties are clearly described. In this case the employer, worker and public authorities can be assured that exposure at or below the OEL does not present an additional lifetime cancer risk to the workers. At the same time, since there is no significant residual risk, this provides a level of confidence that the OEL will not be revised downwards over time as the legislator seeks to further reduce the level of any residual risk. The only scientific reason for revising the OEL would be on the basis of new scientific evidence.

When an OEL is based on an MoA-based threshold, the setting of a STEL for that substance needs special attention, particularly for locally acting carcinogens.

#### 5.3.1 Exposure-response relationship

The shape and steepness of the dose response curve for carcinogenic effect needs to be considered at the lower doses/concentrations, i.e. whether this has implications for the reliability of any threshold indicated by the rest of the data, in particular when the STEL is based on another effect than cancer. This needs to be considered on a case by case basis.

#### 5.3.2 Weight of Evidence

All the evidence from the available studies relating to the genotoxicity and carcinogenicity of a substance, (including epidemiology and detailed information on the

mode of action), should be combined to assess whether a threshold for carcinogenicity can be identified. The key events leading to cancer need to be described with sufficient confidence and they are the focus of the analysis.

Such an informed decision on a possible threshold requires a significant amount of data (significantly more than the standard data requirements under REACH) as well as considerable expert judgement in the analysis of the data. As noted earlier, the current concerns under REACH (and various other legislation) to avoid animal testing could have a negative impact on the generation of data.

## 5.4 Remaining uncertainty

Although a substance may have one or more MoA-based thresholds, it does not necessarily mean that the indicated level is safe - some uncertainties with regards to residual risk may remain. However, there should be sufficient evidence of an overall threshold to indicate that the risks are substantially lower below a certain level of exposure.

Even with convincing threshold effects caused by other modes of action, to fully support any proposed OEL, the potential for genotoxicity at lower doses needs to be accounted for and such uncertainties should be explained. Whereas quantification of the remaining uncertainty is desirable, it is acknowledged that it is unlikely to be feasible for most substances and expert judgement needs to be applied:

- Where the remaining uncertainty is negligible or convincingly low, a safe level may be defined;
- In other cases, uncertainties may lead to the application of an assessment factor. However, the uncertainties should be clearly described and flagged up for the attention of the Commission;
- Clearly, where the uncertainties are too extensive, a threshold should not be applied.

One of the key aspects in applying an MoA-based threshold approach to setting an OEL is to clearly describe the remaining uncertainties.

There are two parts to consider and address: firstly, the uncertainty surrounding the identification of an MoA threshold itself and secondly, the uncertainty in identifying the actual level (value) of the threshold.

The former is more critical to describe and assess in order to allow the regulatory authorities to assess the remaining risks and therefore it is important to ensure there is communication with the relevant national authorities. The remaining uncertainty depends on the weight of the available supporting evidence for the MoA.

When a "credible threshold" is proposed a DMEL would not be set; one approach to describe some of the uncertainties would be to consider those aspects that would normally be addressed if the standard DNEL assessment factor approach was followed.

The actual level of the threshold can be addressed by selecting the point of departure and (related to the MoA for the driving force of the carcinogenicity) the uncertainties dealt with as if it were a normal threshold effect. Any "gaps" in the data should be identified and addressed; for example, if "read across" or "assessment factors" are used then these need to be explained. Expert judgement is usually required to do this.

A substance would only be identified as an MoA-based threshold substance if at the least there was sufficient information on the MoA, in order to be confident that there was a threshold and evidence suggesting that any relevant (usually indirect) genotoxicity is occurring only at doses above the threshold.



For many substances, a concern for residual genotoxicity will remain even where a clear threshold has been identified and therefore it may not be possible or appropriate to use an MoA-based threshold approach. For such cases, a hockey-stick-like dose-response may be considered.

## 5.5 Epidemiology – what is its role and how does it fit in?

With respect to the use of epidemiology data in an MoA-based threshold assessment, such data forms part of the WoE approach. It is important to note that the exposures encountered in occupational epidemiological studies can be orders of magnitude lower than in animal studies. The observations may be in agreement with the toxicological data (animal studies) but in some cases in particular when harvesting better quality (and often more recent) epidemiology data a difference may be seen between the toxicological (animal) data and the epidemiological data: it may be the case that a threshold could be assumed but with better epidemiology data, there may not be the evidence to support the threshold.

When a threshold may not be well supported by high quality epidemiological data, these (epidemiological) data are given a preference over toxicological data (animal studies) in case these do seem to support one.

In general, epidemiological studies with sufficient power can assess excess risk levels which are considerably lower than experimental animal studies. Excess risks may be in the range of 1:1,000, in some cases and depending on the design, to 1:1,000,000 per year and can be used to set exposure limits. Experimental animal studies can estimate excess risk in the range of 1: 5 or 1:10 and need to be extrapolated considerably to derive “risk estimates under real life conditions”, compared to epidemiological observations, which will directly estimate risk at real life exposure conditions.

In general, the quality of epidemiological data has improved over the last decades in particular because of improvements in the exposure assessment methodology. The strengths and weaknesses of both the toxicological data and the epidemiological data need to be assessed in terms of respective modes of action to determine whether an MoA-based threshold is plausible. A weight of evidence approach is required to assess which type of evidence is most adequate for a certain agent combining animal experimental, epidemiological and mechanistic information.

Appendix 2 presents some further considerations on the use of epidemiological data when applied for cancer risk assessment under the SCOEL approach.

## 6. Conclusions

For most genotoxic carcinogens the available data are likely to be inadequate for an effective threshold to be identified with sufficient confidence. The default, or starting assumption, for these carcinogens will be that there is no threshold for the carcinogenic hazard. The two Committees apply similar methodologies for such substances, assuming a linear relationship between exposure and effect and employing T25 and/or BMD methodology. On reflection of recent opinions, it was found that there was often agreement within an order of two.

For those other carcinogens where it might be possible to adapt this threshold approach, and take into consideration a mode of action with a threshold, the following conclusions have been agreed:

1. In general, the SCOEL methodology and underlying principles for establishing MoA-based thresholds are appropriate and feasible for use under REACH with some adaptation.

2. Adaptation under REACH would be possible, provided that the focus remains on the scientific basis of determining a MoA- based threshold. Such adaptations would include:
  - the requirement to explain transparently the remaining uncertainty; it was agreed that this was needed to clearly indicate to the legislator that the limit/level proposed may contain some uncertainties as to a possible residual risk.
  - omission of the SCOEL grouping system as it was not considered a necessary step in the procedure;
  - the use of a transparent approach for correcting the PoD and the application of assessment factors;
  - use of allometric scaling and other adjustment factors as described in the recently revised SCOEL methodology, in the same way as described in the ECHA guidance. However, uncertainty factors used by SCOEL may differ from the assessment factors applied by ECHA.
3. The starting point/default is a non-threshold MoA and only when subsequent analysis of the data allows refinement in the sense that overall the data actually points to a threshold, then a threshold approach can be followed. Without (sufficient) data to conclude this, the default stays a non-threshold MoA.
4. With regard to the use of epidemiological data for risk assessment, both RAC and SCOEL have used such evidence for deriving DMELs or OELs. However, differences exist in the way epidemiological evidence is being used and applied in particular for risk calculations and this requires further harmonization.

## 7. Recommendations

The following recommendations are made:

1. For RAC to consider if the current ECHA guidance is appropriate or whether modifications are needed to accommodate the MoA based threshold approach in addressing carcinogenic risks. This should be considered after the Committee has completed opinions on the currently mandated CMD substances.
2. For SCOEL to consider the outcome of the present evaluation for the revised methodology.
3. When proposing an MoA-based threshold, remaining uncertainties need to be clearly described for (i) the uncertainty surrounding the identification of an MoA threshold itself and (ii) the uncertainty in identifying the actual level (value) of the threshold.



## List of Abbreviations

Abbreviation	Explanation
BGV	Biological Guidance value
BLV	Biological Limit Value
CAD	Chemical Agents Directive
CMD	Carcinogens or Mutagens Directive
DNEL	Derived No-Effect Level
DMEL	Derived Minimal Effect Level
LOAEL/LOAEC	Lowest observed adverse effect level/ Lowest observed adverse effect concentration
MAK	MAK Commission [The Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area in Germany.]
MoA	Mode of Action
NOAEL/NOAEC	No observed adverse effect level/ No observed adverse effect concentration
OEL	Occupational Exposure Limit
PoD	Point of Departure
STEL	Short Term Exposure Limit

## Glossary of Terms & Definitions

Standard term / Abbreviation	Explanation/ Definition
DMEL	<p>Derived Minimal Effect Level</p> <p>As described in ECHA Guidance<sup>10</sup>:</p> <p>" ....a reference risk level which is considered to be of very low concern. DMEL derived in accordance with the guidance should be seen as a tolerable level of effects and it should be noted that it is not a level where no potential effects can be foreseen.</p> <p>A DMEL is not equivalent to a DNEL ..... a DMEL expresses an exposure level corresponding to a low, possibly theoretical, risk."</p>

<sup>10</sup> Guidance on IR & CSA: Chapter R8:  
[https://echa.europa.eu/documents/10162/13632/information\\_requirements\\_r8\\_en.pdf/e153243a-03f0-44c5-8808-88af66223258](https://echa.europa.eu/documents/10162/13632/information_requirements_r8_en.pdf/e153243a-03f0-44c5-8808-88af66223258)

Standard term / Abbreviation	Explanation/ Definition
DNEL	<p>Derived No-Effect Level</p> <p>Defined in REACH Annex I, 1.0.1</p> <p><i>The objectives of the human health hazard assessment shall be [...] to derive levels of exposure to the substance above which humans should not be exposed. This level of exposure is known as the Derived No-Effect Level (DNEL).</i></p> <p>As described in the ECHA Guidance</p> <p>"A DNEL expresses a derived value below which exposures should be controlled – with the underlying assumption that such an exposure level would be below a no-effect-level. For non-threshold effects, the underlying assumption is that a no-effect-level cannot be established."</p>
Genotoxicity	<p>Genotoxic substances will be distinguished as follows:</p> <ul style="list-style-type: none"> <li>• DNA-reactive genotoxic carcinogens: <ul style="list-style-type: none"> <li>○ Chemical agents (or their metabolites) that interact directly with DNA, leading to gene mutations (SCOEL group A or B, depending on the strength of evidence)</li> </ul> </li> <li>• Non-DNA reactive genotoxic carcinogens <ul style="list-style-type: none"> <li>○ Chemical agents that increase the extent of gene mutations and decrease genomic stability due to indirect mechanisms, e.g. by increasing the level of oxidative DNA damage, by interfering with the cellular response to DNA damage or by epigenetic mechanisms (SCOEL group C)</li> <li>○ Chemical agents that act on the chromosomal level alone, e.g. leading to numerical chromosomal aberrations but not increasing the frequency of gene mutations (SCOEL group D)</li> </ul> </li> </ul>
MoA-based threshold	<p>A threshold based on modes of action involving indirect genotoxicity, possibly in combination with other, non-genotoxic modes of action.</p>
NOAEL/NOAEC	<p>No observed adverse effect level/ No observed adverse effect concentration.</p> <p>The NOAEL/NOAEC is defined as "<i>the level of exposure of an organism, found by experiment or observation, at which there is no biologically or statistically significant increase in the frequency or severity of any adverse effects in the exposed population when compared to its appropriate control</i>". (Ref.: U.S. Department of Health and Human Services).</p>

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## Appendix 2. Additional related topic discussed at August and October meetings

### Specific considerations for epidemiological data for risk assessment purposes applied within the SCOEL approach

Some specific issues exist when using epidemiological data for cancer risk assessment.

- Epidemiological cancer studies are often not designed, conducted and analysed in a standardized manner. This requires a review of the quality of the epidemiological evidence to decide which studies can be used for risk assessment purposes. This involves evaluation whether the adequate exposure metric has been applied, and whether bias (e.g. selection or information bias) or confounding cannot explain the observed association between exposure and disease. From a theoretical perspective, biases may always be present but their effect on the measure of association between exposure and cancer should be limited.
- Consideration of particle size in the mode of action discussion (what particle size would cause the cancer?) to estimate lung cancer risk for the most appropriate fraction, respirable or inhalable. Given that lung cancer is in most cases located in the airways, the inhalable fraction is most appropriate. When needed the exposure metric used in the original epidemiological studies should be converted to the inhalable dust metric.
- When interpreting animal and human studies, care should be taken to establish in as far as possible whether the exposures are to respirable or inhalable dust, following standard definitions. When tumours are observed in the respiratory tract in general as opposed to tumours initiated in the alveoli only, ideally the inhalable fraction should be used.
- Related to the estimated cancer risk: the use of Life table analysis (unconditional risk) is often, but not always, preferred from a scientific point of view above the so called conditional method since it takes into account shrinking of the population at risk due to other causes of death. The conditional method should be avoided as it is overestimating risk at a given exposure, leading to too conservative exposure estimates at which a certain risk occurs, especially when the analysis is extended to entire life-time or very old ages. Estimated exposure levels at certain benchmark risk values (1/10 000 per year or 1/1 000 000 per year) might be below the background exposure levels because of this issue. Lifetable analysis also allows implementation of latency times or removal of agents from the body assuming certain half-lives.
- When life-table analysis is being used, some specific issues should be given more explicit consideration because of their effect on the final risk estimates (use of incidence versus mortality data, mortality rates (male, female or average rates), country or countries of origin of the rates (European average rates versus country specific rates), period over which the risk is being calculated (till age 75/85 which have been used in the past as estimates of average life expectancy, end of life), use of latency and removal of the agent after cessation of exposure). Transparency is required in combination with more rigorous harmonization.
- The use of incidence data is preferred to mortality data. Many different tumours do not lead to increased mortality anymore because of improved treatments. As a result, mortality risks might underestimate the risk of developing a tumour considerably. Thus incidence data, obtained from cancer registries, should be used for risk calculations.