

Strategy of the scientific committee on occupational exposure limits (SCOEL) in the derivation of occupational exposure limits for carcinogens and mutagens

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Abstract Setting standards, such as occupational exposure limits (OELs) for carcinogenic substances must consider modes of action. At the European Union level, the scientific committee on occupational exposure limits (SCOEL) has discussed a number of chemical carcinogens and has issued recommendations. For some carcinogens, health-based OELs were recommended, while quantitative assessments of carcinogenic risks were performed for others. For purposes of setting limits this led to the consideration of the following groups of carcinogens. (A) Non-threshold genotoxic carcinogens; for low-dose assessment of risk, the linear non-threshold (LNT) model appears appropriate. For these chemicals, regulations (risk management) may be based on the ALARA principle (“as low as reasonably achievable”), technical feasibility, and other socio-political considerations. (B) Genotoxic carcinogens, for which the existence of a threshold cannot be sufficiently supported at present. In these cases, the LNT model may be used as a default assumption, based on the scientific uncertainty. (C) Genotoxic carcinogens with a *practical* thresh-

old, as supported by studies on mechanisms and/or toxicokinetics; health-based exposure limits may be based on an established NOAEL (no observed adverse effect level). (D) Non-genotoxic carcinogens and non-DNA-reactive carcinogens; for these compounds a *true* (“perfect”) threshold is associated with a clearly founded NOAEL. The mechanisms shown by tumour promoters, spindle poisons, topoisomerase II poisons and hormones are typical examples of this category. Health-based OELs are derived for carcinogens of groups C and D, while a risk assessment is carried out for carcinogens of groups A and B. Substantial progress is currently being made in the incorporation of new types of mechanistic data into these regulatory procedures.

Keywords Occupational exposure limits · Carcinogens · Genotoxicity · Mode of action · Thresholds · Workplace chemicals

Introduction

There is growing recognition that carcinogenic risk extrapolation to low doses, which is a preliminary step for setting standards for carcinogenic substances, must consider the mode of action of the carcinogen in question (Neumann et al. 1998; Sarrif et al. 2000; Seeley et al. 2001; Cohen et al. 2003; Bolt 2003; Kirsch-Volders et al. 2003; Pratt and Barron 2003; Thier et al. 2003; Streffer et al. 2004; Hori and Kitagawa 2006; Boobis et al. 2006). The scientific discussion on this matter in Europe has resulted in new perspectives highlighted by *EUROTOX* in recent years (Bolt et al. 2004; Bolt and Degen 2004; Foth et al. 2005).

At the level of the European Union, the scientific committee on occupational exposure limits (SCOEL) has

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discussed a number of chemical carcinogens and has issued recommendations since 1990. For some carcinogens, health-based occupational exposure limits (OELs) were recommended, while quantitative assessments of carcinogenic risks were performed for others (SCOEL 1998, 2007). Based on this experience and on the above-mentioned discussions within the scientific community, the position taken by SCOEL on the derivation of OELs for carcinogens has been presented in various fora and has been more explicitly described in its methodology.

Possibilities for setting Biological Limit Values for assessed carcinogens, as presented here, have also been considered by SCOEL for almost 17 years (Bolt and Thier 2006).

Genotoxic versus non-genotoxic carcinogens

For risk assessment purposes, there is so far general agreement to distinguish between chemicals acting through genotoxic and non-genotoxic mechanisms of carcinogenesis.

Non-genotoxic carcinogens (e.g. hormones, tumour promoters, TCDD) are characterized by a “conventional” dose–response relationship that allows the derivation of a No-Observed-Adverse-Effect-Level (NOAEL) for induction of tumours. Application of an uncertainty (or safety) factor allows the derivation of permissible exposure levels at which no relevant human cancer risks are anticipated. The risk assessment approach for non-genotoxic chemicals is generally similar among different regulatory bodies worldwide (Seeley et al. 2001). Therefore, OELs derived in this case of “true non-genotoxicants”, are considered by SCOEL “health-based exposure limits”.

For *genotoxic carcinogens*, there is a need for further differentiation, as an array of possibilities exists (Streffer et al. 2004).

Positive effects only at chromosomal level, e.g. aneuploidy or clastogenicity, in the absence of mutagenicity, may characterize a substance that produces carcinogenic effects only at high, toxic doses (Schoeny 1996). These *non-DNA-reactive genotoxicants* include topoisomerase inhibitors (Lynch et al. 2003), or inhibitors of the spindle apparatus or associated motor proteins (Decodier et al. 2002). In such cases, SCOEL agrees on the potential for a threshold, as argued by others (Crebelli 2000; Parry et al. 2000).

For some other chemicals, the genotoxic effect (especially when of local nature, that is at the site of direct interaction chemical/biological tissue) may be relevant only under conditions of sustained local tissue damage and associated increased cell proliferation. Formaldehyde (Morgan 1997) and vinyl acetate (Bogdanffy and Valentine 2003) are

key examples discussed by SCOEL in detail. In these cases, the derivation of a “practical” threshold (Hengstler et al. 2003), seems justified. This category is equivalent to the “apparent” threshold defined by Kirsch-Volders et al. (2000).

In consequence, both groups of the described genotoxic effects may be thresholded, and for substances acting through such mechanisms of carcinogenicity a health-based exposure limit may be set.

However, for DNA reactive, tumour initiating genotoxic carcinogens (e.g. alkylating chemicals or ionizing radiation) the classical linear non-threshold (LNT) extrapolation appears scientifically sound and, therefore, no threshold can be defined in such cases. Streffer et al. (2004) suggested a further differentiation to be made within this group of genotoxicants, including other chemicals for which there is more uncertainty on their dose–response relationship. In such cases, LNT extrapolations may be used as a default procedure.

Altogether, this has led to the consideration, for setting limits purposes, of four groups of carcinogens, displayed in Fig. 1:

- (A) *Non-threshold genotoxic carcinogens*; for low-dose assessment of risk, the LNT model appears appropriate. For these chemicals, regulations (risk management) may be based on the ALARA principle (“as low as reasonably achievable”), technical feasibility, and other socio-political considerations.
- (B) *Genotoxic carcinogens*, for which the existence of a threshold cannot be sufficiently supported at present. In these cases, the LNT model may be used as a default assumption, based on the scientific uncertainty.
- (C) *Genotoxic carcinogens with a practical threshold*, as supported by studies on mechanisms and/or toxicokinetics; health-based exposure limits may be based on

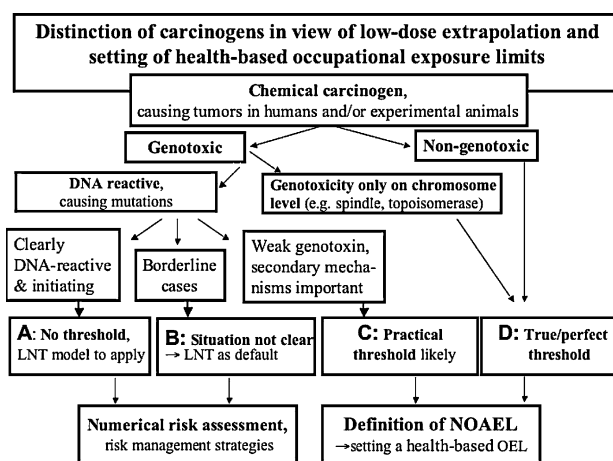


Fig. 1 Flow-chart to distinguish between groups of carcinogens (A–D) for the purpose of risk assessment and standard setting (OELs)

Table 1 Results of SCOEL discussions on individual carcinogens (by 2007) and assignment to the groups of carcinogens based on mode of action, see SCOEL Summary Documents (SCOEL 1998, 2007)

(A) *Non-threshold genotoxic carcinogens; for risk low-dose assessment the linear non-threshold (LNT) model appears appropriate:*
1,3-butadiene (quantitative risk assessment performed), vinyl chloride (quantitative risk assessment performed), methylene dianiline (MDA; 4,4'-diamono-diphenyl-methane), dimethyl sulphate

(B) *Genotoxic carcinogens, for which the existence of a threshold cannot be sufficiently supported at present. In these cases the LNT model may be used as a default assumption, based on the scientific uncertainty:*
Acrylonitrile, benzene, naphthalene, wood dust, hexavalent chromium compounds (quantitative risk assessment performed)

(C) *Genotoxic carcinogens for which a practical threshold is supported and for which a health-based OEL has been proposed:*
Formaldehyde, vinyl acetate, pyridine, silica, lead (provisional OEL proposed)

(D) *Non-genotoxic carcinogens and/or non-DNA-reactive carcinogens; for these compounds a true ("perfect") threshold is associated with a clearly founded NOAEL. A health-based OEL has been proposed:*
Carbon tetrachloride, chloroform, nitrobenzene

an established NOAEL (no observed adverse effect level).

- (D) *Non-genotoxic carcinogens and non-DNA-reactive carcinogens; for these compounds a true ("perfect") threshold is associated with a clearly founded NOAEL.* The mechanisms shown by tumour promoters, spindle poisons, topoisomerase II poisons and hormones are typical examples of this category.

The discussions by SCOEL on individual compounds are consistent with this scheme and underline its applicability (Table 1).

Health-based OELs are derived by SCOEL for carcinogens of groups C and D. A risk assessment is carried out by SCOEL for carcinogens of groups A and B. In both cases, not only the mechanism of action should be well established, but an adequate set of data is needed.

There is actually no difference in these requirements as compared to those needed for setting other types of health-based limit values. The difficulty may arise here in considering mechanisms of genotoxicity at the chromosomal level (group D) or in the differentiation of weak genotoxins with secondary mechanisms of carcinogenesis (group C). The discussions by SCOEL on formaldehyde and vinyl acetate have provided good indications on criteria to be used. Also the distinction between groups B and C is of key importance in the discussion of practical thresholds of carcinogenicity for important industrial chemicals, like acrylamide, acrylonitrile and trichloroethylene (Bolt and Degen 2004) and those currently ranged by SCOEL as group B (see Table 1). For these, a number of processes, including detoxication reactions, cell cycle arrest, DNA repair, apoptosis and immune surveillance, may result in non-linearity of the dose–response, as noted by Dybing and Sanner (2003) in the risk assessment of acrylamide in food. SCOEL, when reviewing *acrylonitrile*, has acknowledged current argumentations in favour of secondary mechanisms of carcinogenicity. Nevertheless, as acrylonitrile appears from the experimental bioassays as a pluripo-

tent (multi-organ) carcinogen, and as an unspecified impact of genotoxicity cannot be ruled out, considered in this case a non-threshold mechanism as a default. The case of the nephrocarcinogenicity of *trichloroethylene* is being discussed in the scientific community, and reference may be made to a compilation of relevant arguments (Harth et al. 2005).

Substantial progress is thus being made in the incorporation of new mechanistic data into these regulatory procedures. Further research effort in this field is needed to overcome scientific uncertainties. The elucidation of mechanisms involved will also help risk managers in the critical process of risk communication (Degen 2003; Hori and Kitagawa 2006).

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