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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* threshold, 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

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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

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. aneugenicity 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 argumented 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

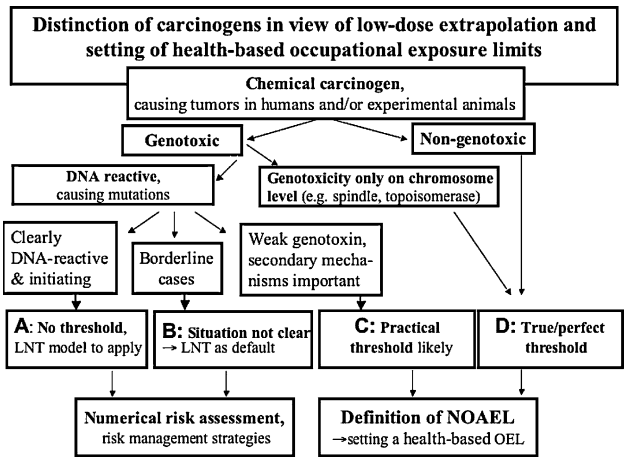

Fig. 1 Flow-chart to distinguish between groups of carcinogens (A–D) for the purpose of risk assessment and standard setting (OELs)

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 genotoxicants 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 pluripotent (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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References

Bogdanffy MS, Valentine R (2003) Differentiating between local cytotoxicity, mitogenesis, and genotoxicity in carcinogen risk assessments: the case of vinyl acetate. Toxicol Lett 140/141:83–98

Bolt HM (2003) Genotoxicity—threshold or not? Introduction of cases of industrial chemicals. Toxicol Lett 140/141:43–51

Bolt HM, Degen GH (2004) Human carcinogenic risk evaluation, part II: contributions of the EUROTOX specialty section for carcinogenesis. Toxicol Sci 81:3–6

Bolt HM, Thier R (2006) Biological monitoring and biological limit values (BLV): the strategy of the European Union. Toxicol Lett 162:119–124

Bolt HM, Foth H, Hengstler JG, Degen GH (2004) Carcinogenicity categorization of chemicals—new aspects to be considered in a European perspective. Toxicol Lett 151:29–41

Boobis AR, Cohen SM, Dellarco V, McGregor D, Meek ME, Vickers C, Willcocks D, Farland W (2006) Crit Rev Toxicol 36:781–791

Cohen SM, Meek ME, Klaunig JE, Patton DE, Fenner-Crisp PA (2003) The human relevance of information on carcinogenic modes of action: overview. Crit Rev Toxicol 33:581–589

Crebelli R (2000) Threshold-mediated mechanisms in mutagenesis: implications in the classification and regulation of chemical mutagens. Mutat Res 464:129–135

Decodier I, Dillen L, Cundari E, Kirsch-Volders M (2002) Elimination of micronucleated cells by apoptosis after treatment with inhibitors of microtubules. Mutagenesis 17:337–344

Degen GH (2003) Einige Anmerkungen zur Risikokommunikation über Chemikalien. Umweltmed Forsch Prax 8:330–334

Dybing E, Sanner T (2003) Risk assessment of acrylamide in foods. Toxicol Sci 75:7–15

Foth H, Degen GH, Bolt HM (2005) New aspects in the classification of carcinogens. Arh Hig Rada Toksikol 56:165–173

Harth V, Brüning T, Bolt HM (2005) Renal carcinogenicity of trichloroethylene: update, mode of action, and fundamentals for occupational standard setting. Rev Environ Health 20:103–118

Hengstler JG, Bogdanffy MS, Bolt HM, Oesch F (2003) Challenging dogma—thresholds for genotoxic carcinogens? The case of vinyl acetate. Annu Rev Pharmacol Toxicol 43:485–520

Hori H, Kitagawa Y (2006) New trends in carcinogenic thresholds—international symposium on "thresholds for carcinogens and mutagens". Shokuhin Eiseigaku Zasshi 47: 3308–3310

Kirsch-Volders M, Aardema M, Elhajouji A (2000) Concept of threshold in mutagenesis and carcinogenesis. Mutation Res 464:3–11

Kirsch-Volders M, Vanhauwaert A, Eichenlaub-Ritter U, Decordier I (2003) Indirect mechanisms of genotoxicity. Toxicol Lett 140/141:63–74

Lynch A, Harvey J, Aylott M, Nicholas E, Burman M, Siddiqui A, Walker S, Rees R (2003) Investigations into the concept of a threshold for topoisomerase inhibitor-induced clastogenicity. Mutagenesis 18:345–353

Morgan KT (1997) A brief review of formaldehyde carcinogenesis in relation to rat nasal pathology and human risk assessment. Toxicol Pathol 25:291–307

Neumann HG, Vamvakas S, Thielmann HW, Gelbke HP, Filser JG, Reuter U, Kappus H, Norpoth KH, Wardenbach P, Wichmann HE (1998) Changes in the classification of carcinogenic chemicals in the work area. Int Arch Occup Environ Health 71:566–574

Parry JM, Jenkins GJS, Haddad F, Bourner R, Parry EM (2000) In vitro and in vivo extrapolations of genotoxin exposures: consideration of factors which influence dose–response thresholds. Mutat Res 464:53–63

Pratt IS, Barron T (2003) Regulatory recognition of indirect genotoxicity mechanisms in the European Union. Toxicol Lett 140/141:53–62

Sarrif AM, Aardema MJ, Albertini S, Arni P, Henderson LM, Kirsch-Volders M, Vrijhof H (2000) ECETOC-EEMS symposium on dose–response and threshold-mediated mechanisms in mutagenesis (Salzburg, Austria; 7 September 1998) General introduction. Mutation Res 464:1–2

Schoeny R (1996) Use of genetic toxicology data in US EPA risk assessment: the mercury study report as an example. Environ Health Perspect 104(Suppl 3):663–673

SCOEL (1998) Occupational Exposure Limits. Recommendations of the Scientific Committee for Occupational Exposure Limits to Chemical Agents 1994–97. European Commission Directorate-General for Employment, Industrial Relatiopns and Social Affairs Unit V/F.5. Luxemburg: Office for Official Publications of the European Communities, ISBN 92-828-4270-3

SCOEL (2007) European Commission, Employment, Social Affairs and Equal Opportunities, Health and Safety at Work. SCOEL Recommendations. http://ec.europa.eu/employment_social/health_safety/recommendations_en.htm. Accessed 27 Sep 2007

Seeley MR, Tonner-Navarro LE, Beck BD, Deskin R, Feron VJ, Johanson G, Bolt HM (2001) Procedures of health risk assessment in Europe. Regul Toxicol Pharmacol 34:153–169

Streffer C, Bolt HM, Føllesdal D, Hall P, Hengstler JG, Jacob P, Oughton D, Priess K, Rehbinder E, Swaton E (2004) Environmental standards—dose-effect relations in the low dose range and risk evaluation. Springer, Berlin

Thier R, Bonacker D, Stoiber T, Böhm KJ, Wang M, Unger E, Bolt HM, Degen GH (2003) Interaction of metal salts with cytoskeletal motor protein systems. Toxicol Lett 140/141:75–81