Genes and Environment, Vol. 30, No. 4 pp. 114–119 (2008)

Review

The Concept of ''Practical Thresholds'' in the Derivation of Occupational Exposure Limits for Carcinogens by the Scientific Committee on Occupational Exposure Limits (SCOEL) of the European Union[1]

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(Received August 11, 2008; Revised September 29, 2008; Accepted October 1, 2008)

In Europe, there has been a scientific discussion on possible thresholds in chemical carcinogens since the late 1990s. Based on this discussion, the Scientific Committee on Occupational Exposure Limits (SCOEL) of the European Union has discussed a number of chemical carcinogens and has issued recommendations. For some carcinogens, health-based Occupational Exposure Limits (OELs) were recommended, while quantitative assessments of carcinogenic risks were performed for others. For purposes of setting OELs the following groups of carcinogens were adopted: (A) Non-threshold genotoxic carcinogens; for low-dose assessment of risk, the linear non-threshold (LNT) model appears appropriate. For these chemicals, the 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, and the ALARA principle may be applied as well. (C) Genotoxic carcinogens with a *practical* threshold is supported by studies on mechanisms and/or toxicokinetics; health-based exposure limits may be based on an established no-observed adverse effect level (NOAEL). (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 tumor 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. In order to highlight the most important differentiation between Groups B and C, the basic reasoning is given for the six compounds formaldehyde, vinyl acetate, acrylonitrile, acrylamide, trichloroethylene and methylene chloride.

Key words: Occupational Exposure Limits, carcinogens, genotoxicity, mode of action, thresholds, workplace chemicals, SCOEL

Introduction

In 1995, the European Commission has decided (Decision 95/320/EC) to set up a permanent advisory committee with the mandate to propose and justify Occupational Exposure Limits (OELs) and Biological Limit Values (BLVs) for chemical exposures at the workplace (1,2). Since 1998 recommendations for health-based OELs have been issued by the Scientific Committee on Occupational Exposure Limits (SCOEL) (3,4). For genotoxic carcinogens, numerical risk assessments were elaborated, when these were possible on the basis of the available data. For clearly non-genotoxic carcinogens health-based OELs were documented based on established No-Observed Adverse Effect Levels (NOAELs), according to commonly accepted procedures (5,6).

By end of the 1990s, the German ''MAK-Commission'' proposed a modification of the general procedure, in order to establish health-based OELs (''MAK values'') for some additional carcinogens (7). There was no general harmonization of the procedures for carcinogenic health risk assessment in Europe at this time (5). However, there was a growing recognition that carcinogenic risk extrapolation to low doses, which is a pivotal step for setting standards for carcinogenic substances, must consider the mode of action. In Europe, landmarks of the scientific discussion were an *ECETOC-EEMS Symposium on Dose-Response and Threshold-Mediated Mechanisms in Mutagenesis* in Salzburg/Austria (8), results the working group ''*Environmental Standards–Dose-Effect Relations in the Low Dose Range and Risk Evaluation*'' of the European Academy

[1]Presented at the *International Symposium on Genotoxic and Carcinogenic Thresholds*, Tokyo, July 22/23, 2008

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Bad Neuenahr-Ahrweiler (9) and a continuous effort of the EUROTOX Speciality Section Carcinogenesis (10–12). Positions taken by SCOEL on the derivation of OELs for carcinogens considered the scientific discussions (13,14) in Europe and elsewhere and were also presented at various fora. The final strategy has been described by SCOEL in a methodology document and was published in the open literature (15).

Genotoxic *versus* Non-Genotoxic Carcinogens

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

Non-genotoxic carcinogens (e.g. hormones, tumor promoters, TCDD-like compounds) are characterized by a ''conventional'' dose-response relationship that allows the derivation of a NOAEL for induction of tumors. Application of an uncertainty factor allows the derivation of permissible exposure levels, at which no relevant human cancer risk is anticipated. The risk assessment approach for non-genotoxic chemicals is similar among different regulatory bodies world-wide (5). Therefore, OELs derived for ''true non-genotoxicants'' are considered as health-based exposure limits.

For the broad array of *genotoxic carcinogens*, there is the need of further differentiation. 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 (16). Such *non-DNA-reactive genotoxicants* include topoisomerase inhibitors (17), or inhibitors of the spindle apparatus or associated motor proteins (18). In such cases, SCOEL agrees to the existence of a threshold (19,20). For some other chemicals, the genotoxic effect may be relevant only under conditions of sustained local tissue damage and associated increased cell proliferation. Formaldehyde (21) and vinyl acetate (22,23) represent such examples, which are explained below. In such cases, the derivation of a ''*practical*'' threshold (23) seems justified. This denomination is equivalent to the ''apparent'' threshold as defined by Kirsch-Volders *et al*. (24). Such genotoxic effects may be thresholded, and for substances acting through such mechanisms of carcinogenicity a health-based exposure limit may be set.

For DNA reactive, tumor 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.* (9) have suggested a further differentiation to be made within this group of genotoxicants, also considering chemicals for which there is more uncertainty on their dose-response relationship. In such cases, LNT extrapolations may be used as a default procedure.

Table 1. Development of nomenclature to distinguish types of threshold for carcinogenic or mutagenic compounds*

Author(s)	Ref.	SCOEL Group C	SCOEL Group D
Seiler *et al.* 1977	**25**	*apparent*	*real*
Kirsch-Volders *et al.* 2000	**24**	*apparent*	*absolute/real* (*statistical for spindle poisons*)
Hengstler *et al.* 2003	**23**	*practical*	*perfect*
Bolt & Degen 2004	**11**	*practical/apparent*	*true/perfect*
Bolt & Huici-Montagud 2008	**15**	*practical*	*true/perfect*

*See text for explanation

Types of Thresholds Discussed for Carcinogens

There has been a debate on the nomenclature of different types of thresholds for carcinogenic compounds (see Table 1). The original idea to differentiate between *apparent vs. real* threshold genotoxins dates back to Jörg Seiler (25) in 1977. More recently, Kirsch-Volders *et al.* (24) discussed this issue, proposing definitions for *absolute*, *real* or *biological*, *apparent* and *statistical* thresholds. Hengstler *et al*. (23) distinguished between *perfect* and *practical* thresholds, again based on different types of mechanisms. Basically, non-genotoxic carcinogens were connected with a *real* (24) or *perfect* (23) threshold. A *statistical* threshold (24) has been attributed to mitotic spindle poisons. Definitions of *apparent* (24) or *practical* thresholds (23) are based on the concept that the chemical should cause no genotoxic effect at very low or even immeasurable target concentrations (25). Such *apparent* thresholds have been connected with rapid degradation (toxicokinetics) of the chemical or to other factors that limit target exposures (24).

Taking these concepts together, it has been proposed to basically distinguish between *perfect* and *practical* thresholds. Thus, *perfect* thresholds (23) include both *real* and *statistical* thresholds as defined by Kirsch-Volders *et al.* (24), and *practical* thresholds (23) are equivalent to *apparent* thresholds, as defined by Kirsch-Volders *et al.* (24).

An international scientific discourse on these matters is still ongoing, and the existence of thresholds at very low doses is being discussed even for highly genotoxic compounds like *N*-nitrosamines (26–28).

The Definitions Adopted by SCOEL

Altogether, the aforementioned discussions and developments have led to the adoption by SCOEL of the following four 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,

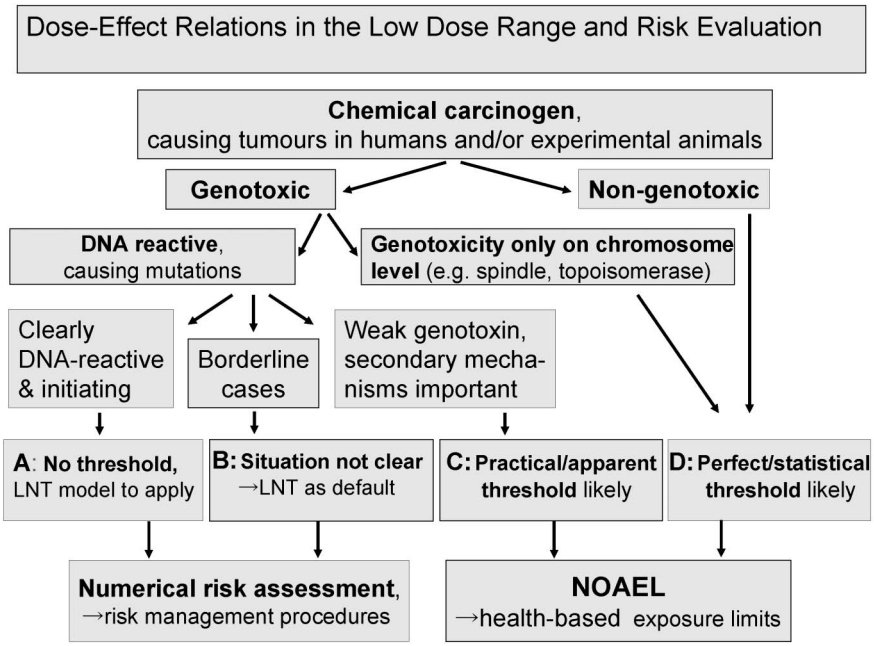

Fig. 1. Flow-chart of the SCOEL procedure to distinguish between carcinogen Groups A-D (15)

risk management regulations 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 is 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 tumor promoters, spindle poisons, topoisomerase II poisons and hormones are typical examples of this category.

The flow scheme to arrive at these categories adopted by SCOEL is presented here as Fig. 1.

Application of the SCOEL Strategy for Carcinogens

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, whenever possible. In cases of Groups C and D, not only the mechanism of action should be well established, but also an adequate set of data is needed.

Problems may arise in considering mechanisms of genotoxicity at the chromosomal level (*e.g.* differentia-

Table 2. Results of SCOEL discussions on individual carcinogens (by 2008) and assignment to groups based on mode of action (published evaluations and evaluations under ''public consultation'')

Group 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), dimethyl sulfate, diethyl sulfate (analogy to dimethyl sulfate), hexamethyl phosphotriamide, methylene dianiline (MDA; *4,4′*-diamino-diphenyl-methane), vinyl chloride (quantitative risk assessment performed), vinyl bromide (risk assessment by analogy to vinyl chloride).
Group 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:*
	acrylamide, acrylonitrile, *o*-anisidine, arsenic, benzene (provisional assignment), *2,6*-dimethylaniline (insuff. data), hexavalent chromium compounds (quantitative risk assessment performed), naphthalene, wood dust.
Group C	*Genotoxic carcinogens for which a practical threshold is supported and for which a health-based OEL is proposed:*
	dichloromethane/methylene chloride, formaldehyde, glyceryl trinitrate, lead (provisional OEL proposed), lead chromate, nickel (under discussion), pyridine, silica, trichloroethylene, vinyl acetate.
Group 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 is proposed:* carbon tetrachloride, chloroform, nitrobenzene

tion between aneugenic and clastogenic effects; Group D) or in the differentiation of weak genotoxicants with secondary mechanisms of carcinogenesis (Group C), but progress is being made in the incorporation of mechanistic data in these instances.

Table 2 presents an overview of current results concerning specific compounds. Summary documents of the assessments by SCOEL have either been published (3,4), or are in the state of ''public consultation''. Examples of argumentations for key compounds are presented in the following. These compounds are also included in Table 1. The examples highlight especially the differentiation between groups B and C, which is most decisive for setting a health-based OEL.

Application of the SCOEL Procedure to Cases of Key Compounds

Case 1; Formaldehyde (Group B or C): The case of formaldehyde has been discussed very much in-depth in many EU countries (29–33). Mechanistic assessments have been published (21). Experimentally, inhaled formaldehyde produces nasal carcinomas in rats, and IARC has categorized formaldehyde as a ''*Group 1*'' carcinogen because the development of human nasopharyngeal carcinomas (34). In its assessment scheme SCOEL has regarded formaldehyde as a Group C carcinogen. The main arguments were that there was no straightforward evidence for a systemic genotoxic and carcinogenic effect, and that cell proliferation following chronic irritation was necessary for the tumor formation. Avoidance of irritancy would therefore lead to a health-based OEL, which was proposed at 0.2 ppm.

Case 2; Vinyl acetate (Group B or C): Vinyl acetate produces local tumors at the site of application after oral and inhalation dosing in rodents. It is instantaneously hydrolyzed at the site of first contact with the organism by ubiquitous esterases to acetic acid and formaldehyde, which is also metabolized to acetic acid. At high doses, the local genotoxic effect of formaldehyde and the cell proliferation stimulus due to acidification by acetic acid together lead to carcinogenicity. Formaldehyde and acetic acid are endogenous compounds of the C_1-metabolism *via* folic acid. If the endogenous level is not substantially exceeded, no carcinogenic effect is to be expected. This reasoning is well documented in the literature (22,23). Accordingly, SCOEL regarded vinyl acetate as a Group C carcinogen and proposed a health-based OEL of 5 ppm, which also avoids local irritancy.

Case 3; Acrylonitrile (Group B or C): Acrylonitrile is acutely toxic due to cyanide formation upon its oxidative metabolism (35). Experimentally, tumors at several target sites are observed in rodents; the assessment of risk is very much debated (36). There are arguments in favor of a threshold for experimental brain tumors, such as the absence of DNA adducts in brain, observed oxidative DNA damage in astrocytes *in vivo*, reversibility of loss in gap junction communication in exposed astrocytes, and a sublinear dose-response curve. Also, the genotoxicity *in vivo* appears not very much straightforward. However, acrylonitrile is an experimental multi-organ carcinogen (brain, spinal cord, Zymbal gland, GI tract [upon oral dosing], mammary gland). This leaves many uncertainties at present, although the existence of a threshold in the carcinogenic response appears possible. Given this uncertainty, SCOEL has regarded acrylonitrile as a Group B carcinogen, based on the present state of knowledge, with no health-based OEL assigned. The high acute toxicity of acrylonitrile and the possibility of uptake through the skin require special attention in the industrial practice.

Case 4; Acrylamide (Group B or C): Similar to acrylonitrile, acrylamide is a multi-organ carcinogen experimentally (tumors in rat brain, mammary gland and tunica vaginalis of the testes). Besides, it is highly neurotoxic. There are argumentations in favor of a threshold in carcinogenicity, but again the multiplicity of target sites and of the possible mechanisms involved renders the case very difficult to assess. Similar to recommendations of others (37,38), SCOEL has preferred to regard acrylamide as a Group B carcinogen, with no health-based OEL assigned for its carcinogenicity. However, for matters of practical handling of the compound, a value was given that can prevent neurotoxicity.

Case 5; Trichloroethylene (Group B or C): Trichloroethylene has caused renal cell carcinomas in workers exposed over several years to high peak concentrations (39,40). According to experimental investigations, a local metabolic activation *via* the glutathione-dependent pathway and renal beta-lyase is involved (39,40). Specific mutation patterns in the von Hippel-Lindau (VHL) tumor suppressor gene have been reported (39,40). An apparent pre-condition of tumor development is nephrotoxicity, for which modes of action have been published. In the ''public consultation'' phase, SCOEL has proposed a health-based OEL of 10 ppm, in order to avoid nephrotoxicity and thereby also nephrocarcinogenicity, categorizing trichloroethylene in Group C.

Case 6; Methylene chloride/dichloromethane (Group B or C): Methylene chloride (dichloromethane) has experimentally produced liver and lung tumors in mice, but not in rats or hamsters. Again, the compound is metabolized through an oxidative (CYP2E1 dependent) and a reductive (GSTT1–1 dependent) pathway (41). The oxidative pathway leads to formation of carbon monoxide, the reductive pathway is thought to be involved in genotoxicity (42). Recent trans-species cancer risk assessments using physiologically-based pharmacokinetics (PBPK) with a probabilistic design (43) resulted in very low theoretical

risk figures for humans: for an exposure to 100 ppm for the entire working life, the cancer risk was 4.9×10^{-5}. The large species difference in susceptibility is supported by biochemical investigations showing a difference in the amino acid sequence between the murine and human GSTT1–1 that renders the murine enzyme much more active toward methylene chloride as substrate (44). Accordingly, in the ''public consultation'' phase SCOEL has grouped methylene chloride in Group C, with the recommendation of an OEL of 100 ppm that would avoid a carbon monoxide load of hemoglobin (CO-Hb) higher than 3–4%.

General Conclusions

With regard to establishment of OELs for carcinogens, SCOEL has employed a strategy to distinguish between four different groups of carcinogens. For justification of a health-based OEL for a genotoxic carcinogen based on a *practical threshold*, the differentiation between Groups B and C is most important (Fig. 1). As exemplified above by six outstanding cases, the most important argument is the prerequisite of cell proliferation and chronic tissue damage at the target site for tumor development (formaldehyde, vinyl acetate, trichloroethylene). Avoidance of such conditions can justify a health-based OEL (Group C). Another argument for Group C is when large species differences between humans and tumor-susceptible animals are well supported, so that the resulting cancer risk for humans, under realistic conditions of exposure, is negligible (methylene chloride).

Again, the mode of action of the individual compound is decisive. If significant open questions or doubts remain, the default position is categorization into Group B. This is not essentially the final position, because more insights into the underlying mechanisms/modes of action may lead to a reconsideration.

The whole matter of definition of *practical thresholds* for carcinogens is under scientific discussion world-wide (13,14,23,26–28,45). But the incorporation of new principles into official regulations is a slow process, and the degree of acceptance of threshold effects differs between regulatory systems (46). Given this, it is the scientist's task to develop and promote new concepts, and to embark into a continuing discourse with stakeholders and regulatory managers.

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