



Background, approaches and recent trends for setting health-based occupational exposure limits: A minireview

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ABSTRACT

The setting of occupational exposure limits (OELs) are founded in occupational medicine and the predictive toxicological testing, resulting in exposure–response relationships. For compounds where a No-Observed-Adverse-Effect-Level (NOAEL) can be established, health-based OELs are set by dividing the NOAEL of the critical effect by an overall uncertainty factor. Possibly, the approach may also be used for carcinogens if the mechanism is epigenetic or the genetic effect is secondary to effect from reactions with proteins such as topoisomerase inhibitors, and mitotic and meiotic spindle poisons. Additionally, the NOAEL approach may also be used for compounds with weak genotoxic effect, playing no or only a minor role in the development of tumours. No health-based OEL can be set for direct-acting genotoxic compounds where the life-time risks may be estimated from the low-dose linear non-threshold extrapolation, allowing a politically based exposure level to be set. OELs are set by several agencies in the US and Europe, but also in-house in major chemical and pharmaceutical companies. The benchmark dose approach may in the future be used where it has advantage over the NOAEL approach. Also, more attention should be devoted to sensitive groups, toxicological mechanisms and interactions as most workplace exposures are mixtures.

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1. Introduction

Within the medical profession, it has been recognised for more than 2000 years that chemical exposures may cause development of diseases. Detailed clinical descriptions are given by Ramazzini (1633–1714), who is considered the founder of occupational medicine (cf. Gochfeld, 2005a). In the period before 1800, the chemically induced diseases were reported mainly in relation to mining, smelting and use of metals, which included lead, mercury and gold (cf. Alessio et al., 2007; Gochfeld, 2005a). Sir Percival Pott (1714–1788) discovered that soot exposure in the London pre-pubertal chimney sweepers caused scrotal cancer (cf. Gochfeld, 2005a). The major progresses in occupational medicine occurred after 1900 where examples of outstanding researchers are Alice Hamilton (1869–1970) who studied effects of lead, Leonard J. Goldwater (1903–1990) who studied the hematotoxicity of benzene, and Irving J. Selikoff (1915–1992) who conducted epidemiological studies on effects of asbestos; for this and several other examples, cf. Gochfeld (2005a,b). The offending effects became established for dust (e.g. from asbestos, quartz and cotton), metals (e.g. beryllium, cadmium, lead, manganese and mercury) and substances with carcinogenic effects (e.g. benzene, chromates, aromatic

amines and vinyl chloride) (Gochfeld, 2005a,b). The importance of occupational medicine in setting occupational exposure limits (OELs) can be emphasised from the OELs set by the scientific organisation, American Conference of Governmental Hygienists (ACGIH); their OELs are termed threshold limit values (TLVs). In the TLV list from 1968, approximately 50% of the values were derived from human data, and approximately 30% were derived from animal data (Paustenbach, 1998).

The history of industrial (occupational) hygiene begins around 1800. Its aim is the control and prevention of hazards arising from workplace exposures. Amongst other things, the years from 1800 to 1900 were devoted to improving working conditions for children, prevention of dangers of power-driven machinery and disastrous fires. However, the need for ventilation to reduce levels of gases and dust was also recognised. In the early 1900s, mercury poisoning in the manufacture of hats, the bodily disfigurement caused by phossy jaw from exposures to yellow phosphorus used in the manufacture of matches, and the respiratory diseases in the pottery industry were investigated in the UK (Luxon, 1984). Courses in industrial hygiene were introduced at several universities in the early 1900s in the US (Bingham and Grimsley, 2001). In the years up to 1930, major scientific progress occurred in the fundamental principles of protection, which included substitution, enclosure and ventilation (Luxon, 1984). Between World War I and II, air sampling and analytical equipment were being

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developed (Gochfeld, 2005b), which formed the basis for establishing quantitative exposure–disease relationships. A major progress occurred around 1960, where small “personal air samplers” were developed, which was carried by the worker and which allowed long sampling periods, e.g. up to 8-h. As the pump and the sampling head were separated, this allowed switching between different types of sampling heads and thus sampling of a wide range of gases, vapours and types of dust. Another important progress was the development of analytical methods for air sampling made by the National Institute for Occupational Safety and Health (NIOSH) in the US; for the founders, the pioneers, and the next generation of US industrial hygienists, cf. Levine (2006). For setting OELs, one of the important findings was that the personal sampling concentrations could be several times that of the fixed location samplers. The new development allowed the establishment of more accurate dose–response relationships (Cherrie, 2003).

World War I played an important role in early toxicology as about 3000–4000 compounds were tested for acute effects to evaluate their potential use as chemical warfare agents. Occupational (industrial) toxicology was a well-established experimental discipline in the mid-1930s. Thus, several large US companies had established in-house toxicological laboratories, which, for example, was the case for DuPont, Dow and Union Carbide. By the 1930s, experimental industrial toxicology was expanding rapidly due to the use of animal studies. However, much toxicological experience came from industries where physicians, industrial hygienists and toxicologists together investigated adverse health effects due to specific chemical exposures. Furthermore, the industries and Federal agencies granted studies at universities, which also promoted occupational toxicology. Many of the studies were on cancer and acute effects (Bingham and Zapp, 2001).

In the late 1940s, *Patty's Industrial Hygiene and Toxicology* was published (Paustenbach, 1998) with its comprehensive collection of data on industrial chemicals, which included physical and chemical properties, uses and toxicological information from animal and human studies, as well as OELs. Frank A. Patty had a degree in pharmacy. He served as a teacher in university chemistry, and later for the U.S. Bureau of Miners, the Fidelity Casualty Insurance Company, and, finally, for the General Motors Corporation (GM). At GM, he promoted the growth of industrial hygiene and realised the need for a comprehensive reference book (Clayton, 1992). This is one of the many examples of the role of industry in the development of industrial hygiene and toxicology.

As several occupational diseases are due to chronic exposure (e.g. silicosis, asbestosis, berylliosis and chronic effects of lead), this gradually led to long-term studies in animals (Bingham and Zapp, 2001). However, with the introduction of new chemicals and the compulsory requirement of toxicological testing, the predictive animal tests are now given priority over experience with humans in the setting of exposure limits (Henschler, 1984).

Several regulatory agencies have set legally binding standards, e.g. the Permissible Exposure Limits (PELs) set by the U.S. Occupational Safety and Health Administration (<http://www.osha.gov/SLTC/pel/>; accessed March 6, 2008), which are grossly outdated and often not a useful performance metric (Cohen, 2008), and the new Workplace Exposure Limits (WELs) set by the UK Health and Safety Executive (<http://www.hse.gov.uk/coshh/table1.pdf>; accessed March 6, 2008). Where possible, the legal standards are often set by a two-step procedure. The first is the scientific step where a health-based OEL is set, which is the foundation upon which feasibility and economic concerns are overlaid to reach the legal binding value (cf. Dourson et al., 1996). The purpose of this review is the recent trend in setting health-based OELs. Several organisations set health-based OELs, e.g. in the US (ACGIH, 2007), Germany (DFG, 2006a), Japan (Omae, 2006) and the EU (EC, 1995).

2. Setting occupational exposure limits for substances with threshold effects

2.1. Principles

Occupational exposure limits (OELs) are set to prevent occupational diseases or other adverse effects, including (sensory) irritation from the airways and the eyes, headache as well as sedation and narcotic effect (e.g. Zielhuis and Notten, 1979; Henschler, 1992; Greim, 2003). In general, an OEL can only be based on reactions where dose–effect/response relationships apply (Zielhuis and Notten, 1979); the relationship between exposure and effect/response in occupational settings is available from several early reviews (Hatch, 1972a; Hatch, 1972b; Stokinger, 1972). Also the reaction(s) should be considered adverse/undesirable (Zielhuis and Notten, 1979). The concept “adverse effect” is important in the OEL setting, but its meaning has changed over time and it is not easy to define exactly (Henschler, 1992; Greim, 2003), but it clearly includes burning and stinging sensations, nauseating effects, headache and health impairment as structural and functional abnormalities, which should always be evaluated from the best available scientific information (Henschler, 1992). General definitions have been proposed. Thus, adverse effects are biochemical changes, functional impairments or pathologic lesions that affect the performance of the whole organism or reduce an organism's ability to respond to additional environmental changes (cf. Dourson et al., 2001). Another definition suggests that an adverse effect is an effect that causes an impairment of functional capacity, a decreased ability to compensate for additional stress and to maintain homeostasis, an enhanced susceptibility to other environmental influences or if such impairments are likely to become manifest in the near future (cf. Alessio et al., 2007). The evaluation of adverse effects of occupational exposures is carried out in a case-by-case manner (Greim, 2003).

OELs refer exclusively to concentrations in the air (Hunter et al., 1997; Greim, 2003; ACGIH, 2007), i.e. the values only prevent adverse effects if no skin absorption occurs. They are for single substances and are set in a case-by-case manner.

For many substances, it is accepted that toxicological reactions no longer appears if the exposure level is sufficiently low, i.e. such substances show no-observed-adverse-effect level (NOAEL) (Stokinger, 1972; Zielhuis and Notten, 1979; Henschler, 1984; Hunter et al., 1997; Paustenbach, 1998; Paustenbach, 2000; Greim, 2003). For example, thresholds are established for many sensory irritants of the eyes, nose and throat (Stokinger, 1972; Nielsen et al., 2007; Gaffney and Paustenbach, 2007) and the adverse effects are used for setting OELs (Feron et al., 2001; Meldrum, 2001; Greim, 2003). A threshold is also observed for the toxic effects of cyanide, which can be detoxified by the organism to a certain level and prevent toxic reactions (Henschler, 1984). It is possible to set “health-based OELs” for substances with NOAEL (Henschler, 1984; Hunter et al., 1997; Topping, 2001), which are able to protect the majority of the population based on the present knowledge, although a minor part of the population may not be protected, including genetically susceptible workers or those otherwise unusually responsive to chemicals because of age, gender, lifestyle, medications or previous exposures (Stokinger, 1972; Zielhuis and Notten, 1979; Bingham and Grimsley, 2001; ACGIH, 2007).

The NOAEL is the common point of departure in risk assessment (Travis et al., 2005). However, the Benchmark Dose (BMD) which is a predetermined level of adverse effect or response (e.g. 10%) and its lower confidence limit (BMDL) are also used as point of departure. In some cases, the BMD approach has advantage over the NOAEL approach (Travis et al., 2005; Schneider et al., 2006).

It has been recommended that susceptibility differences should be given more explicit attention (Lutz, 2002), and methods for evaluation of the population at risk in expressions as “the majority of the population”, “nearly all workers” and “without appreciable health risk” have been attempted (Jayjock et al., 2001; Noisel et al., 2007). This may, for example, require knowledge about toxicokinetic differences, metabolism (Dorne and Renwick, 2005; Dorne, 2007) and renal excretion (Dorne, 2007). Thus, poor metabolizers may be especially prone to accumulate higher levels of substances metabolized by CYP2C19 and CYP2D6 isozymes, whereas extensive metabolizers may be more prone to the toxic effects of the metabolites due to their higher production (Dorne, 2007). Such evaluations may in general be facilitated by means of physiologically based pharmacokinetic (PBPK) methods in combination with established variability within the human population by Monte Carlo methods (Dourson et al., 2001; Clewell and Clewell, 2008). A UK evaluation reached the conclusion that variability and susceptibility in the working population is unlikely to be significantly different from that in the general adult population (cf. Fairhurst, 2003).

The NOAEL from the most sensitive reaction (critical effect) is used in the setting of OELs. OELs are set lower than the experimentally determined NOAEL due to the imprecision of the data and due to differences in sensitivity between and within species (Zielhuis and Notten, 1979; Henschler, 1984; Henschler, 1985; IGHRC, 2003). Additionally, the length of the study, extrapolation from the lowest-observed-adverse-effect level (LOAEL) to the NOAEL as well as an incomplete database is taken into account. In principle, the OEL is set by dividing the NOAEL by a product (\prod) of uncertainty factors (UFs, also termed safety factors and assessment factors), i.e. $OEL = NOAEL / \prod UF_i$ (Zielhuis and van der Kreek, 1979a,b; Zielhuis and Notten, 1979; Paustenbach, 2000), however, many of the leading organisations setting health-based OELs are reporting one UF combining all their considerations, cf. examples in the section Uncertainty factors. Since the preferred NOAELs are from inhalation studies, the OELs are expressed as mg/m^3 of air, which can be converted to parts per million (ppm) for gases and vapours and which is cm^3 of gases or vapours per m^3 of air (DFG, 2006a; ACGIH, 2007). At 1 atm and 25 °C, the conversion is $1 ppm = (\text{the molecular weight of the compound})/24.45 mg/m^3$. OELs for non-volatile airborne particulates (dust, smoke and mists) are given in mg/m^3 (DFG, 2006a; ACGIH, 2007), except for fibres, where the OELs are often set as a number of fibres per cm^3 (ACGIH, 2007).

The OELs are usually the time–weight average (TWA) for an 8-h workday and a 40-h workweek (Greim, 2003; DFG, 2006a; ACGIH, 2007). However, a higher 15-min TWA exposure (STEL) may be set as an additional limit (ACGIH, 2007), which should not be exceeded, to the 8-h TWA limit, for example, for irritants and narcotics. The purpose of a STEL is the limitation of excursion above the 8-h TWA-OEL. Additionally, a ceiling limit may be set for substances where this level should not be exceeded during any time of the workday (Zielhuis and Notten, 1979; ACGIH, 2007). A ceiling limit may be set without setting an 8-h TWA limit (ACGIH, 2007).

2.2. Uncertainty factors

Conceptually, the setting of OELs is similar to the setting of, for example, outdoor air standards and acceptable daily intake (ADI) of food additives; they all departure from the NOAEL or from the estimated NOAEL, for example, from the LOAEL (IGHRC, 2003). For ADIs, the $\prod UF_i$ (overall UF) is traditionally set to 100 as an UF of 10 is used in extrapolation from animals to humans and an UF of 10 is considered to account for the variation within the human population (IGHRC, 2003; Dourson et al., 1996; Dorne, 2007). Similar or greater overall UFs were used in the UK for setting limits for chemicals as food additives and contaminants, agricultural pesticides, veterinary products, air pollutants and in consumer products

(IGHRC, 2003). The used default values can be considered worst-case scenarios, which may deviate strongly from the most likely UFs (Dourson et al., 1996). Also, default values are intended to minimise undue and non-consistent risk assessments, but on the other hand, if default values are used, they may play a greater role in risk assessments than scientific knowledge and data (Rodricks, 2007). In general, the overall UFs used in environmental risk assessment are not used in the setting of OELs, where the overall UFs are closer to the most likely UFs. To avoid the limitations of the default values and the limitations of the case-by-case approach, it would be beneficial if well-founded procedures could be established for setting-specific and data-driven UFs.

It was early proposed to use UFs for establishing OELs, including in the extrapolation from animal studies (e.g. Smyth, 1959; Zielhuis and van der Kreek, 1979a,b). The early experience in extrapolating results from animal studies to TLVs showed that the UFs ranged from 0.2 to 10. For those TLVs, which had been changed, the median UF was 1.3 whereas the median UF was four for TLVs that had not been changed (Smyth, 1959). The more recent size of the overall UFs can be illustrated from an analysis of 24 health-based OELs set in the UK in the period 1990–1993. It showed that if OELs were set from NOAELs from well-conducted human studies, no overall UF (i.e. $\prod UF = 1$) was applied, and if the LOAEL was used, the overall UF was about 2 if the health effect was considered of little significance. For extrapolation from NOAELs from repeated exposures in animals, the overall UFs were in the range from 2.5 to 10 and if LOAELs were used, the overall UFs were from 4 to 12. If the NOAELs were from reproductive effects, the range was from 4 to 12. If the LOAELs were from questionable fetotoxic effects, the range was from 8 to 30 and if the used LOAELs were from teratogenicity studies, the range was from 40 to 60 (Fairhurst, 1995). Clearly, the overall UFs used in the setting of OELs are traditionally lower than in other regulatory areas, which are setting exposure limits. The time trend up to now does not suggest any major increase in overall UFs, for example, as seen for setting German OELs (MAK-values). When the NOAEL has been determined from effects of the substance in man, the MAK value is generally established at the level of the NOAEL (Greim, 2003; DFG, 2006a). When the NOAEL has been determined from effects of the substance in animals, the MAK value is generally established at the level of half of this NOAEL if the NOAEL is set as minimum from a valid 90-day study (Greim, 2003; DFG, 2006a). However, in some cases species differences in sensitivity to the substances must be taken into account, and here the toxicokinetic data are particularly important (Greim, 2003; DFG, 2006a).

The general picture is that the overall UFs used for OEL setting are relatively small although it has to be realised that potentially sensitive individuals as the very young, elderly or infirm people are not included in the working population. Also, OELs are for 8 h/day, 5 days/week for 40 years in general. Nevertheless, the small UFs have caused criticism, for example, of the Swedish OELs as many of their values were high in relation to known no-effect and effect levels, and the degree of protection had a surprising weak correlation with the seriousness of the adverse effect (Hansson, 1997). The small overall UF indicates that the allocation of UFs for setting health-based OELs should be well-founded in and justified from toxicological mechanisms to avoid pitfalls. Also, it has to be mentioned that for some compounds, the MAK value is not protective for the embryo or fetus (Group A and B) (DFG, 2006a), see below.

2.3. Examples

Each endpoint used for setting OELs has its own special difficulties. Sensory irritation of eyes and upper airways is a frequently used endpoint in setting OELs. The evaluation of sensory irritation effects is amongst the less complicated endpoints where the

straight forward procedures and their pitfalls are available from recent reviews (Nielsen et al., 2007; Gaffney and Paustenbach, 2007).

In contrast, setting OELs for immunological reactions can be complicated. Nevertheless, exposure–response relationships for immunologically induced asthma have attracted much interest, which apply to the IgE-mediated (Baur et al., 1998; Nielsen et al., 2002; Baur, 2003; Nielsen et al., 2005; Arts et al., 2006) as well as the non-IgE-mediated mechanisms (Baur et al., 1998; Baur, 2003; Bello et al., 2004; Arts et al., 2006). Exposure–response relationships apply in general, but in contrast to pharmacological and toxicological reactions, the immunological reactions are due to a two stage process (Nielsen et al., 2002; Arts et al., 2006). In the first stage, an immunologically naïve individual is sensitised and in the second stage, a renewed exposure elicits the disease response. A further complication in establishing OELs is that sensitisation may not have been due to an airborne exposure. Skin contact may have been the cause and this may confound exposure–response relationships for the effects of the airborne exposures. For example, this may be the case with isocyanates (Bello et al., 2004; Bello et al., 2007). Allergic asthma has a strong genetic component (e.g. McCunney, 2005; Steinke et al., 2008). Beryllium is used to illustrate the OEL setting by compounds where the key effect is the immunological endpoint.

In the 1940s, it was discovered that beryllium exposure could cause chronic beryllium disease (CBD), which is an allergic lung disease (cf. Kolanz, 2001; Paustenbach et al., 2001; Rossman, 2001). As a hapten, beryllium can interact with proteins forming immunogens that cause T-cell activation, which is followed by sensitisation and development of hypersensitivity. CBD is characterised by formation of chronic lung inflammation, granulomas, fibrosis, decreased lung function, chest radiographic changes and a positive skin patch test. Genetic susceptibility plays a role in CBD as individuals carrying a Glu69 on HLA-DPB1*0201 have a increased risk of CBD. The latency period between beryllium exposure and sensitisation or CBD can range from weeks to many years. In 1949, the U.S. Atomic Energy Commission recommended an OEL of $2 \mu\text{g}/\text{m}^3$ that essentially eliminated acute beryllium disease and drastically reduced new cases of CBD. This value was widely accepted (cf. Kolanz, 2001; Paustenbach et al., 2001). In the 1990s, better diagnostic tools were available, including blood lymphocyte proliferation test for routine surveillance and bronchoscopy, which allowed detection of subclinical CBD. Also, it appeared that the type of beryllium compound, the particle size, solubility and lung burden were important determinants for development of CBD, whereas the total mass of airborne particles was not related with sensitisation or occurrence of CBD (cf. Kolanz, 2001; Paustenbach et al., 2001). In a recent study (Madl et al., 2007), it was shown that the development of beryllium sensitisation and subclinical CBD may be prevented if the concentrations are kept below $0.2 \mu\text{g}/\text{m}^3$ 95% of the time of exposure. However, as it has also appeared that beryllium can cause cancer amongst humans this further influences the setting of an OEL (cf. ACGIH, 2007; DFG, 2006a).

Evaluation of reproductive effects of chemicals in animal studies has been reviewed (e.g. ECETOC, 2002; Reuter et al., 2003; Jahnke et al., 2004) as has risk assessment (Pohl et al., 2005) as well as effects from workplace exposures and their classification by the MAK Commission (Winker and Rüdiger, 2006).

3. Setting occupational exposure limits for carcinogenic compounds

3.1. Human carcinogens

Elements in identifying agents, mixtures, or exposures, which are carcinogenic to humans (Battershill, 2005; Cheeseman, 2005;

Cogliano et al., 2004) are shown in Fig. 1. Occupational carcinogenic exposures have, for example, been identified from increased incidences in specific types of occupation. This was, for example, the case with the increased risks of nasal cancer in woodworkers where the offending agent was the wood dust (Acheson et al., 1968; van den Oever, 1996; Hemelt et al., 2004).

The International Agency for Research on Cancer (IARC) is internationally recognised for evaluation of compounds, complex mixtures and industrial processes with a carcinogenic potential (hazard identification). Frequently, the IARC classification is mentioned in the documentation used for setting an OEL. Also, the first ACGIH classification from 1992 of carcinogenicity was linked as closely as possible with the IARC classification. Additional modifications introduced in 1998 were partly influenced by the MAK classification (Spirtas et al., 2001). Both the Japanese and the Chinese classifications are influenced by the IARC classification (cf. below).

The IARC evaluations rank the compounds, complex mixtures and industrial processes into five groups (Cogliano et al., 2004; Siemiatycki et al., 2004). The detailed evaluations are published in the *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*. In the period from 1972 to 2003, IARC evaluated about 900 types of exposures (Cogliano et al., 2004; Siemiatycki et al., 2004). Examples of workplace carcinogens are shown below (Siemiatycki et al., 2004):

- *Group 1:* Carcinogenic to humans, which is based mainly on studies in humans. This group comprised 28 definite occupational carcinogens, including asbestos, crystalline silica, wood dust, arsenic and arsenic compounds, beryllium, cadmium and cadmium compounds, hexavalent chromium compounds, nickel compounds, benzene, vinyl chloride monomer, 4-aminobiphenyl, benzidine, 2-naphthylamine, ethylene oxide, 1,3-butadiene (recently reclassified to Group 1, cf. below), and coal tars and pitches.
- *Group 2A:* Probably carcinogenic to humans, which is based on sufficient evidences from animal studies. This group comprised 27 probably occupational carcinogens, including benzo[*a*]pyrene, tetrachloroethylene, trichloroethylene, acrylamide, epichlorohydrin, benzidine-based dyes, diethyl sulphate, and formaldehyde.
- *Group 2B:* Possibly carcinogenic to humans, which is based on a combination of effects in humans, animals and other evidences. This group comprised more than 100 occupational exposures, including antimony trioxide, cobalt and cobalt compounds, lead and inorganic lead compounds, naphthalene, acrylonitrile, ethyl acrylate, isoprene, styrene, toluene diisocyanate, acetaldehyde, acetamide, chloroform, 1,2-dichloroethane, dichloromethane, some aromatic amine dyes, some azo dyes (including trypan blue), butylated hydroxyanisole (BHA), catechol, 1,4-dioxane, and hydrazine.
- *Group 3:* Not classifiable as to its carcinogenicity to humans due to limitations in the data set.
- *Group 4:* Probably not carcinogenic to humans, which are based on a combination of effects in epidemiologic and animal studies together with other evidences.

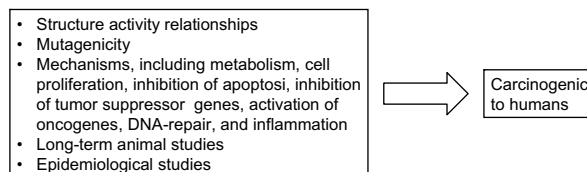


Fig. 1. Elements in identifying agents, mixtures and exposures, which are carcinogenic to humans.

The summary and overall evaluations by IARC are available from the home web of the [International Programme on Chemical Safety](#) (IPCS, cf. reference list). Another comprehensive list with documentations of carcinogenic compounds is available from the U.S. Department of Health and Human Services through the home web of the [National Toxicology Program](#) (NTP, cf. reference list). The list is published biennial and distinguishes between compounds “known to be human carcinogens”, which is based on epidemiological studies, and compounds “reasonably anticipated to be human carcinogens”, which is based on human and/or animal studies as well as on other relevant data. The *Eleventh Report on Carcinogens* contains 246 compounds. The lists are useful as a first choice of information about potential carcinogenic effects. However, hazard identification is only the first step in the risk assessment procedure (Cogliano et al., 2004) and it is used in the European Union (EU) for classification and labelling of chemicals (Pratt and Barron, 2003), but it is not sufficient for setting OELs, which are based on “risk assessment” approaches (Bolt et al., 2004).

3.2. Trend in setting occupational exposure limits for carcinogens

For a long time, regulators had generally adopted the principle that a threshold exists for non-genotoxic carcinogens, but that there was no safe level of exposure to a genotoxic carcinogen (Henschler, 1984; Paustenbach, 1990; Hunter et al., 1997; Pratt and Barron, 2003), but it is clear that risks decrease with decreasing exposures (Henschler, 1984). It was acknowledged that several mathematical models showed that the response will be linear at low doses if carcinogenesis by an external agent acts additively with any already ongoing carcinogenic process (Crump et al., 1976). Although the no-threshold approach may be a conservative assumption, it is generally used as a default assumption. Today, the evaluations are more diversified and driven by mechanistic considerations and potency of carcinogens where possible (Bolt et al., 2004). This is reflected in the setting of OELs in Germany (Greim and Reuter, 2001) and TLVs in the US (Paustenbach, 2000; ACGIH, 2007), and more or less in several European countries (Seeley et al., 2001).

3.3. Mechanistic background for setting occupational exposure limits on carcinogens

The mitotic cell division cycle is divided into four distinct phases (G1, S, G2 and M (mitosis), e.g. Schakelford et al., 2000; Branzei and Foiani, 2007). The DNA synthesis (replication) occurs in the S phase (e.g. Schakelford et al., 2000; Branzei and Foiani, 2007). The segregation of the sister chromatids occurs in the M phase (e.g. Baker et al., 2007; Malmanche et al., 2006; May and Hardwick, 2006), where the sister chromatids are pulled towards the centromeres by means of microtubules (Gardner and Odde, 2006). The DNA is controlled for damage (e.g. Schakelford et al., 2000; Baker et al., 2007; Branzei and Foiani, 2007) and for the proper segregation of the sister chromatids (Malmanche et al., 2006; Baker et al., 2007; May and Hardwick, 2006). Spindle inhibitors may cause aneuploidy (chromosome loss and non-disjunction) and polyploidy (Foth et al., 2005; Kirsch-Volders et al., 2000).

The DNA topoisomerases can change supercoiling and cause unknotting and decatenation of chromosomes by their ability to alter the topology of the DNA. Topoisomerase poisons, which include antimicrobials and anticancer chemotherapeutics, may cause double strand breaks (cf. recent reviews Champoux, 2001; Corbett and Berger, 2004; Schoeffler and Berger, 2005).

Many compounds can react directly or after metabolic transformation with the DNA (direct-acting genotoxic compounds or prox-

imate carcinogens) and cause DNA damage. The reactive oxygen (ROS) and nitrogen (RNS) species, including H₂O₂, NO, superoxide anion and the hydroxyl radical, are able to damage DNA (Schakelford et al., 2000; Valko et al., 2006). The ROS/RNS-induced DNA damages include ssDNA and dsDNA breaks, modification of DNA purine and pyrimidine bases, and DNA cross-links, all of which can cause development of cancer. ROS play an important physiological role as secondary messengers in the normal cell regulation. Effects of ROS and RNS are counteracted by enzymatic (superoxide dismutase, catalase and glutathione peroxidase) and by non-enzymatic antioxidants (e.g. Vitamin C, Vitamin E and glutathione). Excessive ROS/RNS formation is termed oxidative stress, which, for example, can be caused by overexposure to metal (e.g. Fe, Cu, Cr, Co, V, Cd, and Ni) ions or compounds, which may be due to Fenton reactions or to induced inflammation (Valko et al., 2006).

Cells contain several systems for repair of DNA damage (Christmann et al., 2003). DNA damage may cause temporary cell division arrest due to specific “checkpoint” mechanisms (e.g. Schakelford et al., 2000; Bartek and Lukas, 2001, 2007; Branzei and Foiani, 2007) with the activation of repair processes (Bartek and Lukas, 2007; Branzei and Foiani, 2007), attempting to repair the DNA damage before the replication or mitosis. Cells with DNA damage may also undergo programmed cell death (apoptosis) or enter an irreversible G₀ state (Schakelford et al., 2000; Bartek and Lukas, 2007). Nickel, arsenic, cobalt and cadmium compounds can inhibit DNA repair mechanisms, which may cause accumulation of DNA damage from other insults (Hartwig and Schwerdtle, 2002).

The development from DNA damage to a malignant tumour progresses through several stages. In the initiation stage, a non-lethal DNA damage is either repaired or if not repaired or misrepaired, it may during the next cell cycle become a permanent and inheritable mutation. In the promotion stage, the mutated cell undergoes clonal expansion, resulting in a benign lesion if not eliminated by apoptosis. Thus, cell proliferation is an important step in the development towards cancer. The benign lesion can develop to a malignant and invasive tumour with additionally genetic damage and chromosomal instability (e.g. Forastiere et al., 2001; Valko et al., 2006; Azad et al., 2008). The two-stage model (Moolgavkar and Luebeck, 1990) with mutation and cell division rates was used for risk assessment of formaldehyde exposures (Conolly et al., 2003, 2004; Subramaniam et al., 2007) and for the understanding of the carcinogenic effect of vinyl acetate.

3.4. Setting occupational exposure limits based on mechanisms of carcinogenicity

(1) OELs for non-genotoxic (“epigenetic”) carcinogens can be set from their NOAEL and the use of UFs.

Examples of these compounds are hormones, tumour promoters and 2,3,7,8-tetrachloro-benzo-*p*-dioxin (TCDD), where a (“perfect”) NOAEL can be derived (Bolt and Degen, 2004; Bolt et al., 2004; Foth et al., 2005). The non-genotoxic sulphonamide, sulfamethazine, can serve as an example of a hormonal effect (Dybing, 2002). It caused thyroid follicular cell adenomas in mice and adenomas and carcinomas in rats. It reversibly inhibits the thyroid peroxidase activity, altered the circulatory thyroid hormone concentration, and increased the secretion of thyroid-stimulating hormone. Hyperplasia and hypertrophy preceded tumour development, and thyroid enlargement and tumour formation were only seen at doses that altered thyroid hormone homeostasis (Dybing, 2002)—The International Programme on Chemical Safety has recently developed a formal framework for analysis of mode of action of carcinogenic effects in animals with the purpose of evaluating their relevance to humans (Boobis et al., 2006).

For example, the ACGIH has set TLVs for agents classified in carcinogenicity category A3, “confirmed animal carcinogen with

unknown relevance to humans". The category include α -2-urinary globulin-induced male rat kidney cancer, gavage-induced forestomach cancers, reactive hyperplasia in the male rat bladder, peroxisome proliferators, tumour promoters, overwhelming of rat lung clearance for lung cancer and excessive hormonal thyroid stimulation (Spirtas et al., 2001).

(2) OELs can be set from NOAELs for carcinogens with weak genotoxic effects if the genotoxic effect plays no or at most a minor role in the development of tumours.

This can be illustrated from two substances, vinyl acetate and formaldehyde, where data are taken from the reviews, Bogdanffy and Valentine (2003) and Bolt (2003), respectively, if not otherwise indicated.

By inhalation, vinyl acetate is a nasal carcinogen in rats, but not in mice. The NOAEL is 50 ppm. The exposure–response relationship is highly non-linear, suggesting that biological defence mechanisms are overwhelmed above a certain exposure level, which drives the carcinogenic effect. Vinyl acetate is hydrolysed by carboxylesterases to acetic acid and vinyl alcohol that is rearranged to acetaldehyde, which is subsequently oxidised by the aldehyde dehydrogenase to acetic acid; the cellular toxins are acetaldehyde and protons, which can decrease the intracellular pH and which can cause a mitogenic response. Vinyl acetate is largely negative in standard bacterial mutation assays, but both vinyl acetate (in the presence of carboxylesterases) and acetaldehyde cause chromosomal damage (aberration) including chromosomal breaks (clastogenic effect). The clastogenic effect is mostly related to the DNA–protein crosslinking (DPX) of acetaldehyde; the DPX formation is promoted by protons. Nasal turbinate explants have shown that acetic acid was more cytotoxic than acetaldehyde. The reduction in intracellular pH precedes cytotoxic effects and reparative cell proliferation; cell proliferation increases in itself the chance of mutations. Also, the reduction in cellular pH and the elevated exposure of proliferating cells to acetaldehyde can act in combination to yield chromosomal breakage, potential rearrangements and mutations. Acetaldehyde is present in the blood amongst individuals who have not consumed alcohol, suggesting that a “practical threshold” should exist below which the cancer risk is negligible (Bogdanffy and Valentine, 2003).

The TLV TWA for vinyl acetate is set at 10 ppm, the STEL at 15 ppm and it is classified as a category A3 carcinogen—confirmed animal carcinogen with unknown relevance to humans (ACGIH, 2007). No MAK is set (DFG (2006) as the compound is classified as a category 3A carcinogen—an animal carcinogen where effects are not sufficient for classification of the substance in one of the other categories. No OEL is set for vinyl acetate in the Japanese list, but it is classified as a Group 2B carcinogen (possibly carcinogenic to humans) (Omae, 2006). The European Union Scientific Committee on Occupational Exposure Limits (SCOEL) has recently evaluated vinyl acetate and also found that a threshold risk assessment approach is preferred for setting the OEL. The 8-h TWA was set to 5 ppm (17.6 mg/m³) and the STEL to 10 ppm (35.2 mg/m³), which also prevent sensory irritation (*Recommendation from the Scientific Committee on Occupational Exposure Limits for Vinyl Acetate* SCOEL/SUM/122, to be published).

In rats, formaldehyde can induce squamous cell carcinomas in the nasal passage at high-cytotoxic concentrations, causing cell proliferation. This leads to a high concentration of ssDNA, which is susceptible to generation of formaldehyde-induced single-strand breaks and DPX (Bolt, 2003). With daily exposures, the DPX do not accumulate on a day-to-day basis (Conolly et al., 2003), indicating an efficient repair. Nevertheless, the DPX formation is considered an important lesion that is correlated with the formaldehyde-induced tumour development (Conolly et al., 2003). Increased cell proliferation was induced above 2 ppm formaldehyde in the air, which was non-detectable below 2 ppm (Bolt, 2003; Conolly

et al., 2003). Formaldehyde reacts rapidly and reversibly with glutathione to form S-hydroxymethylglutathione, which is oxidised by formaldehyde dehydrogenase to S-formylglutathione, which is then hydrolysed to formate and glutathione (cf. Franks, 2005); at 2.6 ppm half of the detoxification enzymes are saturated (cf. Appel et al., 2006). The DPX formation increased steeply above 2 ppm, also showing a strong non-linear relationship. At high concentrations, epithelial degeneration with regenerative cellular proliferation appears to be the essential driving forces in formaldehyde-induced carcinogenesis (Conolly et al., 2003). A biological-based risk assessment in humans, based on the experiences from modelling the nasal tumour development in rats (Conolly et al., 2003), a computational fluid dynamic model of the respiratory tract, formaldehyde flux into mucosa, and regenerative cellular proliferation suggested an 80-year life-time risk below 10⁻⁶ at a continuous formaldehyde exposure of 0.2 ppm (Conolly et al., 2004). Together with the fact that formaldehyde is formed endogenously, this suggests a “practical threshold” for formaldehyde-induced carcinogenesis (Bolt, 2003). The threshold approach for risk assessment has also been accepted in recent reviews (Appel et al., 2006; Naya and Nakanishi, 2005).

The TLV for formaldehyde is a ceiling value set at 0.3 ppm. Also, it is classified as a sensitizer (SEN) and as a category A2 carcinogen—suspected human carcinogen (ACGIH, 2007). The MAK value has been set at 0.3 ppm (not to be exceeded during any 15 min period). It is classified as a skin sensitizer (Sh), a category 4 carcinogen (genotoxic effects play no or at most a minor part provided that the MAK value is observed), in pregnancy risk group C (there is no reason to fear damage to the embryo or foetus when MAK is observed), and in the germ cell mutagen category 5 (provided that the MAK value is observed, no contribution to genetic risk is expected) (DFG, 2006). The Japanese OEL is set at 0.5 ppm and it is classified as a Group 2A carcinogen (probably carcinogenic to humans), as a Group 2 airway sensitizer (substances which probably induce allergic reactions in humans) and as a Group 1 skin sensitizer (substances which induce allergic reactions in humans) (Omae, 2006). The SCOEL has recently evaluated formaldehyde and used a threshold risk assessment procedure in setting the OEL. The 8-h TWA was set to 0.2 ppm (0.25 mg/m³) and the STEL to 0.4 ppm (0.49 mg/m³), which also prevent sensory irritation. It is also noted that formaldehyde is a skin sensitizer (*Recommendation from the Scientific Committee on Occupational Exposure Limits for Formaldehyde* SCOEL/SUM/125, to be published).

Exogenously induced ROS production will add to the endogenous background production that may lead to a non-linear exposure–effect relationship (Bolt et al., 2004; Foth et al., 2005), which at the very low doses may be negligible compared to the background level. The ROS formation can induce multiple effects, including damage of DNA, lipids and proteins, stimulation of receptors, causing cell growth and apoptosis, and induction of or serving as secondary messengers (Valko et al., 2006). For example, chronic inflammation can induce cytokine production that may suppress apoptosis, promote cell proliferation in addition to ROS and RNS formation, which all may play a role in the development of cancer (Aggarwal et al., 2006; Azad et al., 2008). Thus, ROS is a “double-edged sword” in cellular processes, where low-dose effects can differ from those at high doses, where the high internal doses are clearly genotoxic (Bolt et al., 2004; Azad et al., 2008). In general, ROS-mediated processes of carcinogenesis should at least have a (“practical”) threshold (Bolt et al., 2004; Foth et al., 2005).

(3) For the direct-acting genotoxic compounds and for ionising radiation, the conservative low-dose linear non-threshold (LNT) extrapolation is a commonly usual approach for risk assessment of occupational exposures (Bolt et al., 2004).

The LNT extrapolation of rodent results is to levels that are far below the studied exposure levels. This approach is not generally

accepted in the UK as the risk estimates depend on the selection of a particular model and the estimates may vary up to several orders of magnitude (Guess and Crump, 1978; Paustenbach, 1990; Topping, 2001; SC, 2005). The LNT approach is based on the assumption that a single transforming event can directly cause tumour formation (the “one-hit” model); the LNT approach is often used as a default assumption for risk evaluation of genotoxic carcinogens if the existence of a threshold cannot be sufficiently supported (Bolt et al., 2004).

Where possible, a risk assessment should be based on epidemiological studies. However, this approach is only possible for a limited number of compounds, and risk assessment has to be based on animal studies in most cases. In this case, several points of departure are used in risk assessments in combination with various extrapolation models. One point of departure is the lower 95% confidence limit (BMDL10) of the BMD, causing a 10% increase in cancer (BMD10); the BMD approach uses all the dose–response data (for discussion, cf. Gold et al., 2003; SC, 2005). The BMD, the BMDL and extrapolations can be obtained by means of the US EPA software: <http://www.epa.gov/ncea/bmds/about.html> (accessed March 6, 2008).

Another point of departure is the T25 value, which is the daily dose in long-term animal studies, which causes an increase of 25% in tumours at a specific tissue site after correction for the background incidence (e.g. Sanner et al., 2001). The cancer risk estimates were very close to results obtained by the linearised multistage model that has been used by the U.S. Environmental Protection Agency (Sanner et al., 2001) reflecting their reliance on similar mathematical approaches (Roberts et al., 2001). However, estimates based on the T25 correlated well with results obtained directly from epidemiological studies (Sanner and Dybing, 2005a). There was also a strong correlation between T25 and *in vivo* genotoxic effects (Sanner and Dybing, 2005b).

A life-time risk of $<10^{-5}$ (“safe” dose) can be calculated directly as BMDL10/10,000, which is “equivalent” to the NOAEL approach where BMDL10 (life-time risk 10^{-1}) is divided by a product of UFs, an UF for extrapolation from animals to humans (default value of 10), an UF accounting for the interindividual variation amongst humans (default value of 10), an UF for extrapolation from 10% (~lowest-observed-effect level) to a lower value (“NOAEL”) (default value of 10), and an UF for a potential increased sensitivity of children (including the unborn) (default value of 10), giving the combined UF of 10,000 (Gold et al., 2003).

The risk assessment approach for non-threshold compounds can be illustrated by 1,3-butadiene; it has recently been upgraded by IARC to “carcinogenic to humans” (Group 1). Butadiene can produce neoplasms in multiple organs in rodents and chronic lymphocytic and myelogenous leukaemia in humans. It is metabolized to epoxides, which can react with DNA to form alkylated products and other genotoxic effects (Grosse et al., 2007). Butadiene has recently been evaluated by the SCOEL. The risk estimate was based on epidemiological studies from which the excess death of leukaemia was estimated to be between 0 and 11 cases during a 40-year working life at 1 ppm among 1000 exposed individuals (*Recommendation from the Scientific Committee on Occupational Exposure Limits: Risk Assessment for 1,3-Butadiene* SCOEL/SUM/75, to be published). For compounds where the genotoxic effect is prominent, SCOEL does not set an OEL. Neither is a MAK value set as the compound is classified as a category 1 carcinogen—makes a significant contribution to cancer risk in man. Additionally, 1,3-butadiene is classified as a category 2 germ cell mutagen—compounds that have been shown to increase the mutant frequency in the progeny of exposed mammals (DFG, 2006). In contrast, ACGIH (2007) sets a TLV at 2 ppm for 1,3-butadiene and classifies the compound as a Group 2A carcinogen which comprises suspected human carcinogens. No

OEL has been set in the Japanese list, but 1,3-butadiene is classified as a Group 1 carcinogen (carcinogenic to humans) (Omae, 2006).

4. Further considerations to justify a NOAEL for certain types of genotoxic carcinogens

A NOAEL risk assessment approach may be used where genotoxicity arises from a non-DNA target, which secondarily causes a genotoxic effect (Kirsch-Volders et al., 2003). In this case, the primary interaction is with proteins and not with DNA (Bolt and Degen, 2004). The mechanisms include inhibition of repair enzymes (Kirsch-Volders et al., 2003), topoisomerases (Foth et al., 2005; Bolt and Degen, 2004; Lynch et al., 2003), and mitotic and meiotic spindle assembly (Kirsch-Volders et al., 2003; Bolt and Degen, 2004; Foth et al., 2005). Additional mechanisms are methylations of DNA which can modify the expression of recessive mutations, changes in intracellular communications and all types of modulators of gene expression (Kirsch-Volders et al., 2000).

Topoisomerase inhibitors cause a transient stabilization of the topoisomerase–DNA complex, which in turn can cause a DNA strand break (clastogenic effect). If not repaired, clastogenicity may cause cytotoxicity and mutations. Comprehensive *in vitro* cell culture studies have shown that the clastogenic effect of the type II topoisomerase inhibitors showed a NOAEL (Lynch et al., 2003), demonstrated from etoposide (used in chemotherapy), doxorubicin (used in chemotherapy; at low concentrations, its primary effect is topoisomerase inhibition), the phytoestrogen genistein and the antibiotic ciprofloxacin.

Spindle inhibitors, e.g. the chemotherapeutic compounds colchicine, *Vinca* alkaloids, taxol (Kirsch-Volders et al., 2003; Foth et al., 2005; Gigant et al., 2005) and the pesticide carbendazim (Kirsch-Volders et al., 2003), can interfere with tubulin assembly in mitotic and meiotic cells (Kirsch-Volders et al., 2003; Bolt and Degen, 2004; Foth et al., 2005). This interference may cause aneuploidy (chromosome loss and non-disjunction) and polyploidy (Foth et al., 2005; Kirsch-Volders et al., 2000). In the human lymphocytes in *in vitro* experiments, thresholds were observed for aneuploidy caused by colchicine, carbendazim, mebendazol and nocodazole. Apoptosis is shown to play a role in the elimination of cells with aneuploidy (Kirsch-Volders et al., 2003). The *in vitro* test systems were much more sensitive than the corresponding *in vivo* test systems (Kirsch-Volders et al., 2003). Thus, the NOAEL for the aneugenic effect in mitotic cells shows a (“statistical”) threshold (Kirsch-Volders et al., 2000) that also may be a true threshold due to the redundancy in dividing cells as a genotoxic effect requires most fibres to be damaged (Foth et al., 2005).

Aneuploidy is present in about 35% of human spontaneous abortions and 0.3% of livebirth; maternal age is a prominent risk factor. In human sperm and oocytes (the zygotes), aneuploidy is at least 5% but possibly as high as 25%, whereas the spontaneous aneuploidy in rodents is only 1%, which indicates that extrapolations from rodents to humans have to be taken cautiously. Most genetically engineered mouse strains, where meiosis was affected, were sterile. In mice, not only the spindle poisons, but also topoisomerase inhibitors, affected the meiotic cell cycle progression. Aneugenic effect in human sperm has mostly been associated with cancer therapy and mostly being negative in relation to occupational exposures (Pacchierotti and Ranaldi, 2006).

The spindle inhibitor nocodazole showed a threshold for aneuploidy in *in vitro* in mouse oocyte experiments, which was close to the threshold observed *in vitro* in cultured human lymphocytes (Kirsch-Volders et al., 2003). In general, the female zygote is more sensitive to spindle poisons than the male zygote (Pacchierotti and Ranaldi, 2006). This may reflect more efficient checkpoints in the male germ cells, more efficient apoptotic pathways, the different

mechanisms for assembling the meiotic spindle, and the blood testes barrier, although the prevulatory oocytes are also protected against exogenic toxicants (Pacchierotti and Ranaldi, 2006). Also, pharmacokinetics may play an important role in modulating the effects of environmental toxicants that may cause germ cell aneuploidy (Pacchierotti and Ranaldi, 2006). Overall, the evaluation of effects on germ cells constitutes an important part of the OEL settings, but data on this point are limited.

A summary of evaluation methods of carcinogenic workplace exposures is shown in Fig. 2.

5. Absorption through the skin

In many European countries and in the US, a skin notation is used to warn about skin contact where it can add significantly to the body burden in addition to that caused by inhalation (Drexler, 1998; Sartorelli, 2002; Kupczewska-Dobecka and Czerczak, 2006; DFG, 2006a; ACGIH, 2007). The *stratum corneum* provides the greatest barrier against hydrophilic compounds, whereas the viable epidermis is most resistant to highly lipophilic compounds (EC, 2004). Skin absorption depends on the physicochemical properties (e.g. octanol–water partition coefficient ($P_{o/w}$), molecular weight, electron structure and dissociation constant (pK_a)) of the compound (EC, 2004), but also on interactions with other compounds (Drexler, 2003; Nielsen and Grandjean, 2004; EC, 2004) and on the skin condition (Drexler, 1998; Drexler, 2003). Additionally, vehicle, occlusion, concentration, exposure pattern and the site of the skin also play a role (EC, 2004).

Skin notation setting is not standardised across countries and agencies (Drexler, 1998; Sartorelli, 2002; Nielsen and Grandjean, 2004; Kupczewska-Dobecka and Czerczak, 2006). In Germany, a skin notation (“Haut” (H)) is set from clinical experiences (e.g. casuistics), animal studies (e.g. dermal doses that can cause toxic effects or percutaneous absorption), from *in vitro* skin permeation

studies and from theoretical models (Drexler, 1998; DFG, 2006a). In Poland, the skin notation (Sk) was set mainly based on a dermal LD₅₀ being below 1000 mg/kg (Czerczak and Kupczewska, 2002; Kupczewska-Dobecka and Czerczak, 2006). In general, compounds with the Sk notation in the Polish list also had a skin notation in the TLV list (Czerczak and Kupczewska, 2002). A more recent Polish study showed that for the more recently evaluated compounds, estimated skin absorption was also taken into consideration (Kupczewska-Dobecka and Czerczak, 2006). In the Netherlands, the Dutch Expert Committee on Occupational Standards (DECOS) recommends a skin notation when the amount absorbed by both arms and forearms in 1 h could amount to more than 10% of the amount absorbed via the lungs on exposure to the 8-h OEL (De Cock et al., 1996). In the EU, SCOEL accepts a skin notation if absorption through the skin contributes 10% or more of the dose absorbed from an 8-h exposure at the OEL level (EC, 1999). In general and irrespective of the country, about one-third of the compounds with an OEL also have a skin notation. However, it is highly variable, which compounds are assigned a skin notation in the different countries (Nielsen and Grandjean, 2004).

Even where criteria exist for setting a skin notation, the evaluations should not be considered straight forward due to possible limitations in methods, which have to be considered in the overall evaluations. Thus, dermal LD_{50s} can vary considerably between species and if the LD₅₀ is used as such, it does not capture chronic effects. Also, LD_{50s} may strongly depend on the vehicle that was used by the application (Chen et al., 2003). Additionally, a dermal LD₅₀ can depend on the size of the exposed area, differences in toxicity after oral and dermal exposure may be influenced by first-pass effects and the absorption percentage depends on the applied dose (EC, 2004). However, the flux (in mg/cm²/h) derived from *in vitro* studies can be used for semi-quantitative comparison of absorption of chemicals between species, and between compounds within one species (EC, 2004). Across compounds, the *in vitro* dermal absorption was in the order mouse > rat > human (Boogaard et al., 2000; van Ravenzwaay and Leibold, 2004); rat skin was in mean about 10-fold more permeable than human skin (e.g. van Ravenzwaay and Leibold, 2004). Studies in human and rat skin, both *in vitro* and *in vivo*, showed that saturation of absorption was frequently observed at higher exposure levels. Furthermore, *in vitro* rat skin was more permeable than *in vivo* rat skin (van Ravenzwaay and Leibold, 2004). Together this suggests that an optimal estimate of human skin absorption should be based on the combined of *in vivo* and *in vitro* data, using the following equation (EC, 2004; van Ravenzwaay and Leibold, 2004):

$$\% \text{ In vivo human dermal penetration} = (\% \text{ rat in vivo dermal penetration}) \times (\text{in vitro rate dermal penetration human}) / (\text{in vitro rate dermal penetration rat})$$

Physicochemical parameters may be used to establish quantitative structure–permeation relationships (QSPeRs), which may be used to predict skin absorption of compounds that have not been tested. Thus, the estimated dermal absorption was calculated for 132 compounds and suggested being the basis for skin notations (Fiserova-Bergerova et al., 1990). However, the reliability of the estimates has been questioned (cf. Moss et al., 2002). Theoretically, skin absorption depends amongst others things on the volume of the molecule and hence on the molecular weight of a compound as well as on the hydrophobic and hydrogen binding properties, which are often based on the $P_{o/w}$. QSPeRs have been discussed in several reviews (e.g. Moss et al., 2002; Moody and MacPherson, 2003; Geinoz et al., 2004). Often, the same permeability data are included in the different QSPeRs and, in general, the data are from different literature sources, which cause a high degree of variability (Moss et al., 2002; Geinoz et al., 2004). The U.S. National Institute for Occupational Safety and Health (NIOSH) has a free service that allows the calculation of a skin permeation coefficient (k_p) for

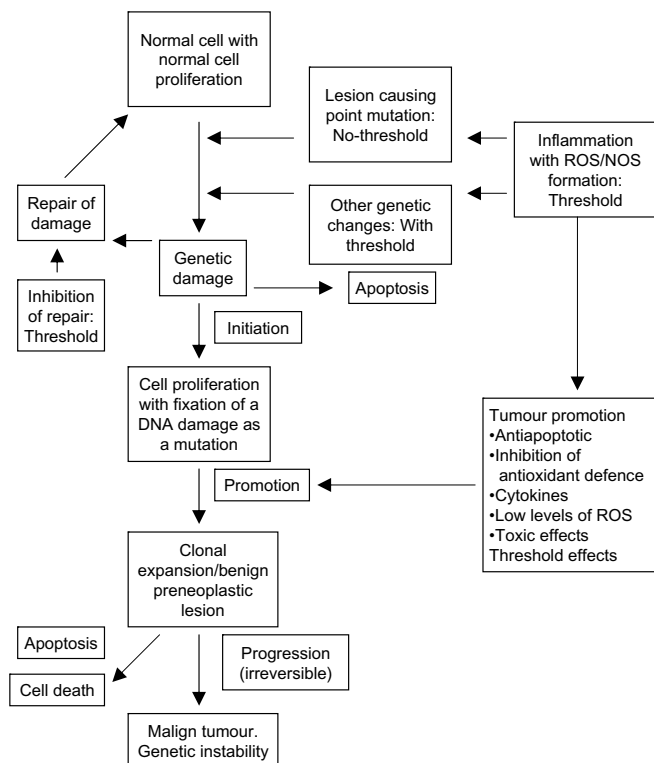


Fig. 2. Evaluation of no-threshold or threshold mechanisms by workplace carcinogens, for explanations cf. text.

substances: <http://www.cdc.gov/niosh/topics/skin/skinPermCalc.html> (accessed March 3, 2008). Also, skin penetration data can be obtained from the EDETOX database (<http://www.ncl.ac.uk/edetox/>; accessed March 3, 2008).

In the EU, compounds with a skin notation are considered priority candidates for setting Biological Limit Values (Bolt and Their, 2006).

6. Biomarkers

Biomarkers are used to determine the total body burden from all exposure routes, e.g. from concentrations of parent compounds or their metabolites in blood, urine or exhaled air, to determine biological effective doses, e.g. from protein or DNA adducts, and to determine early biological effects, e.g. from biochemical or blood cell effects. Additionally, biomarkers are used to determine susceptibility to genetic polymorphisms, different levels of metabolizing enzymes and other health risk indicators (Au et al., 2005; Kakkar and Jaffery, 2005; Paustenbach and Galbraith, 2006). In the scientific literature, there are numerous examples, which show the usefulness of biomarkers, but only few examples are mentioned below, which are related to the use of biological monitoring for OELs.

6.1. Chemical compounds and their metabolites

The body burden has been determined from blood and urinary concentrations of heavy metals (Kakkar and Jaffery, 2005), and benzene or its metabolites (Au et al., 2005). However, biomarkers in relation to occupational exposures are often obtained from simultaneous measurement of airborne exposures and measurement of the parent compound or its metabolites in blood, urine or exhaled air.

To evaluate biomarkers for toluene, the end-of-shift urine concentration of *o*-cresol and toluene has been studied in occupationally exposed subjects. Smoking increased the excretion of *o*-cresol but not of urinary toluene. The urinary toluene level had higher specificity and sensitivity, lower background values, was better correlated with airborne exposure and was not influenced by cigarette smoking, suggesting that urinary toluene is the superior biomarker (Fustinoni et al., 2007).

In a controlled chamber study, the toxicokinetics of methyl *tert*-butyl ether and *tert*-amyl methyl ether were studied with the purpose of establishing biomonitoring action limits of the parent compound post-shift in urine and exhaled air, or from the next morning urine levels of their respective (alcohol) metabolites, *tert*-butanol and *tert*-amyl alcohol (Vainiotalo et al., 2007).

The total daily boron exposure from occupational air as well as from food and fluid intake was correlated with the boron concentration in post-shift urine as well as with its blood and semen concentrations; the semen concentration is interesting in relation to epidemiological studies as reproductive effects have been observed in animal studies. Overall, the study suggested that the post-shift urine boron concentration can be used as a biomarker for workplace exposures (Xing et al., 2008).

Biomarkers are also useful for determination of the relative contribution from inhalation and skin contact. Thus, the body burden of organophosphate pesticides has been determined from the urinary concentrations, and the relative contribution from inhalation and skin contact was determined from air samples, levels of skin contamination and concentration in the urine. Absorption through the skin occurred not only from contaminated hands, but also from skin not in direct contact with the pesticides due to penetration of protective clothing (Aprea et al., 2001).

Toxicokinetic modelling of biological exposure indicators have shown large interindividual variability of indicators. The concen-

tration of the parent compound in blood, alveolar air or urine was less variable than the concentrations of the metabolites in blood and urine. In most cases, alveolar ventilation and cardiac output were the prime parameters determining the biological variability (Truchon et al., 2006). Assuming exposures at OELs, the knowledge about pharmacokinetics of substances allows estimation of concentrations in blood, urine and exhaled air (Leung and Paustenbach, 1988; Droz and Fiserova-Bergerova, 1992).

6.2. Adducts

Biological effective doses can also be obtained from levels of adducts in the organism. In occupational settings, absorption of the neurotoxic and carcinogenic acrylamide occurs both from inhalation and from skin contact. The acrylamide haemoglobin adduct is a valuable biomarker for the overall occupational exposure, which causes a higher adduct formation than the low-adduct level due to diet and smoking (Jones et al., 2006).

Adducts in nasal lavage fluid can also serve as source of biomarkers. Thus, the air exposure levels of the strongly sensitising hexahydrophthalic anhydride were highly correlated with the albumin adducts in lavage fluid (Kristiansson et al., 2004).

6.3. Effect monitoring

Organophosphate and carbamate pesticides can reduce serum cholinesterase activity (e.g. Nielsen and Andersen, 2002), which is an example of a biomarker for an early biological effect. Lead inhibits several enzymes in the haeme formation pathway, including δ -aminolevulinic acid (ALA) dehydratase, resulting in accumulation of ALA in blood and urine. As urinary ALA is used as a biomarker for lead, it is another example of a biomarker of an early biological effect (Kakkar and Jaffery, 2005).

6.4. Organisations and biological limit values

Several countries and organisations have set health-based Biological Limit Values (BLVs) for occupational exposures, which includes Japan (Omae et al., 1999), ACGIH (2007) in the US, which termed the values Biological Exposure Indices (BEI), and Germany (DFG, 2006a), which termed the values Biologischer Arbeitsstoff-Toleranz-Wert (BAT) or Biological Tolerance Values. In the EU, SCOEL has set health-based BLVs for compounds where the OELs for air concentrations may not be sufficient to protect against exposures and where biological monitoring is more appropriate to determine the body burden. Where OELs are based on systemic effects, the body burden at the OEL is similar to the body burden at the BLV (cf. Bolt and Their, 2006 and references therein). For the historical development, cf. Bolt and Their (2006).

7. Examples of occupational exposure limits set by different organisations or agencies

7.1. Historical examples

Proposals for OELs appeared from the mid-1800s. The proposals mentioned below are selected as examples. Max Gruber from Munich proposed an OEL for carbon monoxide in 1883, which was based on animal studies and self-exposure (Paustenbach, 1998; Paustenbach, 2000). Also from Germany, K.B. Lehmann proposed several short-term OELs based on exposures of his laboratory servant as well as from animal studies. The reports were published from 1886 and during the next 40 years (Henschler, 1984; Henschler, 1985; Paustenbach, 1998; Paustenbach, 2000). The U.S. Bureau of Miners published a list with 33 values in 1921 (Paustenbach,

1998; Paustenbach, 2000). From 1920 in Europe, K.B. Lehmann and F. Flury systematically evaluated occupational chemicals with the aim of long and short-term exposure limits based on a combination of animal and human studies. Until 1938, about 100 chemicals were evaluated and the results were published in original papers or monographs (Henschler, 1985). In Great Britain, OELs were established for a few substances such as cotton dust and asbestos in the 1930s (Topping, 2001). However, it was the TLVs from the ACGIH, which were the basis of the OEL settings in Europe after the Second World War (Henschler, 1985).

In a recent study (Schenk et al., 2008), OELs established by 18 different organisations or national regulatory agencies were compared. A total of 1341 substances with a CAS number had an OEL on one or more of the lists, but only 25 substances were on all 18 lists. The average level of OELs differed substantially between the lists, which may be due to the risk assessment and/or the risk management part as most countries take economical and technical feasibility as well as human health into account when setting OELs. The non-European countries, except the Japan Society for Occupational Health, are all closer to the ACGIH than the European countries, except France. Organisations that have few uniquely regulated substances tend to be closer to the ACGIH. The European countries do not, in the same way, cluster around the OEL set by the EU. Finland is an exception as the number of substances exclusively regulated (189) is exceptional high. Over the years, the overall level of the OELs have decreased, but the decrease has levelled off in general.

7.2. United States—Threshold Limit Values (TLVs)

In the US, at least six agencies or organisations promulgate OELs or guidelines (Paustenbach, 1998; Paustenbach, 2000), but only those from the ACGIH are widely accepted (Paustenbach, 2000) as they are intended to be health-based and updated regularly. The ACGIH was formed in 1938 and released its first list of OELs in 1941 (Paustenbach, 1998; Paustenbach, 2000); one of the founders of the TLV setting was Professor Warren Cook (Levine, 2006). The setting of TLVs started as an ad hoc effort on the part of industrial hygienists, largely employed by the government. The values have had a large influence in reducing workplace exposures. They were set by the ACGIH TLV Committee with seldom more than 20 scientists where members came from government agencies, universities and the industry. The Committee was funded only from the income from the selling of the TLV booklet and the associated documentation, and from the association dues and from contribution of time and effort of its members (Culver, 2005).

TLVs are intended to be guidelines to be used by professional industrial hygienists (ACGIH, 2007). TLV–TWAs are considered upper control limits for each exposure day, which should not be exceeded. In consequence, in a controlled work environment the long-term, life-time average exposure for each individual worker has to be less than the TLV–TWA (Hewett, 1997).

The TLV–TWA applies to an 8-h workday and a 40-h workweek, the STEL value applies to a 15-min TWA exposure level that should not be exceeded at any time during a workday, and the Ceiling value is the concentration that should not be exceeded at any time during a workday. For each compound, the TLV-list mentions the critical effect that is used for deriving the TLVs. ACGIH classifies compounds in five categories for carcinogenic effect (ACGIH, 2007; Spirtas et al., 2001): A1—Confirmed Human Carcinogens, which is based on epidemiological studies, A2—Suspected Human Carcinogens, which is based on conflicting or insufficient epidemiological results and/or adequate and relevant animal studies, A3—Confirmed Animal Carcinogen with Unknown Relevance to Humans, which is based on animal studies where the conditions mostly are considered irrelevant for humans and where epidemio-

logical studies do not confirm the animal results, A4—Not Classifiable as a Human Carcinogen, where concern is raised, but data are inadequate, and A5—Not Suspected as a Human Carcinogen, which is based on adequate epidemiological studies and/or adequate animal studies that is supported by mechanistic data.

The TLV system does not directly link the carcinogenicity category with the numerical TLV for a substance, but the TLV Committee attempts to assign both a carcinogenicity category and an exposure level for all agents. A comprehensive discussion of similarities and differences in classifications by the TLV and the MAK Commissions has been published (Spirtas et al., 2001).

If dermal contact can contribute significantly to the body burden of a compound, this is indicated by a skin notation (“Skin”) and if a compound can cause sensitisation, this is indicated by the “SEN” notation. Furthermore, the list contains a special section on Biological Exposure Indices (ACGIH, 2007).

The TLVs have been criticised for including non-published experiences and studies from industry, for inconsistencies, and for lacking appropriate data on many endpoints (Ziem and Castleman, 1989), not being thresholds (Ziem and Castleman, 1989; Roach and Rappaport, 1990) as well as for being set to levels thought to be achievable at the time (Roach and Rappaport, 1990; Rappaport, 1993). Although some of the critics presumably were correct, the historical context of the TLV setting and the apparent progress the TLVs created at that time have to be taken into account. However, the critic had consequences for the later TLV setting procedures (cf. Culver, 2005). Overall, it is not difficult to understand that TLVs were and are used as an input by many national authorities for setting their own national standards or guidelines (Paustenbach, 1998; ACGIH, 2007).

The list of *Threshold Limit Values for Chemical Substances and Physical Agents & Biological Exposure Indices* is published annually and a documentation giving the key references on which the TLVs are based are published in the *Documentation of the Threshold Limit Values and Biological Exposure Indices*.

7.3. Germany—Maximale Arbeitsplatz-Konzentration (MAK)

After 1968, Germany no longer copied the TLV list but initiated to make its own list (Henschler, 1984), which was termed “Maximale Arbeitsplatz-Konzentration” (MAK). MAK values are health-based OELs set exclusively on a scientific basis by the Deutsche Forschungsgemeinschaft—Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (Greim, 2003; DFG, 2006a). MAK values apply to an 8-h workday and an average 40-h working week (Greim, 2003; DFG, 2006a).

The MAK list contains a classification of carcinogenic substances (Greim and Reuter, 2001; DFG, 2006a). *Category 1*: substances that cause cancer in man and can be assumed to make a significant contribution to cancer risk, which is based on epidemiological studies that may be supported by knowledge about a mode of action. *Category 2*: substances that are considered to be carcinogenic to man because sufficient data from long-term animal studies or limited evidence from animal studies substantiated by evidence from epidemiological studies indicate that they can make a significant contribution to cancer risk. Limited data from animal studies can be supported by evidence that the substance causes cancer by a mode of action that is relevant to man and by results of *in vitro* tests and short-term animal studies. *Category 3*: substances that cause concern that they could be carcinogenic for man but cannot be assessed conclusively because of lack of data. The classification in *Category 3* is provisional. *Category 4*: substances with carcinogenic potential for which a non-genotoxic mode of action is of prime importance and genotoxic effects play no or at most a minor part provided that MAK and BAT values are observed. Under these conditions, no significant contribution to human cancer risk is ex-

pected. The classification is supported especially by evidence that, for example, increases in cellular proliferation, inhibition of apoptosis or disturbances in cellular differentiation are important in the mode of action. To characterise the cancer risk, the manifold mechanisms contributing to carcinogenesis and their characteristic dose–time–response relationship are taken into consideration. *Category 5*: substances with carcinogenic and genotoxic effects, the potency of which is considered to be so low that, provided the MAK and BAT values are observed, no significant contribution to human cancer risk is to be expected. The classification is supported by information on the mode of action, dose-dependence and toxicokinetic data pertinent to species comparison.

MAK categories 1, 2 and 3 are linked to the EU classification and labelling system (Spirtas et al., 2001) that is a hazard identification system.

Also, the list indicates if a compound is a sensitizer to the skin (Sh), the airways (Sa) or is a photosensitizer (SP). Where percutaneous absorption can contribute significantly to the body burden, this is indicated by “H” (DFG, 2006a).

The MAK list also evaluates whether substances are able to cause prenatal or developmental toxicity and divides the evaluations into four groups (DFG, 2006a; Winker and Rüdiger, 2006). *Group A*: Damage to the embryo or foetus in humans has been unequivocally demonstrated and is to be expected even when the MAK and the BAT values are observed. *Group B*: According to current available information, damage to the embryo or foetus must be expected even when the MAK and the BAT values are observed. *Group C*: There is no reason to fear damage to the embryo or foetus when the MAK and the BAT values are observed. *Group D*: Either there are no data for an assessment of damage to the embryo or foetus or the current available data are not sufficient for classification in one of the groups A–C. The MAK list also contains a system for classification of germ cell mutagens (DFG, 2006a; Winker and Rüdiger, 2006). Finally, a list of Biological Tolerance Values (BAT values) is included (DFG, 2006a).

The MAK list, *List of MAK and BAT Values*, is published annually and a detailed documentation of the toxicological evaluations is also published in *Toxikologisch-arbeitsmedizinische Begründung von MAK-Werten* (e.g. DFG, 2006b).

7.4. The Japan Society for Occupational Health (JSOH)

Since 1960, the non-governmental academic society of occupational health professionals in Japan, JSOH, has recommended health-based occupational exposure limits (Omae et al., 1999). The OEL-mean (OEL-M) is the mean exposure concentration (TWA) at or below the limit where no adverse health effect occurs in most workers exposed for 8 h/day, 40 h/week at a moderate workload. Also, an OEL-ceiling (OEL-C) may be set, which is the maximal exposure concentration during a working day. Below the ceiling value no adverse health effects do appear in most workers. The compliance with the OELs is determined by personal sampling. The OEL values presuppose that no absorption takes place through the skin. Also, biological limit values are set for several compounds (Omae et al., 1999; Omae, 2006).

Substances that may be absorbed through the skin at significant levels are indicated in the OEL lists by the “S” mark (Omae et al., 1999; Omae, 2006; Takahashi and Higashi, 2006). Additionally, notations indicate whether compounds are occupational airway or skin sensitizers. Both airway and skin sensitizers are divided into two groups: Group 1 substances induce allergic reactions in humans and Group 2 substances probably induce allergic reactions in humans (Omae, 2006).

The classification scheme for carcinogens adopted by JSOH resembles that of IARC (Takahashi and Higashi, 2006). The classification is made by strength of evidence, but does not reflect the car-

cinogenic potency. Group 1 substances are carcinogenic to humans. Group 2 substances are divided into Group 2A—probably carcinogenic to humans and Group 2B—possibly carcinogenic to humans. For carcinogens in group 1, Reference Values are set that corresponds to life-time excessive risk of 10^{-3} and 10^{-4} (Omae, 2006). For example for benzene (Group 1 carcinogen), 1 ppm benzene is considered to cause an excess risk of leukaemia of 10^{-3} at 40 years of exposures and 0.1 ppm a risk of 10^{-4} (Omae, 2006; Takahashi and Higashi, 2006). Sometimes, occupational carcinogens may have an OEL which must be used with caution. Although not always the case, some of these substances have shown carcinogenic effects in epidemiological or animal studies at significantly higher concentrations than those for the non-carcinogenic health effects (Omae, 2006).

The English summary of the Recommendation of Occupational Exposure Limits (2006–2007) (Omae, 2006) is freely available from the web (<http://joh.med.uoeh-u.ac.jp/e/index.html>; accessed March 4, 2008).

7.5. Examples of other national activities

In Europe, Holland and Sweden were amongst the countries that followed Germany and introduced their own systems for establishing OELs (Henschler, 1985). In Holland, the first step towards the establishment of a health-based OEL is the scientific evaluation of the data on the toxicity of the substance that is made by the Dutch Expert Committee on Occupational Standards (DECOS); for genotoxic carcinogens, DECOS does not derive an OEL but presents an exposure–response relationship. The comprehensive Dutch criteria documents can be accessed free of charge from the web site (www.gr.nl) (accessed March 6, 2008).

Sweden has the secretariat for The Nordic Expert Group (NEG) for Criteria Documentation of Health Risks from Chemicals (<http://www.av.se/arkiv/neg/>) (accessed March 6, 2008). The NEG group also publishes comprehensive criteria documents, which are used for setting national OELs in the Nordic countries. The criteria documents are published in *Arbete och Hälsa*, now from the University of Göteborg, and the documents can be downloaded free of charge from the web. NEG has co-operation with the U.S. NIOSH and DECOS.

China has updated and developed new OELs (>400) in 2002. The OELs can be expressed as an 8-h Time–Weight Average (TWA), a ceiling level and a 15-min TWA short-term exposure limit (STEL). For the carcinogenic compounds, their classification is based on the IARC classification scheme. A two-step procedure is used for setting a statutory-based OEL. First, a health-based recommendation is set, i.e. “how safe is safe” based on risk assessment, followed by a second step that takes into account socioeconomic and technological considerations (“how safe can we afford”) (Liang et al., 2006).

Web sites with addresses to OELs in several European countries are listed in Table 1.

7.6. European Union

The European Union has established a legal basis for setting OELs and Biological Limit Values (BLVs) for compounds with threshold effects (ECD, 1998). The OELs are termed Indicative Occupational Exposure Limit Values (IOELVs). They are set to protect workers from chemical risks, i.e. they are health-based limits, and they are based on the latest available data. For compounds with IOELVs and BLVs, the Member States shall establish national values, taking into account the EU values.

The legal basis for setting OELs and BLVs for carcinogens and mutagens is the Directive on exposure to carcinogens or mutagens at work (ECD, 2004). The values are termed Binding Occupational

Table 1
Web sites with access to occupational exposure limits in several European countries

Country	Web address
Denmark	http://www.at.dk/graphics/at/04-Regler/05-At-vejledningner/C-vejledningner/C-0-1-Graensevaerdilisten/C-0-1-Graensevaerdilisten-2007.pdf
Finland	http://www.ketsu.net/htp/index.htm
Norway	http://www.arbeidstilsynet.no/c26983/artikkel/vis.html?tid = 28880
Sweden	http://www.av.se/dokument/afs/AFS2005_17.pdf
The Netherlands, DECOS	http://www.gr.nl/wgd.php
The SCOEL	http://ec.europa.eu/employment_social/health_safety/recommendations_en.htm
United Kingdom	http://www.hse.gov.uk/coshh/table1.pdf

Exposure Limit Values (BOELVs) and Binding Biological Limit Values and intend to provide a level of minimum protection for all workers in the Community. The Member States shall establish binding national values, which must not exceed the EU values (ECD, 1998).

To assist the Council of the European Union in setting exposure limits, the Scientific Committee on Occupational Exposure Limits was established (EC, 1995). The SCOEL consists of 21 members, which are selected from experts proposed by the Member States, with scientific expertise within chemistry, toxicology, epidemiology, occupational medicine, industrial hygiene and general competence in setting OELs (EC, 2006). The primary task of the SCOEL is to propose health-based 8-h time-weighted average values (TWA), short-term/excursion limits (STEL) and BLVs. To ensure consistency across evaluation of compounds, the SCOEL has settled procedures for the evaluations of compounds (EC, 1999). Furthermore, to ensure transparency, the SCOEL prepares a short summary document (SCOEL/SUM) on each compound. Once the SUM document is agreed by the SCOEL members, it is circulated to interested parties for comments. After a comment period of about 6 months, the SCOEL re-discusses the document in the light of the received comments. After clarification of the raised questions, the final version is adopted and submitted to the Commission for publication. When available, the EU Risk Assessment Reports (<http://ecb.jrc.it/existing-chemicals/> (accessed March 6, 2008)) are used as basis for the SCOEL/SUM document. History and procedures are available from reviews (Hunter et al., 1997; Cross et al., 1997; Their and Bolt, 2001; Bolt and Their, 2006).

The new general regulation within the EU on chemicals and their safe use (EPCR, 2006) deals with Registration, Evaluation, Authorisation and Restriction of Chemical substances (REACH); the regulation will generate "OELs" for a very large number of compounds. Thus, REACH will make toxicological evaluations (comprising toxicokinetic, acute and repeated dose toxicity, sensitisation, carcinogenicity, mutagenicity and reproductive toxicity) available for the public. The evaluations include the establishment of Derived No-effect Levels (DNELs) for workers, consumers and humans liable to exposure indirectly via the environment. For the derivation of DNELs, uncertainties, intra- and inter-species variations, severity of effects and sensitivity of the human (sub-)populations have to be taken into account. The DNELs are used in the evaluation of the required exposure scenarios (risk characterisation) and in the establishing of risk management procedures.

7.7. Setting of occupational exposure limits within corporations

In the 1960s in the US, many corporations who handled or manufactured chemicals began to establish internal OELs, intended to protect their employees as well as their costumers who purchased

their chemicals (Paustenbach and Langner, 1986; Paustenbach, 2000; Ettinger, 2005). They included Dupont, Union Carbide, Exxon, Dow Chemical, Rohm and Haas and Upjohn Pharmaceutical (Paustenbach and Langner, 1986). These OELs intended to supplement the OELs set by professional societies and regulatory agencies. A similar development occurred in Europe for compounds with sufficient toxicological data (ECETOC, 2006); the procedures for the OEL setting followed the above outlined approaches. However, these approaches cannot be used for many compounds due to limitation in the database. For these compounds, short-cut procedures for setting OELs have recently been developed (ECETOC, 2006).

Industrial exposures for active pharmaceutical compounds have resulted in reporting of several cases of adverse pharmacological and toxicological reactions, including skin and airway allergy, as reviewed (Heron and Pickering, 2003). Nevertheless, a very limited number of official OELs are available for pharmaceutical compounds. For example, ACGIH (2007) has set TLVs for compounds used for systemic effect in the body: acetylsalicylic acid and disulfiram (used for treatment of alcohol abuse), the anaesthetic enflurane, the anticoagulant warfarin, nicotine (used for replacement of tobacco), the vasodilator nitroglycerin, and essential compounds (Fe, Mn, Mo and Se); several of these OELs are presumably set due to non-medical related exposures. Additionally, compounds are included in the list for their human or veterinary use due to anthelmintic, contact insecticidal, ascariocidal, nematocidal, antimicrobial and coccidioidal effects, and due to antiseptic properties. Magnesium oxide is also included; it is used due to the antacid and laxative properties as well as by hypomagnesemia. Therefore, the pharmaceutical industry early began to set limits for some of their intermediates and final products (Sargent and Kirk, 1988; Naumann and Sargent, 1997; Paustenbach, 2000; Binks, 2003). Together with typical dust exposures (default values) by different pharmaceutical processes, the OEL estimates may be used by in-house risk assessment (Naumann and Sargent, 1997) with the purpose of risk management and duty of care principle.

Threshold of Toxicological Concern (TTC) is the level where an exposure to a compound no longer possesses toxicological effects and thus requirement of toxicological information and studies at this and lower levels is no longer relevant. To obtain maximum benefit of the limited resources allocated to setting OELs, the TTC concept may be useful for identifying compounds where little or no benefit is expected if resources are allocated to OEL settings.

Thus, from a large database of animal studies, it was shown that an exposure level corresponding to 1 µg/day of carcinogens was not likely to cause a life-time risk exceeding 10⁻⁶ if five alert structures, steroids, polyhalogenated dibenzo-*p*-dioxins and dibenzofurans, aflatoxin-like, azoxy- and *N*-nitroso compounds, were excluded (Dolan et al., 2005). For compounds with a threshold effect, the ADI approach was used to propose TTC values. For example, a pharmaceutical database on active ingredients was evaluated and it appeared that 94% of the compounds had ADIs greater than 10 µg/day. Also, the distribution of oral Reference Doses (RfDs) from the U.S. EPA Integrated Risk Information System (IRIS) database and the Minimum Risk Levels (MRLs) from the Agency for Toxic Substances and Disease Register (ATSDR) was studied. This showed that the 10 µg/day dose was below 90% of the RfDs/MRLs and that the 100 µg/day dose was below 75% of the RfDs/MRLs (Dolan et al., 2005). Thus, the authors proposed 1 µg/day dose to be used as TTC for carcinogenic compounds without the alert structures, and for compounds with NOAELs, the 10 µg/day dose to be used as TTC for compounds that are likely to be potent or highly toxic, and 100 µg/day being used for compounds that are not likely to be potent, highly toxic or carcinogenic (Dolan et al., 2005).

8. Mixtures

Although not directly related to the OEL settings, knowledge about interaction is a key to the use of OELs as workers usually are exposed to mixtures of and not to single chemical compounds to which OELs have been set. Only few OELs are set for mixtures (e.g. Mumtaz et al., 2007). Overall, the effect of a mixture may be less than the effects of its individual components, i.e. an antagonistic effect, the effect of the components may be additive or the effect of the mixture may be greater than the sum of the effect of the individual components, i.e. synergistic or potentiating effects (McCarty and Borgert, 2006; Mumtaz et al., 2007; Teuschler, 2007). However, the interaction can be fairly complex if it is necessary to take absorption, distribution, metabolism, excretion, mechanism-of-action, mode-of-action and concentrations into account (El-Masri, 2007; Teuschler, 2007).

Thus, the German MAK commission refrains from setting up procedures for evaluating effects of mixtures due to the current methodological limitations (Greim, 2003; DFG, 2006a). On the other hand, ACGIH (2007) considers non-carcinogenic compounds that have a similar toxicological effect on the same target organ to have additive effect in the absence of information about the contrary. In this case, a mixture effect is evaluated from the hazard index of each compound ($H.I.(i) = [(Concentration\ of\ compound\ (i)) / TLV(i)]$) and the TLV of the mixture are considered exceeded if the sum exceeds one ($\sum H.I.(i) > 1$). Also, JSOH evaluates mixtures from the H.I. index: "When workers are exposed to a mixture of chemical substances and there is no reliable evidence to the contrary that the effects of the chemicals are assumed to be additive, the effects should be assumed as additive" (Omae, 2006). A web-based computer tool has been developed where the toxicological endpoints are divided into 32 classes. The tool calculates the H.I. for compounds belonging to the same classes. Additionally, it adds information on known supra- or infra-additivity of mixtures (Vyskocil et al., 2007). The program is accessible freely at (http://www.irsst.qc.ca/files/outils/intertox/jsndx_en.htm) (accessed March 5, 2008).

Based on experimental studies, the additive approach is considered reasonable for sensory irritants (cf. Nielsen et al., 2007). However, if one compound inhibits the metabolism of another compound in a mixture (toxicokinetic interaction) and the effect is due to a systemic effect, the effect of the mixture may exceed the effect estimated from the H.I. Additionally, in this case the work load may have a pronounced influence on the effect due to the effect of the work load on the ventilation rate. Such interactions can be studied by PBPK modelling (Dennison et al., 2005).

9. Future development

Hardly needed to be mentioned, an efficient system for setting OELs has to produce a certain number of new and revised values each year to keep up with the number of substances used (Culver, 2005; Ettinger, 2005). Partly, this may be fulfilled by the new REACH regulation in the EU, which intends to set DNELs for a large number of compounds. Also, several issues were identified in the above text, which we address below.

Reliable OELs allow toxicological decisions to be transparent and ranked according to risks (Ettinger, 2005; Henschler, 1984). However, the lack of sufficient data on many endpoints is one of the weak part in setting OELs for many compounds, gaps that should be filled in the future where relevant (Fairhurst, 2003). To obtain maximum benefit of the resources allocated to setting OELs, the TTC concept may be useful for identifying compounds where little or no benefit is expected if resources are allocated to such compounds.

The setting of OELs based on the departure from the NOAEL is well established. However, the use of the benchmark dose approach may increase in the cases where it has advantage over the NOAEL approach.

The trend is to use toxicological mechanisms in the OEL settings. For example, setting OELs for topoisomerase and spindle inhibitors should be possible from the NOAEL approach as indicated from their mode-of action. In general, findings in acute, sub-acute and long-term studies can be supported by mechanistic studies, including studies on toxicokinetics, metabolism and understanding of species differences (Haber et al., 2001). Such data should be included in OEL documentations and used for an optimal setting of UFs.

As genetic polymorphisms can influence the activity of enzymes, they can play an important role in the variation in inter-individual sensitivity amongst workers (Haber et al., 2002). Therefore, the metabolism of compounds should, where possible, be addressed in sufficient details, e.g. which cytochrome P450 (CYP) enzyme is involved, with the purpose to identify individuals with a low or high metabolism and thus the identifying sensitive subgroups where the toxic effects will depend on whether the parent compound or its metabolites are the offending agents. For example, exposure to benzene in individuals having both a rapid CYP2E1 enzyme activity and a low NAD(P)H: quinone oxidoreductase-1 activity was associated with an appreciable risk for development of hematotoxicity (cf. Au et al., 2005). Overall, evaluation of whether sensitive subgroups exist and their influence on the OEL setting may attract more attention in the future and be an area where specific impacts on the UFs will be evaluated, for example, by means of PBPK methods in combination with estimated variability from Monte Carlo methods.

Currently, the study of metabolites (metabonomics or metabolomics) should possess several advantages compared to the study of genomics and proteomics. First, a limited number of metabolites are generated from each compound, which can be detected in body fluid such as urine and blood. The level of parent compounds and their metabolites are those responsible for the biological effects. Also, their level and their types are directly integrated and reflected in the genetic differences, including sex, as well as the complex homeostatic and feedback mechanisms (van Ravenzwaay et al., 2007).

In the future, mechanistic studies may come from studies in genetically engineered animals (e.g. Bolon, 2004) and from relationships between changes in gene expression and toxicological effects (e.g. Mattes et al., 2004). For example, it was recently attempted to develop biomarkers of formaldehyde exposures from gene expression by microarray analysis of more than 23,000 genes (Li et al., 2007). Although it was mentioned that genetics has not yet had a major impact on occupational safety and health, the question "how far away are we from genetic impacting worker health" (Schulte, 2007) was also raised.

Although not directly related to the OEL settings, knowledge about interaction is a key to the use of OELs as many workplace exposures are to mixtures and not to a single chemical compound to which an OEL has been set. Taking into account the current comprehensive discussion about interaction, it has to be expected that this discussion will cause a cross-fertilisation of evaluation of mixture effects at occupational exposures.

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Appendix A

The search profiles in PubMed were: (1) “occupational exposure limits” AND history, (2) “occupational exposure limits” AND review, (3) “uncertainty factor*”, (4) cancer AND “occupational exposure limit*” AND review, (5) topoisomerase* AND review AND mechanism*, (6) “mitotic spindle” AND review, (7) spindle AND poisoning, (8) formaldehyde AND “exposure limit*”, (9) “skin notation”, (10) “biological monitoring” AND TLV, (10) “biological monitoring” AND “occupational exposure limit*”, (11) “biological monitoring” AND MAK, (12) “biological limit value*”, (13) TLV AND review, (14) MAK AND review, (15) European Union AND “occupational exposure limit*”, and (16) “occupational exposure limit*” AND review, (17) Paustenbach DJ, (18) Dourson ML, (19) Rodricks JV, (20) Crump KS and (21) isocyanate* AND review AND “occupational exposure limit*”. In addition to the literature search, articles have been identified by personal reference lists, which include publications that were available from meetings in the SCOEL. GDN is a member of the SCOEL and SØ is the observer for the European Free Trade Association (EFTA) in the SCOEL.

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