Comparison of Data Used for Setting Occupational Exposure Limits

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It has previously been shown that occupational exposure limits (OELs) for the same substance can vary significantly between different standard-setters. The work presented in this paper identifies the steps in the process towards establishing an OEL and how variations in those processes could account for these differences. This study selects for further scrutiny substances for which the level of OELs vary by a factor of 100, focussing on 45 documents concerning 14 substances from eight standard-setters. Several of the OELs studied were more than 20 years old and based on outdated knowledge. Furthermore, different standard-setters sometimes based their OELs on different sets of data, and data availability alone could not explain all differences in the selection of data sets used by standard-setters. While the interpretation of key studies did not differ significantly in standard-setters' documentations, the evaluations of the key studies' quality did. Also, differences concerning the critical effect coincided with differences in the level of OELs for half of the substances. *Key words*: occupational exposure limits; chemicals regulation; regulatory toxicology; risk assessment; risk management.

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INTRODUCTION

Governments and professional organizations determine occupational exposure limits (OELs) to protect workers from adverse health effects caused by chemical exposures. An OEL specifies an average airborne concentration of a substance below which health risks are taken to be acceptably low. The setting of an OEL starts with a toxicological evaluation, in which primary data are used to estimate the size and nature of risks associated with different exposures. In combination with the toxicological information, including the severity of suspected health effects, the level of precaution considered justified and feasible is influenced by technical and socioeconomic factors, such as the number of potentially exposed workers.

Toxicological evaluations usually aim at estimating a dose-response relationship for a *critical effect*. The critical effect is the main adverse effect that the exposure limit should protect against. The *point of departure* is the dose level from which the OEL is ultimately extrapolated. The point of departure can be derived from animal or human data. Since conclusive epidemiological data are sparse, the point of departure is usually based on animal data. The point of departure can be a "no observed adverse effect level" (NOAEL) or a "lowest observed adverse effect level" (LOAEL). The LOAEL is the lowest tested dose that has caused a statistically significant adverse effect in an animal experiment. The NOAEL is the dose tested adjacent to the LOAEL on the lower bound, in other words, the highest dose tested that did not cause a statistically significant adverse effect. The NOAEL and LOAEL values per definition must be one of the tested doses. Furthermore, the definitions of LOAELs and NOAELs are statistically-based and inherently become less reliable when using fewer animals per tested dose. Since the number of animals in toxicological testing is limited for several reasons, so is the statistical power of the data derived from such tests. It is important to evaluate the quality of a particular study in this respect in order to assess the study's potential to sufficiently detect small effects. A different approach to determine a point of departure is the Benchmark Dose approach, first suggested by Crump.[1] This method uses a complete data set to derive a model with which an acceptably low effect level can be calculated.

To derive the OEL, an extrapolation from the point of departure to the OEL is performed. Uncertainties concerning the validity and reliability of the point of departure and the severity of effects may influence the magnitude of the extrapolation factor or factors. In addition, this step could be significantly influenced by policy since it is related to the level of precaution that is considered feasible for technical and economic reasons.

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AIMS OF THIS STUDY

This study concerns the toxicological evaluations performed in order to derive a number of currently enforced OELs. The objective of the study is to identify reasons why different organizations and authorities have determined different OELs for the same substance. The present work aims at identifying scientific or policy-motivated explanations of these differences by scrutinizing the OEL documentations from different sources for a number of individual substances. This study describes differences in the selection, interpretation, and evaluation of primary data in the documentations of highly variable OELs and analyzes reasons for differences between different documentations. The aim of this work is also to be able to contribute to making toxicological evaluations more transparent.

METHODS

Identification of Substances and Sources of Documentation

Substances for which the OELs varied by a factor of 100 or more were identified by cross-referencing 18 different lists in force in 2005,[2–25] using the Chemical Abstract Services (CAS) number for substance identification. By cross-referencing, the differences between eight-hour weighted averages and short-term exposure limits were accounted for. Exposure limits for substances without a CAS number were excluded. Documentation for the identified substances' OELs were searched for. Language restrictions determined the final choice of standard-setting agencies and substances to be included. Only documentation available in English, French, or any Nordic language was reviewed. Fourteen substances were identified fulfilling the selection criteria. These substances and their OELs were collected from eight organizations: the American Conference on Governmental Industrial Hygienists (ACGIH),[2] the Office of the Australian Safety and Compensation Council,[21] the Deutsche Forschungsgemeinschaft (DFG),[6] the European Commission,[8-14] the Finnish Ministry of Social Affairs and Health,[15] the French Insititut National de Recherche et de Sécurité (INRS),[16] the Swedish Work Environment Authority,[24] and the US Occupational Safety and Health Administration (US OSHA).[20]

ACGIH and DFG are non-governmental organizations that produce recommendations and documentation for health-based OELs. The year of the literature review given in DFG documentations might differ from the year of publication since several OEL documentations are published in one volume. In the tables relevant to the results section of this study, the year of literature review of the individual documentation is noted; in the reference section, the year of publication of the volume in question is cited. The other organizations do not always produce documentation for the OELs themselves. Substantiation (or sources of substantiating documentation) for the OELs of the Australian Safety and Compensation Council can be found at: http://hsis.ascc.gov.au. The basis for the European Commission OELs are recommendations and documentations from the Scientific Committee on OELs (SCOEL), a group formalized in 1995.[26] Previous to SCOEL, OEL documentations were compiled by the EU Scientific Expert Group (SEG). Previously, IARS was responsible for both issuing and substantiating French OELS. Since 2005, the OELs from INRS are substantiated by documentations from the Agence Française de sécurié sanitaire de l'environment et du travail (AFSSET) (e-mail communication, AFSSET 2008 September 30). The Swedish Work Environment Authority currently uses two main sources of documentations, the Swedish Criteria Group and the Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals (NEG); they have also used ACGIH as a source. The NEG is a collaboration between the Nordic countries, including Sweden and Finland (www.nordicexpertgroup.com). The US OSHA was created by Occupational Safety and Health Act of 1970, and a first list of OELs was issued in 1971. In 1989 OSHA proposed a final rule lowering 212 OELs and adding OELs for 164 new substances.[27] A number of industrial groups sued to overturn both the new exposure limits and the revisions, and a later court decision remanded both the new and the revised limits. After 1993 these limits were no longer enforced and the exposure limits set mostly in 1971 were reinforced. This court decision did not necessarily affect the state regulation of chemical exposure limits. In 1993 some states used the 1989 list of OELs (www.cdc.gov/niosh/ npg, Appendix G, 2010-04-25). No documentation for the OELs issued in 1971 was retrieved for the purpose of this study. However, the remanded OELs and the comments from the preamble of the 1989 Final Rule on Air Contaminants[27] have been included in the analysis of data selection.

The OEL documentations were collected mainly through the web pages of these organizations and via e-mail communication with them; published material was identified through the Riskline and Toxline databases. When more than three OELs from different sources were set for a substance, the documentation for the highest and lowest limit in the range was selected, in addition to the available documentation from the ACGIH, the DFG, and the Swedish Work Environment Authority, since these three organizations are acknowledged as particularly influential in the international arena.[28,29]

The main use of the 14 substances included in this study are presented in Table 1. Considering the selection criteria, the included substances were not representative of all substances with OELs, especially in the case of substances that have carcinogenic properties. All the individual exposure limits for these 14 substances set by the selected agencies were compiled, and

TABLE 1 The Studied Substances with Chemical Abstract Services (CAS) Numbers and Main Industrial Use

Substance	CAS	Use and Occurence
Benzo(a)pyrene	50-32-8	Occurs in automobile exhaust and smoke from combustion of organic material; used as a surrogate measure for total exposure to polycyclic aromatic hydrocarbons (PAHs).
Carbon tetrachloride	56-23-5	Solvent; degreasing agent.
p-Dichlorobenzene	106-46-7	Deodorants, hygiene products.
Dichlorofluoromethane (FC-21)	75-43-4	Refrigerants (such as Freon), aerosols, and solvents.
Enflurane	13838-16-9	Anesthetics; substitute for halothane.
2-Ethoxyethanol	110-80-5	Solvents.
Ethylene dibromide	106-93-4	Automotive products; formerly used in pesticides.
Halothane	151-67-7	Anesthetics.
2-Hexanone	591-78-6	Solvents.
Hydrazine	302-01-2	Corrosion inhibitors; catalysts in polymerization.
Nickel subsulfide as(Ni)	12035-72-2	Intermediates.
Phenyl glycidyl ether (PGE)	122-60-1	Polymerization.
Tetranitromethane	509-14-8	Explosives / propellants; analytical reagents.
Vinyl cyclohexene dioxide	106-87-6	Intermediate polymers.

it was determined whether these OELs were claimed by the standard-setters to be purely health-based or also influenced by socioeconomic and technical considerations (Table 2).

Tabulation of Information

The data used in this paper were based on reviews of the primary data used by OEL-setting bodies. Documentations were analyzed to identify the critical effect, point of departure, and key studies used in setting the OELs. The first step was to identify the critical effect. However, the term "critical effect" is not always used in the documentation of an OEL, and in those instances, the adverse health effect that the OEL primarily should prevent was cited as the critical effect. Following the identification of the critical effect, the dose-response information for that effect was used to identify the point of departure used for setting the OEL. It was expected that the point of departure information would belong to one of the following five categories: (1) animal data NOAEL; (2) animal data LOAEL; (3) human data no-effect level; (4) human data effect level; or (5) benchmark dose from animal data. If the dose level that had been used as point of departure was not specified in the documentation, the lowest dose level given for the critical effect was used, corresponding to one of the five specified categories above. Some documentations identified several effects of concern instead of one critical effect, and in those instances the effect with the lowest LOAEL or NOAEL was used for comparison. Conclusions concerning carcinogenicity were noted when it was not the critical effect.

A study that was cited in at least one documentation as being either the source of the point of departure, as defined above, or as giving substantial weight to the concluded point of departure is referred to as a *key study* in this paper. The evaluations and interpretations of these key studies were compared when the same key study was cited in more than one documentation. Comparisons of agencies' data selection, interpretation, and evaluation were thus based on the references they accorded the most weight, rather than all references cited. The key references in the documents have been sorted into four different categories: +++ corresponds to the highest weight, that is, the study from which the point of departure was derived; ++ means that the study was cited as giving strong support to the point of departure; + means that the study was cited but not given any specific weight in the derivation of the point of departure; and (+) means that the study was cited in the documentation but that the interpretation or evaluation was significantly different from that presented in the other documentations. Studies assigned the weight of ++ or +++ were denoted key studies in this paper.

The aim of the procedures described thus far was to identify the scientific arguments used to substantiate OELs. The final step in scrutinizing the documents included the identification of explicit policy statements in the key studies. Policy statements were defined as

TABLE 2 Occupational Exposure Limits (OELs)[a] Set by Eight Organizations[b] for the most Variable Substances, including Ratios between Highest and Lowest OEL

Organization	ACGIH	Office of the Australian Safety and Compensation Council	European Commission	Finnish Ministry of Social Affairs and Health	INRS	DFG	Swedish Work Environment Authority	US OSHA	Max/min Ratio[c]
Basis of OEL	H[d]	F[e]	H	H	F	H	F	F	
Substance (unit of measure)									
Ethylene dibromide (ppm)	No OEL[f]	—	—	0.1	—	No OEL[g]	Permit[h]	20	200 (–)
Tetranitromethane (ppm)	0.005	1	—	0.05	1	No OEL	0.05	1	200 (200)
Enflurane (ppm)	75	0.5	—	10	—	20	10	—	150 (150)
2-Ethoxyethanol (ppm)	5	5	—	2	5	5	5	200	100 (2.5)
Benzo(a)pyrene (mg/m^3)	No OEL	—	—	0.01	—	No OEL	0.002	0.2	100 (5)
Carbon tetrachloride (ppm)	5	0.1	1[i]	1	2	0.5	2	10	100 (50)
p-Dichlorobenzene (ppm)	10	25	20	20	0.75	No OEL	10	75	100 (33)
Dichlorofluoromethane (ppm)	10	10	—	10	10	10	—	1000	100 (1)
Halothane (ppm)	50	0.5	—	1	—	5	5	—	100 (100)
2-Hexanone (ppm)	5	5	—	5	5	6	1	100	100 (6)
Hydrazine (ppm)	0.01	0.01	—	0.1	0.1	No OEL	Permit	1	100 (10)
Nickel subsulfide (as mg Ni/ m^3)	0.1	—	—	0.1	1	No OEL	0.01	—	100 (100)
Phenyl glycidyl ether (ppm)	0.1	1	—	0.5	1	No OEL	10	10	100 (100)
Vinyl cyclohexene dioxide (ppm)	0.1	10	—	0.5	—	No OEL	—	—	100 (100)

[a]Eight-hour time-weighted averages.
[b]The American Conference on Governmental Industrial Hygienists (ACGIH), the Office of the Australian Safety and Compensation Council, the Deutsche Forschungsgemeinschaft (DFG), the European Commission, the Finnish Ministry of Social Affairs and Health, Institut National de Recherche et de Sécurité (INRS), the Swedish Work Environment Authority, and the US Occupational Safety and Health Administration (US OSHA).
[c]Value in parentheses: excluding US OSHA.
[d]Health-based OEL.
[e]Feasibility-based OEL.
[f]The ACGIH does not assign numerical OELs to all substances for which they publish documentation.
[g]The DFG does not assign numerical OELs to all substances for which they publish documentation.
[h]Substance is not regulated with an OEL; permission is needed from authority before using it.
[i]This limit is a recommendation from the Scientific Committee on OELs (SCOEL), but has not been adopted by any EU directive.

those which considered a target level of protection, identified and accounted for sensitive subgroups, or explicitly discussed other factors that impacted the extrapolation of the OEL, including technical feasibility or use of safety factors in the extrapolation. For the sake of brevity, only five substances are discussed in detail below; however, all 45 scrutinized documentations concerning 14 substances were included in the analysis.

RESULTS

In total, 85 key references were identified, but only eight documentations covered all studies that had been defined as a key study. Nine of the key studies were given the highest weight (+++) in more than one toxicological evaluation. For 10 substances, the oldest OEL was also the highest (Table 2). The time of the data review was identified, as were three different steps of toxicological evaluation—data selection, data evaluation, and identification of critical effect—as factors to which differences in various OELs could be traced. Not unexpectedly, policy issues were found to have an influence on the final OEL. Five substances were selected to exemplify these factors and are presented below. While alphabetical order of the substance names was used to select these five substances, each factor or policy issue influencing OELs was represented by at least one of the five substances; duplication was avoided when possible. For these substances the information sought concerning critical effect, point of departure, and use of key references was tabulated and is presented below. In the text findings are reported as follows: (1) the range of

TABLE 3 Carbon Tetrachloride: Reviewed Occupational Exposure Limits (OELs) and Critical Effects

Agency	OEL	Year of Limit	Year of Documentation	Critical Effect	NOAEL	LOAEL
Scientific Committee on OELs	1 pmm	*	2008[a]	Liver toxicity	5 ppm (A)	*
Swedish Work Environment Authority[b]	2 ppm	1978	*	Liver toxicity	10 ppm (H)	10 ppm (A)
Australian Safety and Compensation Council	0.1 ppm	1995	*	Liver toxicity	1 ppm (A)	*
Deutsche Forschungsgemeinschaft	0.5 ppm	2001	2000	Liver toxicity	*	1 ppm (H)
American Conference on Governmental Industrial Hygienists	5 ppm	1981	2001	Liver toxicity	10 ppm (A)	*

* = Not stated or not possible to derive; A= animal data; H=human data.
[a]Documentation sent for public consultation in 2008.
[b]Based on ACGIH documentation (1971).

exposure limits specifying the highest and the lowest OEL; (2) the documentations that were included in this analysis; (3) the absence of any significant documentations; (4) conclusions on carcinogenicity; (5) the determination of critical effect; (6) selection and evaluation of key references; (7) explicit policy statements, when available. Reporting according to this system for the documentations of the other nine substances can be found in the Appendix (published online at www.ijoeh.com).

Benzo[a]pyrene. The Swedish Work Environment Authority and US OSHA have determined OELs for benzo[a]pyrene at 0.002 mg/m^3 and 0.2 mg/m^3 respectively. The ACGIH[2] and the DFG[30] concluded that benzo[a]pyrene exposure did not have a threshold safe level due to carcinogenicity, and therefore they have not established an OEL. The Swedish Work Environment Authority (authored by the Swedish Criteria Group)[31] and the ACGIH[2] documents were included in our analysis, but no DFG documentation on benzo[a]-pyrene in particular, or polycyclic aromatic hydrocarbons (PAHs) in general, was available; however, the index of available DFG documents did refer to these substances in the documentations on passive smoking and diesel exhaust.[30] No documentation related to the OEL established by US OSHA was available. The substance was classified as a suspected human carcinogen (A2) by ACGIH and is considered to be a human carcinogen (Cat. 2) by the DFG. Benzo[a]pyrene is not a chemical handled at the workplace (Table 1), but it was used as a surrogate measure for total exposure to PAHs. This complicated exposure or dose assessments since the health effects of PAHs were evaluated as well as the suitability of benzo[a]pyrene as an index. Nevertheless, all documentations defined carcinogenicity as the critical effect. It was not possible to identify any NOAELs or effect levels in these documentations. A comparison of the data on effects in humans reviewed by the Swedish Criteria Group, the DFG, and the ACGIH showed that these three documentations had very different data selections; no epidemiological study was reviewed by more than one expert group. The ACGIH document was published in 2001, but of the five epidemiological studies cited in it, the most recent was from 1981. By comparison, the Swedish documentation was published in 1983 and included 14 epidemiological studies, of which four were published in 1982 or 1983.

In short, only regulatory agencies chose to give a numerical OEL for this compound, while the non-regulatory standard-setters gave a more restrictive recommendation. Technical and socioeconomic factors may have influenced this, as regulatory agencies face political demands not necessarily encountered by non-governmental groups (Table 2).

Carbon tetrachloride. The OELs for carbon tetrachloride ranged from the Office of the Australian Safety and Compensation Council's 0.1 ppm to US OSHA's 10 ppm (Table 2). Five OELs for carbon tetrachloride were studied in detail and listed in Table 3. The Scientific Committee on OELs (SCOEL) published a documentation and recommendation for an indicative OEL,[32] although this has not been adapted in any EU directive yet. The Swedish OEL is based on the 1971 ACGIH[33] documentation; other documentations used were from the Office of the Australian Safety and Compensation Council,[21] DFG,[34] and ACGIH (2001).[2] The substance is considered to be carcinogenic by ACGIH, DFG, SCOEL, and the Swedish Work Environment Authority. The Australian documentation found the evidence on carcinogenicity inconclusive. There was consensus in these five documents on the hepatotoxicity of carbon tetrachloride.

That the industrial use of carbon tetrachloride has been restricted in many countries might be a contributing factor as to why all of the identified key studies (Table 4) were of considerable age. In the SCOEL documentation, the most recent in this selection, no primary study dated later than 1999. Of the key studies, only one—Adams et al.[35]—was given the highest weight in two different documents (Table 4). No documentation included all of the available key studies. The Adams et al.[35] study was cited in all five documents and was explicitly mentioned as contributing to determining the OEL in the Australian, DFG, and SCOEL docu-

TABLE 4 Carbon Tetrachloride: Coverage of Key References

	Swedish Work Environment Authority[a]	Australian Safety and Compensation Council	Deutsche Forschungs-gemeinschaft	American Conference on Governmental Industrial Hygienists	Scientific Committee on OELs
Year of Documentation	1971	1995	2000	2001	2008
Elkins 1942[38] (H)	+	++	–	+	–
Adams et al. 1952[35] (A)	+	+++	++	+	+++
Stewart et al. 1961[39] (H)	+	—	+	+++	+
Prendergast et al. 1967[36] (A)	–	+++	–	(+)	–
Rabes 1972[40] (H)	–*	++	–	–	–
Bruckner et al. 1986[41] (A)	–*	–	++	–	+
Tomenson 1995[42](H)	–*	–*	+++	–	++

* = data not available at the time of assessment; A = animal data; H = human data.
+++ Used to derive the point of departure.
++ Important as support to the point of departure.
+ Referenced in documentation.
(+) Referenced in documentation, but differences in interpretations of the effects were found.
– Not referenced.
[a]Based on ACGIH documentation (1971).

mentations. The effect reported at the lowest exposure was unspecific inflammation of the lung, found in several animal species after exposures as low as 1 ppm by Prendergast et al.[36] The ACGIH described this finding, but a probable error in the references was found. Nonspecific inflammatory changes in the lungs in several animal species was reported by Prendergast et al;[36] the ACGIH document regarding this effect referred to a study by Wong and DiSefano[37] which concerned the accumulation of carbon tetrachloride in renal fat in cats. This has been communicated to the ACGIH. However, the interpretation of these nonspecific inflammatory changes differed between the documents. The Australian document cited Predergast et al.[36] as reporting an animal NOAEL at 1 ppm, and also gave it the weight of a key study.

The Australian group of experts was the only one that explicitly defined a safety factor; since adverse effects have been seen in humans at a level close to the animal NOAEL used as a point of departure, they applied a safety factor of 10. The Australian documentation was also the only one indicating that the OEL should protect against the potentiating effect of alcohol consumption on the substance's hepatotoxicity. The ACGIH documentations clearly stated that consumption of alcohol would lessen the margin of safety.

For this substance, the differences in OELs seemed to be the result of differences in the evaluation of key references as well the consideration of an explicit safety factor and the inclusion of a sensitive subpopulation.

p-Dichlorobenzene (1,4-dichlorobenzene). The OELs for p-dichlorobenzene ranged from the French INRS's 0.75 ppm to US OSHA's 75 ppm (Table 2; Table 5); DFG has not determined an OEL as they classified p-Dichlorobenzene as a carcinogen. Documentations were included from US OSHA (1989),[27] the NEG,[43] the DFG,[44] the French Expert Group on Health,[45] the EU SEG,[46] and the ACGIH.[2] The highest exposure limit was the one determined by OSHA, for which it was not possible to retrieve the original documentation. However, OSHA comments for their Final Rule of 1989[27] did recommend that the level of 75 ppm should be retained. The substance was listed as a potential carcinogen by ACGIH, DFG, the Finnish Ministry of Social Affairs and Health, and the INRS. However, the ACGIH concluded that the exposures that had been shown to lead to tumors in animals "were not typical of a working environment." The NEG and the EU SEG both concluded that the substance was a confirmed animal carcinogen, but that the mode of action lacked relevance for humans. The 1989 OSHA evaluation, on the other hand, commented that there had been reports of a scientific controversy concerning carcinogenicity. The conclusions on the critical effect of p-dichlorobenzene varied. The DFG and INRS listed carcinogenicity as the critical effect. The ACGIH identified eye irritation as the critical effect, the NEG eye and respiratory irritation, the 1989 OSHA evaluation cited eye damage, and the EU SEG, liver and kidney toxicity.

The data selection in the different documents also varied (Table 6). The key study in the ACGIH documentation was a Dow Chemical report to the US EPA that was not reviewed by any other assessor. The Hollingsworth study[48] was given substantial weight by two assessors, the EU SEG and NEG, but its reliability was criticized by the DFG, due to insufficient reporting. A two-year inhalation study from 1995 on mice and rats from the Japanese Bioassay Research Center[49] was reviewed and given the weight of a key study in the DFG and INRS documentation. Even though this report was potentially available to ACGIH and NEG, it was not

TABLE 5 p-Dichlorobenzene: Reviewed Occupational Exposure Limits (OELs) and Critical Effects

Agency	OEL	Year of Limit	Year of Documentation	Critical Effect	NOAEL	LOAEL
US OSHA	75 ppm	1989	*	Eye damage: vertigo	*	*
European Commission[a]	20 ppm	2000	1994	Liver and kidney toxicity	95 ppm (A)	*
Swedish Work Environment Authority[b]	10 ppm	2000	1998	Irritation	*	50 ppm (H)
ACGIH	10 ppm	1993	2001[b]	Eye irritation	*	17 ppm (H)
Deutsche Forschungsgemeinschaft	No OEL	2001	2001	Carcinogenicity	*	20 ppm
Institut National de Recherche et de Sécurité[c]	0.75 ppm	*	2003	Carcinogenicity	75 ppm (A)	*

* = Not stated or not possible to derive; A = animal data; H = human data.
[a]Based on documentation from the Scientific Expert Group.
[b]Based on documentation from the Nordic Expert Group.
[c]Based on documentation from the French Expert Group on Health.

reviewed by them (Table 6). However, it should be noted that this was a report from a research center and was not published in a peer-reviewed journal. The DFG referred to it as a "brief summary report to the Minstry of Labour in Japan." In two documents, explicit safety factors were given: INRS applied a factor of 100 and the EU SEG applied a factor of 5, both to an animal NOAEL for the respective critical effects.

The main reasons for the differences in the OELs for p-dichlorobenzene seemed to be differences in data selection as well as the identification of critical effect. In addition, the explicit consideration of safety factors influenced certain OELs.

Enflurane. Table 7 lists four OELs for enflurane, ranging from the Office of the Australian Safety and Compensation Council's 0.5 ppm to ACGIH's 75 ppm. Documentations were included from the Swedish Work Environment Authority (with OEL documentation adopted from ACGIH in 1980 as cited in ACGIH[54]), the Australian Safety and Compensation Council, [21] DFG,[55] and the ACGIH (2001).[2] The more recent ACGIH evaluation expressed concern that the substance might be a human carcinogen but that data were insufficient for assessment; the DFG also stated that there was a lack of data, but that carcinogenicity was unlikely; the other two documents did not include any assessment of carcinogenicity.

No critical effect or point of departure was stated in the older ACGIH documentation;[54] their data review was brief, and the basis for that proposal was the statement that enflurane was safer as an anesthetic than halothane: "[A]ll studies in man and animals indicate that its adverse effects are more rare than those of halothane." The Office of the Australian Safety and Compensation Council document referenced the ACGIH documentation from 1986 and stated that the toxicity of enflurane was similar to that of halothane,

TABLE 6 p-Dichlorobenzene: Coverage of Key References

	US OSHA	Scientific Expert Group	Nordic Expert Group	American Conference on Governmental Industrial Hygienists	Deutsche Forschungs-gemeinschaft	French Expert Group on Health[a]
Year of Documentation	**1989**	**1994**	**1998**	**2001**	**2001**	**2003**
Hollingsworth et al. 1956[48] (H)	–	+++	+++	+	(+)	–
Dow Chemical Co. 1978[47] (H)	–	–	–	+++	–	–
ICI 1980[50] (A)	–	–	–	–	+++	–
Riley et al. 1980[51] (A)	–	++	–	–	–	–
NTP 1987[52] (A)	–	-	+	–	+++	–
JBRC 1995[49] (A)	*	*	–	–	+++	+++
EPA 1996[53] (A)	*	*	–	–	+++	–

* = data not available at the time of assessment; A= animal data; H = human data.
+++ Used to derive the point of departure.
++ Important as support to the point of departure.
+ Referenced.
(+) Referenced and criticized.
– Not referenced.
[a]This documentation is an update of a previous literature review, the table only concerns this update.

TABLE 7 Enflurane: Reviewed Occupational Exposure Limits (OELs) and Critical Effects

Agency	OEL	Year of Limit	Year of Documentation	Critical Effect	NOAEL	LOAEL
Swedish Work Environment Authority[a]	10 ppm	1981	1980	*	*	*
Australian Safety and Compensation Council	0.5 ppm	1990	*	Feasibility[b]	*	*
Deutsche Forschungsgemeinschaft	20 ppm	1994	1994	Liver toxicity	20 ppm (H) 200 ppm (A)	700 ppm (A)
American Conference on Governmental Industrial Hygienists	75 ppm	1988	2001	Neurotoxicity; cardiovascular effects	*	2500 ppm (H ST)

* = Not stated or not possible to derive; A= animal data; HST=human short-term exposure.
[a]Based on the ACGIH documentation; assuming use of the most recent documentation available in 1980.
[b]This limit was deemed as technically possible to achieve.

although it was "generally considered to be safer." The other two assessors identified different critical effects: the DFG document cited liver toxicity and the more recent ACGIH documentation stated neurotoxicity and cardiovascular effects. The DFG concluded that since no effect had been noted in humans exposed to 20 ppm, that this was suitable limit. The more recent ACGIH documentation referred to short-term human exposure data and, as in the older documentation, the assumption that enflurane is a safer anesthetic agent than halothane or trichloroethylene.

The DFG document included the most comprehensive data review: all primary key studies available were included. Five of the eight key studies were defined as such by the DFG; however, only two additional primary studies and one review were identified as key studies by other evaluators (Table 8). The Office of the Australian Safety and Compensation Council's OEL relied heavily on the NIOSH documentation on anesthetic gases[56] and did not include any of the primary studies that were used as key references by the other assessors. For enflurane, the Australian OEL was determined from the perspective of how low it would be feasible to keep the exposures (as identified by NIOSH[56]) rather than the identification of a safe level.

Differences in the selection and evaluation of key references, as well as the identification of different critical effects and policy issues were interacting factors causing the different OELs for enflurane.

Tetranitromethane. Four OELs for tetranitromethane were included, ranging from ACGIH's 0.005 ppm to US OSHA's 1 ppm (Table 9). The DFG has not determined an OEL. The documents reviewed were from NEG,[64] DFG,[65] and ACGIH.[2] Only ACGIH and DFG evaluated the substance's carcinogenic potential. The DFG found the evidence sufficient to classify tetranitromethane as carcinogenic to humans, while the ACGIH concluded

TABLE 8 Enflurane: Coverage of Key References

	Swedish Work Environment Authority[a]	Deutsche Forschungsgemeinschaft	Australian Safety and Compensation Council	American Conference on Governmental Industrial Hygienists[b]
Year of Documentation	**1980**	**1994**	**1995**	**2001**
NIOSH 1977[56] (R)	+	–	+++	+
Strout et al. 1977[57] (A)	–	++	–	–
Bentin et al. 1978[58] (H)	+	+	–	++
Cook et al. 1978[59] (H)	+	+	–	++
Halsey et al. 1981[60] (A)	*	++	–	–
Wharton et al. 1981[61] (A)	*	++	–	–
Green et al. 1982[62] (A)	*	++	–	–
De Zotti et al. 1983[63] (H)	*	+++	–	–

* = data not available at the time of assessment; A = animal data; H = human data; R = review.
+++ Used to derive the point of departure.
++ Important as support to the point of departure.
+ Referenced.
– Not referenced.
[a]Based on ACGIH documentation (1971).
[b]No point of departure is identified, the recommendation on how to derive an OEL seemed to be to use the assumption that enflurane is safer than halothane or trichloroethylene.

TABLE 9 Tetranitromethane: Reviewed Occupational Exposure Limits OELs and Critical Effects

Agency	OEL	Year of Limit	Year of Documentation	Critical Effect	NOAEL	LOAEL
Swedish Work Environment Authority[a]	0.05 ppm	1993	1988	Irritation	*	0.5 ppm (A)
Deutsche Forschungsgemeinschaft	No OEL	1991	1991	Carcinogenicity	*	0.5 ppm (A)
American Conference on Governmental Industrial Hygienists	0.005 ppm	1993	2001	Irritation; respiratory carcinomas	*	0.5 ppm (A)

* = Not stated or not possible to derive; A= animal data.
[a]Documentation from the Nordic Expert Group.

that the available information was of unknown human relevance. The NEG and ACGIH considered respiratory and eye irritation to be the critical effect. In addition, the ACGIH specified respiratory carcinomas as an effect of concern. The DFG concluded that carcinogenicity was the critical effect.

The data reviewed in the different documents implied that tetranitromethane was not shown to be carcinogenic until the late 1980's since no studies indicating carcinogenicity were cited in the NEG documentation. It was noteworthy that the selection of key references for the DFG and the ACGIH was very similar (Table 10); however, DFG refrained from setting an OEL while the ACGIH chose to set an OEL 100 times lower than the LOAEL (Table 9). The NEG documentation was older, and thus not all studies were available to the NEG at the time for their evaluation.

For tetranitromethane time-related data availability as well as the evaluation of the key references influenced the identification of critical effect and hence, the final OELs.

Assessing Carcinogenicity

Of the 14 substances included in this study, 11 had their carcinogenic potential explicitly classified in one or more documentations. For nine substances, carcinogenicity or genotoxicity was deemed to be the critical effect by at least one assessor. These substances were: benzo[a]pyrene, p-dichlorobenzene, ethylene dibromide, halothane, hydrazine, nickel subsulfide, phenyl glycidyl ether, tetranitromethane, and vinyl cyclohexene dioxide.

Table 11 presents carcinogenicity classifications, recatgorized by the author into a common system, from the four OEL-setters that were judged to have the largest impact internationally, as well as from the World Health Organization's International Agency for Research on Cancer (IARC). While admittedly crude, the recategorization allows for easier comparison. In the Swedish Work Environment Authority's list of OELs, the potential for carcinogenicity was only indicated as present or not, without further distinction; this was deemed to mean that such substances were classified by the Swedish authority as a confirmed human carcinogen. The ACGIH, INRS, and DFG lists contained three to five categories of carcinogenicity. The Finnish Ministry of Social Affairs and Health list included the risk-phrases according to Annex III of the European Union classification and labelling directive.[72] The ACGIH has in several instances expressed carcinogenicity in more vague terms than the DFG or the IARC. A table is included with the original classifications in the Appendix (published online at www.ijoeh.com).

DISCUSSION

The overall aim of reviewing risk decisions made by standard-setters and specifically, their toxicological evaluations is to improve the regulatory process. Such reviews can provide knowledge on how scientific data has been evaluated and how OELs have been set. This in turn can help improve the efficiency and transparency of the decision process. The aim of this particular study was to investigate the motivations for the current OELs for a number of substances and different organizations. Towards this aim, 45 documentations were scrutinized. The year of publication for these documents ranges from 1971 to 2008. Inherent in this study design was the fact that some exposure limits were old and possibly determined according to practices or policies that are no longer in use. But even if some of the scrutinized documentations were old, the OELs they substantiated were the ones valid when this study was initiated. This section will discuss the factors found to be plausible as reasons for the differences in OELs and carcinogenicity classifications.

Several factors were identified as having an influence on the outcome of the toxicological evaluation and hence, the final level of exposure limits. *Time of data review* was identified as perhaps the most influential factor; US OSHA had the oldest and highest OEL for most substances (Table 2). It has also been shown previously that as OELs are revised they tend to be gradually decreased,[28,73] this emphasizes the need for regular revisions of OELs. But the differences found in levels of OELs were not explained by the case of OSHA alone.

Data selection was estimated through the comparison of key references between documentations. From the

TABLE 10 Tetranitromethane: Coverage of Key References

	Nordic Expert Group	Scientific Expert Group	American Conference on Governmental Industrial Hygienists
Year of Documentation	1988	1991	2002
Kawai et al. 1987[66] (A)	+	++	+
Stowers et al. 1987[67] (A)	+++	+	+
Zeiger et al. 1987[68] (A)	–	++	+
NTP 1990[69] (A)	*	+++	+++
Würgler et al. 1990[70] (A)	*	++	+
Bucher et al., 1991[71] (A)	*	–	+++

* = data not available at the time of assessment; A = animal data.
+++ Used to derive the point of departure
++ Important as support to the point of departure
+ Referenced
– Not referenced

45 OEL documentations, 85 key references were identified. Only eight documentations covered all available primary studies (not including reviews) that were deemed as key studies in at least one documentation. In addition, there might be policy questions concerning data selection, for example whether standard-setters should review non-published material in the toxicological evaluation or not.

The *evaluation of data quality* varied considerably between the assessors. Only nine out of the 85 identified key studies were used in more than one documentation to derive the point of departure. However, key references were often cited in several documents without having further importance attached to them (that is, a document that would be scored as +++ in one documentation might be designated + in several other documentations). In addition to such differences in the evaluation of individual studies made by standard-setters, two other aspects of more explicitly stated evaluation differences (denoted by (+) in the tables) were found in this study: the first concerned the reliability of the data considered by standard-setters. For example, regarding p-dichlorobenzene, the SEG identified Hollingsworth et al.[48] as a key study while DFG found the reporting in it lacking (Table 6). The second difference regarded the relevance or severity of the health effects described. For example, in the case of carbon tetrachloride, ACGIH referred to the Prendergast et al.[36] reporting of 1 ppm as causing an effect while the documentation from the Office of the Australian Safety and Compensation Council referred to the study as reporting an NOAEL at 1 ppm (Table 4).

Data selection and evaluation most probably were factors effecting the determination of *critical effect*, and differences in critical effect seemed to be a possible explanation for the differences in several OELs. For instance, for p-dichlorobenzene the critical effect determined by the standard-setters differed significantly, as did the data selection in the substantiating documentations. In the case of tetranitromethane the older and higher OELs were based on irritation as the critical effect, but the more recently discovered carcinogenicity of the substance was discussed by both DFG and ACGIH, who selected similar data. DFG chose not to set an OEL while ACGIH set an OEL with a safety factor of 100 from the LOAEL in mice. However it should be noted that differences in what was determined to be the critical effect did not necessarily lead to different OELs, and different data selection did not always lead to dissimilar conclusions on critical effect. For benzo[a]pyrene and carbon tetrachloride the data selection was very different between organizations but the conclusions on critical effect were similar.

Policy issues were also important as they affected several aspects of the determination of OELs. The policy issues identified in this study material can be summarized into four aspects:

1) How to perform the extrapolation from point of departure to OEL. Explicit safety factors were given in four documentations: the Office of the Australian Safety and Compensation Council for carbon tetrachloride, the SCOEL and the French INRS for p-dichlorobenzene, and US OSHA for 2-ethoxyethanol (see Appendix, published online at www.ijoeh.com).
2) Allowing the exposure limit to be established by technical feasibility in either measuring very low concentrations or limiting exposures. One documentation used technical feasibility as a substitute for a point of departure, as in the case of the Office of the Australian Safety and Compensation Council's limit on enflurane.
3) Including or excluding the protection of sensitive subgroups, as in the case of carbon tetrachloride.
4) Whether to regulate non-threshold effects by determining a sufficiently low risk level or by not specifying a numerical OEL. For example, the DFG does not set OELs unless a threshold can be identified;[6] the SCOEL recently published their strategy concerning the setting of OELs for carcinogens and

TABLE 11 Overview of Carcinogenicity Classification

Substance	ACGIH	European Commission	DFG	Swedish Work Environment Authority[a]	IARC
Benzo(a)pyrene	2	2	2	1	1
Carbon tetrachloride	2	3	1	1	2
p-Dichlorobenzene	3	3	2	*	2
Dichlorofluoromethane	*	–	*	–	–
Enflurane	5	–	*	*	–
2-Ethoxyethanol	*	*	*	*	–
Ethylene dibromide	3	2	2	1	2
Halothane	5	–	*	*	–
2-Hexanone	*	*	*	*	–
Hydrazine	3	–	2	1	2
Nickel subsulfide (as Ni)	1	1	1	1	1
Phenyl glycidyl ether	3	2	2	*	2
Tetranitromethane	3	–	2	*	2
Vinyl cyclohexene dioxide	3	*	2	–	2

Note: Taken from the lists of the American Conference on Governmental Industrial Hygienists (ACGIH), Deutsche Forschungsgemeinschaft (DFG),the World Health Organization's International Agency for Research on Cancer (IARC), Annex I and III of the EEC classification and labelling directive.[72] The respective classifications have been transformed to a common system for simplification of the comparison.

Classification System:
– = Substance not assessed.
* Carcinogenicity not evaluated.
1 = Confirmed human carcinogen.
2 = Suspected or probable human carcinogen.
3 = Carcinogenic to animals; insufficient evidence concerning human carcinogenicity.
4 = Substance probably not carcinogenic to humans.
5 = Insufficient evidence to determine carcinogenicity.

[a]Since the Swedish list of OELs only indicated carcinogenic or not, without any further classification, all substances given a carcinogenicity note in the Swedish list have been given the 1 classification in this table.

mutagens.[74] The SCOEL, similar to the DFG, only recommends health-based OELs for genotoxic carciongens with a practical threshold or non-genotoxic and non-mutagenic carcinogens. For other carcinogens a risk assessment is carried out but no health-based OEL recommended. Obviously, socio-economic and technical factors might affect the policies on non-threshold effects.

This study has shown that several OELs were based on outdated information. Regularly bringing the documentation and the associated OEL up to date should be a higher priority. Also, the documentation of the OELs is crucial for understanding the effects that exposures to these substances can give rise to and what effects the limits actually aim at protecting. Hence it is important that these documents are readily available to users of harmful substances and that the deduction of an acceptable effect level is transparent to the users.

In summary the main conclusions of this study were as follows:

- The older limits for these 14 substances were generally higher.
- Differences in the identification of critical effect coincided with differences in the level of the OELs for 50% (seven out of 14) of the substances studied.
- Time-related availability of data was not the main factor explaining differences in data selection; only 18% (eight out of 45) of the documents referred to all studies available at the time for evaluation and deemed as key studies in at least one documentation.
- Evaluation of the quality and relevance of studies varied considerably among organizations; only 11% (nine out of 85) of the key studies were given the highest weight in more than one documentation.
- Only 9% (four out of 45) of the documentations explicitly stated a use of safety factors.
- For one substance (one out of 14) different OELs were determined with different accounts regarding the protection of sensitive groups.
- ACGIH is the organization that has classified the carcinogenicity of the largest number of substances (11 out of 14), however it has given less restrictive classifications to six of these compared to either the DFG or the IARC.

RECOMMENDATIONS

Documentation concerning OEL-setting needs to be easily accessible, and considering current technology and infrastructure, a database published on the web is the most obvious possibility for this in industrialized countries. Although admittedly challenging, writers of

the documentations should aim at transparently describing the interactions between risk assessment and risk management. Instances when policy influences the final level of the limit need to be described. When chemical similarities to another substance are referred to, mechanistic data need to be accounted for and references given. Sometimes, or even most times, conclusions need to be drawn even if the available data are insufficient to untangle all possible effects. In order to accomplish this, it is very important to regularly update documentation, for example, by performing literature searches on a regular basis. Even if such searches do not result in any changes in the documentation, the time for last literature search should be provided in the documentation. This process should be feasible using web publication. The handling of uncertainty needs to be discussed in the documentation, that is, the safety factors or other methods of extrapolation need to be openly stated. If using non-published data in the toxicological evaluation, these data should be accessible through contact with the authoring organization.

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