ResearchGate

See discussions, stats, and author profiles for this publication at: https://www.researchgate.net/publication/46402572

Use of Uncertainty Factors by the SCOEL in their derivation of health-based Occupational Exposure Limits

Article *in* Critical Reviews in Toxicology · October 2010

DOI: 10.3109/10408444.2010.507628 · Source: PubMed

CITATIONS
22

READS
278

2 authors:



Linda Schenk
Karolinska Institutet
68 PUBLICATIONS **398** CITATIONS

SEE PROFILE



Gunnar Johanson
Karolinska Institutet
245 PUBLICATIONS **4,921** CITATIONS

SEE PROFILE

Some of the authors of this publication are also working on these related projects:

Acute effects View project

Surveillance of accidental chemical exposures at work using poison control data View project

All content following this page was uploaded by Gunnar Johanson on 30 May 2014.

The user has requested enhancement of the downloaded file.

Critical Reviews in Toxicology, 2010; 40(9): 791–798

informa
healthcare

REVIEW ARTICLE

Use of Uncertainty Factors by the SCOEL in their derivation of health-based Occupational Exposure Limits

Linda Schenk[1] and Gunnar Johanson[2]

[1]*Division of Philosophy, Royal Institute of Technology, Stockholm, Sweden, and* [2]*Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden*

Critical Reviews in Toxicology Downloaded from informahealthcare.com by (ACTIVE) Karolinska Institutet University Library on 01/12/11
For personal use only.

Abstract

The aim of this study was to investigate how the Scientific Committee on Occupational Exposure Limits (SCOEL) of the European Commission uses uncertainty factors when proposing health-based indicative occupational exposure limit values (IOELVs). In total, 75 IOELVs in 62 summary documents published from 1991 to 2003 were analyzed. For 31 of the IOELVs, no explicit uncertainty factor (EUF) was stated. For these, we calculated an implicit safety margin (ISM) as the ratio between the point of departure (POD, derived from the NOAEL or LOAEL of the critical effect) and the proposed IOELV. We further analysed whether date of recommendation, type of critical effect, nature of POD or amount of available data influenced the magnitude of the EUFs and ISMs. The ISMs varied little (range 1-5), while the EUFs showed more variability (range 1-50). The EUFs remained unaffected over time and the ISMs decreased slightly. Significant differences in the magnitude of the EUFs, but not ISMs, were found between critical effects, however, contrary to expected the average EUFs and ISMs for irritation were similar to those for more severe systemic effects. The nature of the POD affected the ISMs and EUFs only slightly and less than expected. Both EUFs and ISMs showed a weak but significant negative correlation with the amount of available toxicological data, measured as the number of relevant publications in PubMed, whereas SCOEL statements on data sufficiency had no influence. Overall, the most striking difference was that between EUFs and ISMs, the former being on average 2.1 times higher.

Key words: *Assessment factor; regulatory toxicology; risk assessment; risk management; safety factor*

Copyright © All Rights Reserved
Not for Sale or Commercial Use
Unauthorized use prohibited. Authorized personal view and print is a single copy

Contents

Introduction 791
Method 793
Statistical analyses 794
Results 794
Discussion 795
Acknowledgements 798
Declaration of interest 798
References 798

Introduction

Occupational exposure limits (OELs) aim to protect workers from exposure airborne chemicals at levels that might compromise their health. Various organisations develop or issue OELs and the legal status and policy claims of the different OEL systems vary. A common feature is that the OELs are maximum allowable concentrations expressed as time-weighted averages (TWAs). The most common type of OEL is the 8-h TWA, but

Short Term Exposure Limits (STELs, usually 15-min) and Ceiling Limits (CL, often 5-min) are also frequent.

An important organisation that issues OELs is the American Conference of Governmental Industrial Hygienists (ACGIH) which was formed in 1938. ACGIH is a professional

Address for Correspondence: Linda Schenk, Division of Philosophy, Teknikringen 78b, 10044 Stockholm, Sweden. Telephone +46 8 790 9520 E-mail: schenk@kth.se

(Received 24 April 2010; revised 07 July 2010; accepted 07 July 2010)

ISSN 1040-8444 print/ISSN 1547-6898 online © 2010 Informa Healthcare USA, Inc.
DOI: 10.3109/10408444.2010.507628

RIGHTSLINK

Critical Reviews in Toxicology Downloaded from informahealthcare.com by (ACTIVE) Karolinska Institutet University Library on 01/12/11
For personal use only.

association of industrial hygienists and practitioners of related professions.. When the first list of its Threshold Limit Values (TLVs) was published in 1946 it became the single most influential actor in the area of OELs (Piney, 1998). The TLVs were adopted by several national authorities during the 1960′s and 1970′s, many of which now have their own procedures for setting of OELs (Piney, 1998). From the 1990′s and on the EU has begun to issue OELs. Most of the EU OELs are indicative values (IOELV). Although the numerical values are not mandatory, the IOELVs play an important role as they have to be considered by the member states when implementing the work environment legislation at the national level. A few of the OELs are binding values (BOELV), and these (or lower values) must be integrated in the national legislation. The BOELVs are not further considered in this paper as they are of a more administrative character than IOELVs.

The European Commission adoption of IOELVs is based on scientific advice from a committee of independent experts, the Scientific Committee on OELs (SCOEL). In developing proposals for health-based OELs the SCOEL produces so called summary documents. When possible the SCOEL uses recent criteria documents from other standard-setters as a starting point for the evaluation. Thus, the SCOEL frequently uses documents produced by the Dutch Expert Committee on Occupational Standards (DECOS), the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG), and the Nordic Expert Group (NEG). The DECOS is an advisory committee to the Health Council of the Netherlands, which produces recommendations and documentations for health-based OELs. The documents are available in English and can be downloaded via the webpage of the Health Council of the Netherlands (www.gezondheidsraad.nl, July 1, 2010). The DFG is a self-governing research funding organisation in Germany, and it is a commission under the DFG that gives proposals for health-based OEL, known as Maximale Arbeitzplatzkonzentrationen or MAK-values. The DFG also publishes scientific substantiation for these recommendations, in both German and English. The DFG documents are published in the series *Essential MAK Value Documentations*, previously called *Occupational Toxicants*. The NEG is a collaboration between the Nordic countries Denmark, Finland, Norway and Sweden. The purpose of this group is to produce extensive documentation on chemicals that can be used by the national administrations to set OELs. The scientific expertise is collected from the four participating countries. The NEG criteria documents are published in English in the series *Arbete och Hälsa* [Work and Health] and can be downloaded via the NEG homepage (www.nordicexpertgroup.org, July 1, 2010).

The setting of a health-based OEL starts with a review of toxicological data to identify health effects of concern and a point of departure (POD). The POD is the starting point for the extrapolation from toxicological data to an exposure limit. The POD can take several forms but is a quantification of some sort of exposure in relation to an adverse effect, based on empirical data. The POD might be derived from epidemiological studies, from controlled exposures of human volunteers or, often, from experimental animal data. In cases where the exposure is well controlled or well known, such as human and animal experiments, the lowest observed adverse effect level (LOAEL) or, preferably, the no observable adverse effect level (NOAEL) is commonly used as the POD. Another approach to determine a POD is the Benchmark Dose (BMD) approach, first suggested by Crump (1984). This method uses the complete data set for each end-point, unlike the NOAEL approach, to derive a model with which an acceptably low effect level can be calculated. The POD might need correction for differences in duration and route of exposure, for example when based on oral toxicity data.

The response of the (working) population to chemical exposure, and hence also the POD, is associated with variability as well as uncertainty. The susceptibility to a chemical exposure may vary both within and between species, and the less available data, the larger degree of uncertainty. There might also be uncertainties regarding the reliability and relevance of the database, with respect to exposure assessments, confounding factors etc.

In order to address variability and uncertainty some regulators apply predefined uncertainty or assessment factors (hereafter called uncertainty factor, UF). This practice started in the area of food safety and historically the explicit use of UFs has, at least until recently, been uncommon in the area of occupational hygiene. In food safety, a total UF of 100 (10 for interspecies uncertainty time 10 for interspecies variability) is commonly used to derive an exposure limit or guidance value (e.g. Acceptable Daily Intake, ADI). Another factor of 10 is recommended to use if the exposure limit (e.g. ADI) is based on a LOAEL instead of a NOAEL. The factor of 100 when departing from an animal NOAEL to derive an exposure limit for human was first suggested by Lehman and Fitzhugh (1954). Although the 10-fold factors have been shown to be protective for the average chemical (Dourson and Stara, 1983) the approach of multiplying factors of 10 has been challenged repeatedly since the 1950′s, since it neglects several important aspects that may vary between chemicals, e.g. the slope of the dose-response relationship, the sample size and the variability in response (e.g. Pohl and Abadin, 1995; Dourson et al., 1996; Vermeire et al., 1999; Dorne and Renwick, 2005). ICPS (2005) proposes that whenever possible, chemical specific UFs should replace the default factors, taking known differences in toxicokinetics and toxicodynamics into account. This approach might yield UFs lower (as for instance in Dourson et al 1998) or higher than the default UFs of 10.

In the SCOEL guidance note (SCOEL, 1999; 2009) UFs are mentioned as the means used for extrapolation but no numerical recommendations are given. Aspects that these UFs should cover according to the SCOEL are: nature and severity of the critical effect (e.g. local or systemic effect), nature of the POD, (e.g. animal or human data, NOAEL or LOAEL), known species differences, consistency (i.e. agreement between different toxicity data sets), slope of the dose response curve and information on absorption, distribution, metabolism and excretion (ADME). The SCOEL contrasts

RIGHTSLINK

Critical Reviews in Toxicology Downloaded from informahealthcare.com by (ACTIVE) Karolinska Institutet University Library on 01/12/11
For personal use only.

its use of UFs on a case-by-case basis with the UFs of 10, 100 or 1000 (where 100 is the default) used to derive limit or guidance values for the general public. The SCOEL also argues that UFs used to derive OELs should be lower than the ones applied when setting guidance values for the general population. The arguments are that (1) workers are less heterogeneous than the general population and do not include the very old and young, implying less variability, (2) workers are not exposed for a full life time, but for 8h/day, 5 days /week 204 days/year up to 45 years, and (3) workers' health may be controlled by occupational health surveillance and monitoring programs. The guidance note further gives advice on how to define an adverse effect, how to identify the critical effect and which kind of information that is relevant for the derivation of an OEL.

There are some previous studies concerning the use of UFs when setting OELs. Fairhurst (1995) presented an analysis of health-based OELs for 24 substances set in the UK between 1990 and 1993. For these OELs the severity of the critical effect seems to have had some influence on the UF. Hansson (1997) calculated the ratio between the POD and the OEL for Swedish OELs based on human data, and found an unsatisfactorily distinction between LOAELs and NOAELs. Roach and Rappaport (1990) analysed the references and the implicit safety margins of the 1976 Threshold Limit Value (TLV) Documentation from the American Conference and Industrial Hygienists and concluded that the TLVs had a stronger correlation to the measured exposure in industry than to the levels associated with negative health effects. A review of different approaches to the application of UFs is also presented by Paustenbach (2002), with examples of historical practice mainly derived from US based organisations and authorities.

One aspect of setting pro-active OELs is they to a larger extent will be substantiated by animal data. For many substances data on human exposures are not available, or only concern short-term and/or low-level exposures. This emphasises the need for a well-functioning and transparent manner of extrapolation from the POD to derive an OEL. The aim of this study was to investigate to what extent the SCOEL uses explicit uncertainty factors (EUFs) when deriving health-based IOELVs. The EU-SCOEL values were chosen as they are implemented across Europe and thus warrant extra interest compared to national OELs. In cases when the EUF is not given in the summary document, we calculate an Implicit Safety Margin (ISM) as the ratio between the POD and the OEL (see Methods for a more detailed description). We further investigate whether date of the SCOEL recommendation, the type of critical effect, the nature of POD and the amount of available data influences the magnitude of the EUFs and/or ISMs.

Method

The summary documents analysed in this study have been produced by either the SCOEL or its predecessor the scientific expert group (SEG). Seventyfive IOELVs, described in 62 summary documents were used. For 3 substances SCOEL documents have been published but were not available to the authors. For another 12 IOELVs, no SCOEL or SEG documentation has been published. For yet another 12 substances, the SCOEL has more recently published updated summary documents where the OEL recommendations deviate from the IOELVs in the directives. Since the old documents were not available to us, these substances have also been excluded. The summary documents issued by the SCOEL are numbered and documents included were: 2, 3, 5-13, 16-26, 28-30, 33-42, 44, 45, 49-52, 54-56, 58, 65-70, 73, 74, 76, 79, 81, 91, 93, 95, 99-101. Many of the SCOEL summary documents are available through the website of the European Commission (ec.europa/social/keyDocuments.jsp?langId=en, April 22, 2010).

The SCOEL documents were first analysed used to identify any explicit UFs used and then to identify the POD used to derive an OEL. In cases where no EUF was stated in the summary document, an implicit safety margin (ISM) was derived by dividing the POD by the OEL. It should be taken into account that the ISMs calculated in this paper are affected by the preferred value approach of the SCOEL, i.e. the use of decimals of the integers 1, 2 or 5. If the POD was obtained from an oral animal study, the corresponding concentration in air was calculated assuming 100% absorption via both routes (oral and inhalation), a human (worker) body weight of 70 kg and a total ventilation of 10 m^3 per 8 hour work-shift (ECHA, 2008).

If not explicitly stated in the summary document, we assigned as POD the critical effect and its NOAEL or LOAEL that the document states that the OEL is primarily aimed at preventing. Some documents identify several effects of concern, in those instances we used as critical effect the one appearing at the lowest dose-level.

In order to analyse possible time trends, the UFs and ISMs were compared in relation to the year of adoption the SCOEL summary document. The handling of intra- and interspecies variation was elucidated by categorizing the ISMs according to the nature of POD, i.e. whether it was an effect or no effect level and whether it was based on animal or human data. The PODs were also categorized by the duration of the exposure using four categories were identified, acute (exposures < 8 h), sub-acute (>2 wk), sub-chronic(>3 mo) and chronic (>1 y or occupational exposure). Consideration was also given to the duration of exposure in studies cited as supporting the POD. For instance if the POD was derived from a subchronic study, but supported by chronic data, the POD was categorized as chronic. The ISMs and EUFs were also categorized according to the type of critical effect.

It is further of interest to investigate to what extent data richness influences the EUFs and ISMs. We used four proxies for data richness, the first being a binary classification of whether the summary documents contain an explicit statement in lack of data or not. The second proxy was the number of references in the summary document from which the EUF or ISM was derived. Thus we assumed that the number of references is proportional to the amount of available data, although some,

RIGHTSLINK

Critical Reviews in Toxicology Downloaded from informahealthcare.com by (ACTIVE) Karolinska Institutet University Library on 01/12/11
For personal use only.

but not all, of the SCOEL summary documents rely on full criteria documents and hence only include key references. The third proxy was the number of relevant studies available at the time when the summary document was developed. This number was obtained for each substance by searching the PubMed toxicology subset with the conditions that the chemical name (including synonyms given in the summary document) should be present in the title and that the paper should be published at least one year prior to the SCOEL summary document. The searches were performed between February 8 and February 12, 2010. The PubMed search lists were filtered manually from non-relevant papers, for instance papers on production of the chemical, use-efficiency, analytical chemistry or with other chemicals with similar names. For substances with more than 200 hits, the total number of publications was estimated by manual analysis of 100 papers, selected as five random samples of 20 consecutive hits. For instance the search '((((Phenol[Title]) OR benzenol [Title]) OR carbolic acid [Title]) OR hydroxyl benzene [Title]) AND "0"[Publication Date] : "2002"[Publication Date]' yielded 1071 hits after limiting to the subset topic toxicology. A manual analysis of papers 21-40, 181-200, 461-480, 940-960 and 1041-1060 indicated that 47% of these papers were relevant. Hence the number of available publications was estimated to be 503. A fourth proxy of data richness was whether information on ADME is given in the OEL document or not. Again, we used a binary classification scheme for this purpose. Common features of these quantitative measures are that they do not give any indication of the quality of the available data, nor of the agreement between data sets.

Statistical analyses

Trends were analysed by linear regression analysis using log transformed ISM and EUF values. The difference between two categories was tested with Welch's t-test while differences between more than two categories were tested by ANOVA, again using log transformed values. The software used for the analyses was R (version 2.6.2).

Results

The SCOEL summary documents cover a publication range of 13 years, from 1991 to 2003. In total, 44 EUFs were retrieved and 31 ISMs were calculated. The SCOEL states that UFs should be given for every OEL recommendation; however, in approximately one third of the documents no UF is explicitly stated. The EUFs are on average 2.1 times higher than the ISMs, the geometric means being 4.6 and 2.2, respectively ($p < 0.0001$ in Welch's t-test on log-transformed values). There is also a noticeable difference in variability between EUFs and ISMs; EUFs ranged from 1 to 50 while the ISM ranged from 1 to 5.

No clear trends over time are seen in fig 1. However, a linear regression analysis of the log-transformed values indicates that the ISMs are subject to a decreasing trend, not seem for the EUFs, or the two combined (ISM $r^2 = 0.13$, $p = 0.04$; EUF $r^2 = 0.03$, $p = 0.29$; combined $r^2 = 0.02$, $p = p = 0.24$; fig 1). The use of EUFs relative to ISMs seems to have decreased over time, but this is not a statistically significant observation ($r^2 = 0.29$, $p = 0.07$, linear regression analysis).

One might expect that less severe effect such as irritation results in lower ISMs and EUFs. With respect to irritation, one might also expect the ISM or EUF to be lower because the effect level can be determined with more accuracy and because animals and humans are more likely to respond similarly to local effects that are not affected by metabolic or toxicokinetic differences (ECHA, 2008). Contrary to this expectation, no obvious difference was found for neither ISMs, nor EUFs, between the different kind of critical effects (ISM: $p = 0.87$ EUF: $p = 0.11$ in ANOVA using log-transformed values; fig 2). As there only are 3 to 13 observations for category of systemic critical effect, a detailed analysis of the sensitivity of the end-points within each such category was not deemed purposive. It was not possible to separate the influence of the sensitivity of the end-point within each category from other factors as lack of human data, LOAEL to NOAEL extrapolation and lack of long term data.

Thirtyone of the IOELVs are based on human data. Of the remaining 44 IOELVs based on animal data, 12 are based on LOAELs. In fig 3 the ISMs and EUFs are compared depending on the nature of the POD. The EUFs and ISMs associated to PODs derived from animal data are expected to be comparatively higher than those associated to a human POD. In addition, ISMs and EUFs associated to LOAEL-based POD are expected to be higher than those associated to NOAEL-based PODs. These expectations were met only to some degree in the statistical analyses performed with ANOVA on log-transformed values. Thus, no significant differences between any of the four categories of PODs (human / animal / NOAEL / LOAEL) are seen in a combined analysis of EUFs and ISMs ($p = 0.08$). However separate analyses show that ISMs based on animal LOAELs are significantly higher than ISMs based on human NOAELs ($p = 0.0007$ in ANOVA on log-transformed values) and that EUFs based on animal data are on average higher than EUFs based on human data ($p = 0.02$ in ANOVA on log-transformed values), regardless of whether the POD is a LOAEL or a NOAEL. However, the detected differences are not as pronounced as expected, as the lower bound of the ISMs and EUFs for all four categories are within a factor of 3.

In fig 4 the ISMs are categorized according to duration of exposure of the POD study. The distribution of the ISMs over these categories are opposed to the expected, as the higher ISMs are associated to chronic data and IOELVs substantiated only by acute data have among the lowest ISMs. This negative trend is significant for the ISMs ($p = 0.03$) but not so for EUFs ($p = 0.15$). One likely explanation is that the IOELVs substantiated by acute data are mainly related to irritation effects, as the trend was weakened by removing these IOELVs ($p = 0.53$ for ISMs and 0.86 for EUFs, in ANOVA on log-transformed values).

For 23 of the 75 IOELVs a lack of data for the substance at hand was stated in the summary document. The magnitude of the EUFs was the same regardless of whether lack of data

RIGHTSLINK

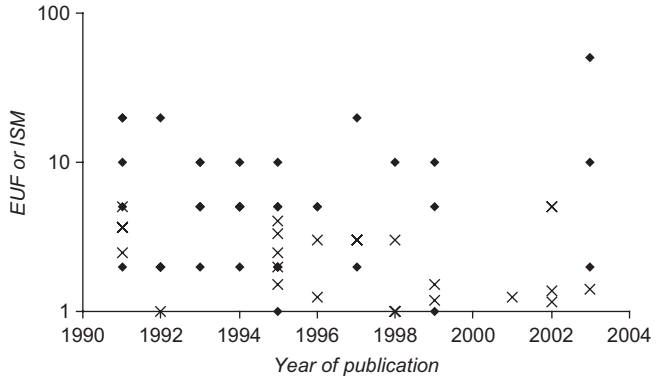


Figure 1. Explicit Uncertainty Factors (EUF, ♦) and Implicit Safety Margins (ISM,×) versus year of the publication of the SCOEL summary document.

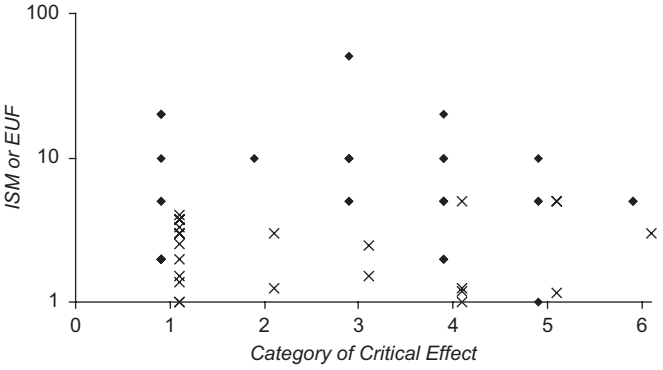


Figure 2. Comparison of the Explicit Uncertainty Factors (EUF, ♦) and Implicit Safety Margins (ISM, ×) based on critical effect, number of IOELVs in parentheses: 1-Irritation (32), 2-hematotoxic effects (3), 3-Liver and kidney toxicity (9), 4- Neurotoxicity (13), 5- Damage to airways and lungs (7), 6- weight loss (4). Critical effects represented by only one substance or IOELV are not included.

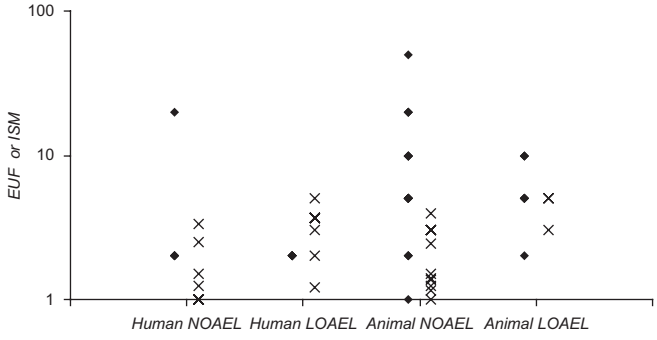


Figure 3. Comparison of the Explicit Uncertainty Factors (EUF, ♦)and Implicit Safety Margins (ISM, ×) based on nature of point of departure.

was stated or not (geometric means 4.9 (n=14) versus 4.5 (n=30), p=0.79 in Welch's t-test on log-transformed values). Also the ISMs were the same (geometric means 2.2 (n=9) versus 2.2 (n=22), p=0.99 in Welch's t-test on log-transformed values), as was the combination of the two (geometric means 3.6 (n=23) versus 3.3 (n=52), p= 0.74 in Welch's t-test on log-transformed values). Thus it seems as statements on data sufficiency do not affect the size of ISMs or EUFs.

Assuming that the proxies of data richness are representative, one would expect negative relationships between these and the EUFs and ISMs. Considering number of cited references (second proxy), no such relationship is seen (fig 5), linear regression analysis on log-transformed values yields r^2=0.059 (p=0.11) for EUFs, r^2=0.00004 (p= 0.97) for ISMs and r^2=0.03 (p=0.12) for the combined. However, the number of citations has increased over time (fig 6, r^2=0.31, p<0.001 in linear regression analysis). With respect to number of available references (third proxy), a weak negative relationship is indeed seen, the r2 values being 0.16 (p=0.008), for ISMs 0.24 (p=0.004) and for the combined 0.14 (p=0.0009), linear regression analysis on log-transformed values. A slightly different search strategy (human data only as opposed to all species, substance name as general search term and not only in the title) gave no significant correlations.

Considering the fourth proxy, data on ADME and e.g. species differences therein, is expected to reduce the uncertainty allowing for lower safety margins. The 32 IOELVs for which the critical effect is irritation would be an exception, as ADME with few exceptions is not expected to significantly alter this direct, local effect. Of the remaining 43 IOELVs with a critical effect other than irritation, 13 had a section on ADME. The geometric means of the EUFs and ISMs having an ADME description (4.8 (n=7) and 2.1 (n=6), respectively) are somewhat lower than those lacking a description (5.8 (n=21) and 1.8 (n=9), respectively). For the two combined the geometric mean of those 13 with an ADME description is 3.3 and 4.1 for those 30 without. However the differences are not statistically significant (p=0.71 for EUFs, 0.64 for ISMs and 0.47 for the combined in Welch's t-test on log-transformed values), and rather suggests that the presence or absence of ADME data do not affect the size of the EUFs and ISMs.

Discussion

In this study we attempted to investigate how the SCOEL explicitly and implicitly uses UFs and how the magnitude of these is affected by the quality of the data base. Surprisingly the most obvious influential factor is the use of explicit UFs. Thus, the EUFs are on average (expressed as ratio of geometric means) 2.1 times higher than the ISMs. A potential explanation could be that the EUFs were used selectively by the SCOEL, e.g. predominantly for chemicals with limited toxicity data base (e.g non-inhalation data or acute toxicity data only), with more severe critical effects, or with animal data suggesting flatter dose-response curves. However, we could not find any textual support for this interpretation. It should be noted that we did not attempt to analyze the steepness of the dose-response, as this fell outside the scope of the study. Stouten et al. (2008) suggested that the introduction of EUFs was a major reason why the reassessment of the Dutch OEL list from 1994 led to markedly lower OELs for 79% of the reassessed health-based OELs. In these reassessments the uncertainty factor most often used to cover within and between species variation was 9. Haber and Maier (2002) discovered that differences in methodology and scientific

Critical Reviews in Toxicology Downloaded from informahealthcare.com by (ACTIVE) Karolinska Institutet University Library on 01/12/11
For personal use only.

RIGHTSLINK

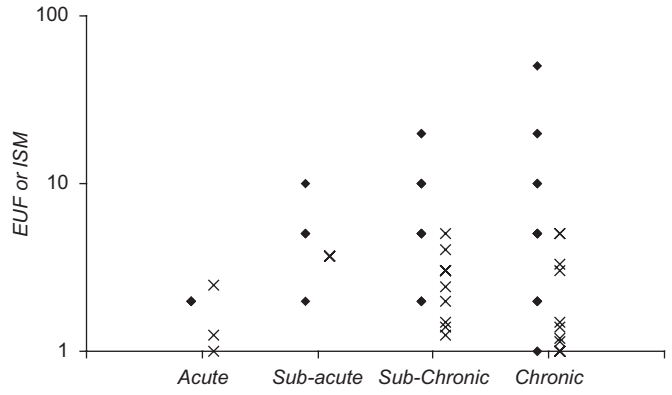


Figure 4. Comparison of the Explicit Uncertainty Factors (EUF, ♦) and Implicit Safety Margins (ISM, ×) based on duration of exposure in the point of departure.

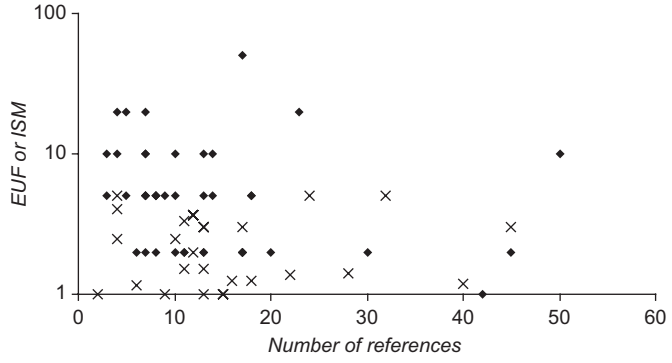


Figure 5. Explicit Uncertainty Factors (EUF, ♦)and Implicit Safety Margins (ISM, ×) versus the number of references in the document.

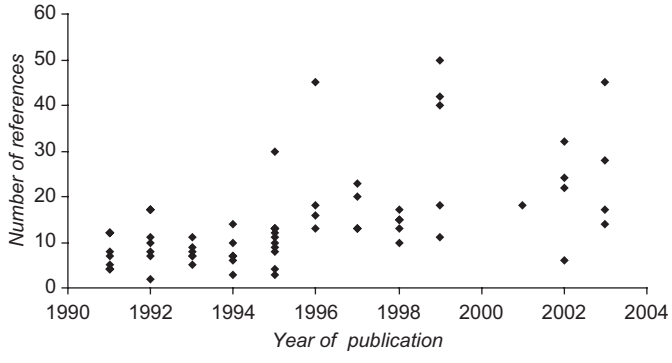


Figure 6. Number of references in the SCOEL summary documents versus year of publication.

policy lead to large variations in the OELs set for chromium, even when similar data was reviewed. They further recommended a number of scientific criteria for setting OELs. Two of the recommendations were to harmonise the approach for interspecies extrapolation and define default UFs.

It has previously been shown that OELs tend to be gradually decreased as they are revised (Schenk et al, 2008; Hansson, 1998). Furthermore, studies concerning limits for specific substances show that the OELs are lowered as more and better information on adverse effects becomes available (Markowitz and Rosner, 1995; Greenberg, 2004). In contrast to this observation, we saw no clear time-trend regarding EUFs and a weak decrease in ISMs (fig 1). The lack of a clear time-trend may be due to short observational time-span and/or the homogeneity of the expert composition (i.e. members) and scientific traditions in SCOEL.

Other factors alike, one would expect substances with the same critical effect to have the same EUFs and ISMs, the latter after correction for the preferred value approach. One would further, in line with the generic use of UFs (Falk-Filipson et al., 2007; Paustenbach, 2002; Vermeire et al., 1999), expect a relationship between the nature of the POD and the size of the EUFs and ISMs, with lower margins for NOAEL-, compared to LOAEL based OELs, inhalation data compared to other routes, human compared to animal data, chronic compared to subchronic data etc. Contrary to this expectation, no or small difference in margins were detected, regardless of the nature of the POD. For EUFs a difference was discernible between animal and human PODs but not between NOAELs and LOAELs. For ISMs the only difference identified was the one between animal-LOAEL and human-NOAEL PODs. However, these differences are not as pronounced as expected, as the lower bound for all categories of PODs are within a factor of 3. Hansson (1997) made a similar observation when analyzing a number of substances regulated by Swedish OELs, showing that the ISM differed only marginally between OELs based on a NOAEL and those based on a LOAEL. Further, the SCOEL EUFs and ISMs seem small to commonly suggested values (see e.g. Falk-Filipson et al., 2007; Vermeire et al., 1999), even after considering that intraspecies variability is expected to be smaller for the worker population compared to the general population. The relatively small UFs applied by the SCOEL compared to commonly suggested values have also been noted by Nielsen and Øvrebø (2008).

For 24 health-based OELs set in the UK between 1990 and 1993, an UF of 1 was used to derive OELs from human NOAELs from studies judged of high quality (Fairhurst, 1995). When the OEL was derived from a human LOAEL and the critical effect was of little health significance an average UF of 2 was applied. For OELs derived from animal NOAELs and LOAELs, the UFs used ranged from 2.5 to 11 and from 4 to 12, respectively. If the OELs were based on reproductive or teratogenic effects the average UF were higher, and the range of UFs wider (Fairhurst, 1995).

According to the introduction in the booklet of MAK values (DFG, 2009), a human NOAEL is generally considered as a suitable level for the MAK-value (ISM=1), whereas no MAK value is derived in cases where no NOAEL can be identified (DFG, 2009).. If the MAK value is based on an animal NOAEL "the MAK value is generally established at the level of half of this NOAEL [ISM=2], however, in some cases species differences in sensitivity to the substance must be taken into account" (DFG, 2009 p13). The MAK ISM of 2 is strikingly similar to the average SCOEL ISMs of 2 for chronic and 2.6 for subchronic animal PODs.

Critical Reviews in Toxicology Downloaded from informahealthcare.com by (ACTIVE) Karolinska Institutet University Library on 01/12/11
For personal use only.

RIGHTSLINK

Critical Reviews in Toxicology Downloaded from informahealthcare.com by (ACTIVE) Karolinska Institutet University Library on 01/12/11
For personal use only.

The duration of exposure in the POD seemingly affects the SCOEL safety margins in the opposite direction of the expected, as the highest EUFs and ISMs are associated with OELs derived from chronic PODs (fig 4). However, the unexpected trend is not discernible when OELs derived from human data and irritation PODs are removed from the graph. Both types of PODs require smaller UFs and both are more prevalent among the acute and subacute categories.

The most difficult aspect to assess and evaluate is the amount of available knowledge. To this end, two different continuous measures of available knowledge are included: (1) number of references in the summary document and (2) the number of available toxicology publications on the substance of interest up to the year previous to the publication of the summary document. The first measure might be a weak indicator from a theoretical point of view as one may expect that the most studied substances are addressed in a higher number of scientific publications, whereas they are at the same time more likely to be covered in a recent criteria document or other toxicological review paper. Since the SCOEL only includes the key bibliography (preferably a recent toxicological review along with the key papers) the relation between amount of knowledge and number of references could work in both ways. Accordingly, no correlation between number of references and EUF or ISM is found. However, the use of references in the summary documents seems to increase over time (fig 7). Regarding the number of available publications, relatively weak, but statistically significant negative correlations are found.

Two additional categorical measures related to available knowledge were given, namely explicit statements on data sufficiency and inclusion of data on ADME, the latter only applied on IOELVs based on animal data and non-irritation effects. Neither of the two measures appeared to affect the magnitude of the EUFs or ISMs. Thus, the results concerning the influence of available knowledge are conflicting as the EUFs and ISMs are seemingly independent of the SCOEL's own assessment of data sufficiency, yet on the other hand they correlate negatively with the number of available studies.

There are some indications that the explicit use of UFs might be increasing in the context of OELs, For instance, the DECOS decided in the 1990's to use UFs in their update of existing OELs (Stouten, 2008) The most clear-cut example is that of the new European chemicals legislation, commonly called REACH. The REACH guidance document (ECHA, 2008) has introduced a systematic use of UFs for deriving safe levels of chemicals for workers as well as the general population. For substances within the scope of REACH that are produced in quantities above 10 tonnes a chemical safety report has to be prepared. One of the requirements of the chemical safety report is to identify so called Derived No-Effect Levels (DNELs) for substances that have identifiable threshold effects. The DNELs do not have a regulatory power per se, but are meant to be used for risk communication and, along with exposure scenarios, for risk assessment and risk management purposes. In the guidance document (ECHA, 2008) workers are mentioned as a subpopulation that requires a specific DNEL, and an overview of how to derive worker-DNELs is given in chapter R.8, together with default UFs. The most obvious difference between working and general population is that of the default UF for intraspecies (population) variability which is 5 for the former and 10 for the latter group.

An additional UF of 3 to 10 should be used if the POD is a LOAEL instead of a NOAEL. Additional UFs are given for extrapolation from animal data to humans, other routes of exposure to inhalation and from short to long-term exposure. In view of the REACH guidance, the SCOEL EUFs and ISMs are strikingly low.

In conclusion, the EUFs and ISMs used by the SCOEL in the years 1991-2003 do not seem to be systematically predictable by any of the factors expected on a theoretical basis to cause differences in the magnitude of the ISMs. However, our analyses suggest that the safety margins become higher when UFs are explicitly used to derive the OELs. Explicit use of UFs also increases the transparency of the toxicological evaluation for OELs, as also pointed out by e.g. Haber and Maier (2002). The use of EUFs is therefore expected to increase in the future, a development in line with the ambition expressed also by the SCOEL in their guidance document (SCOEL, 1999; 2009).

In our opinion, the handling of uncertainty should be transparently documented in the summary documents, i.e. the UF or other methods of extrapolation should be openly stated. Hence, we think it is important to specify what kind of uncertainties are considered in the UF and also the weight given to each component of the uncertainty. Even though the UFs should be chemical specific to the extent that the available data allow, referring to expert judgment cannot justify a non-transparent documentation. Based on the data presented herein, we recommend that the SCOEL should develop and adhere to a more articulate framework for their use of UFs. The first step would be to define default numerical values for sub-factors that account for typical situations such as extrapolations from animal to human, from oral to inhalation and from sub-chronic to chronic exposures in the guidance document (SCOEL 1999, 2009). Secondly, the choice of

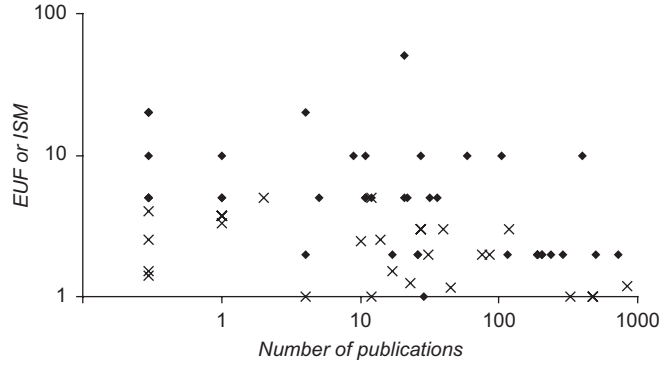


Figure 7. Explicit Uncertainty Factors (EUF, ◆) and Implicit Safety Margins (ISM,×) versus the number of toxicology publications with the substance name in the title published up to the year previous to the publication of the summary document. For seven substances no publications fulfilling the search criteria were available (plotted leftmost).

RIGHTSLINK

UFs and their rationales should be clearly described in the Recommendation sections of the SCOEL summary documents. Such efforts are likely to greatly enhance the consistency and transparency of the SCOEL recommendations.

Acknowledgements

We are grateful to Professors Christina Rudén and Sven Ove Hansson for valuable comments during the elaboration of this manuscript.

Declaration of interest

The work has been partly performed as part of an ongoing project financed by the Swedish Work Environment Authority with the aim to elucidate the methodologies to derive OELs and DNELs. The authors' affiliations are as shown on the cover page. Gunnar Johanson is a member of the SCOEL. The authors have sole responsibility for the content and writing of the paper.

References

Crump K.S. (1984) An improved procedure for low-dose carcinogenic risk assessment from animal data. J Environ Pathol Toxicol Oncol 5:339–348.

Deutsche Forschungsgemeinschaft [DFG]. 2009. List of MAK and BAT Values 2009, report No. 45 Weinheim: Wiley VCH Verlag.

Dorne JLCM, Renwick AG (2005) The refinement of Uncertainty/Safety factors in Risk Assessment by the Incorporation of data on Toxicokinetic variability in Humans. Toxicol Sci 86(1):20–26.

Dourson ML and Stara JF. (1983). Regulatory history and experimental support of uncertainty (safety) factors. Regul Toxicol Pharmacol 3:224–238.

Dourson ML, Felter SP, Robinson D. (1996). Evolution of Science-Based Uncertainty Factors in Noncancer Risk Assessment. Regul toxicol Pharmacol 24:108–120.

Dourson M, Maier A, Meek B, Renwick A, Ohanian E, Poirier K (1998) Boron Tolerable Intake - Re-evaluation of Toxicokinetics for Data-Derives Uncertainty Factors. Biological Trace Element Research 66:453–463.

European Chemicals Agency [ECHA]. (2008). Guidance on the implementation of REACH. Guidance on information requirements and chemical safety assessment Chapter R.8: Characterisation of dose [concentration]-response for human health.

Fairhurst S. (1995). The uncertainty factor in the setting of occupational exposure standards. Ann occup Hyg 39(3): 375–385.

Falk-Filipsson A, Hanberg A, Victorin K, Warholm M, Wallén M. (2007) Assessment factors--applications in health risk assessment of chemicals. Environ res 104(1):108–127.

Greenberg M. (2006). Revising the British Occupational Hygiene Society asbestos standard:1968-1982. Am J Ind Med 49(7):577–604.

Haber LT, Maier A. (2002). Scientific criteria used for the development of occupational exposure limits for metals and other mining related chemicals. Regul Toxicol Pharmacol 36:262–279.

Hansson SO. (1997). Critcal effects and Exposure Limits. Risk Analysis 17(2):227–236.

Hansson SO. (1998). Setting the Limit. Occupational health standards and the limits of science. New York: Oxford University Press.

ICPS–International Programme on Chemical Safety (2005) Chemical-specific adjustment factors for interspecies differences and human variability: guidance document for use of data in dose/concentration-response assessment. Available at: http://whqlibdoc.who.int/publications/2005/9241546786_eng.pdf (July 1, 2010)

Lehman AJ and Fitzhugh OG. (1954) 100-fold margin of safety. Bull Assoc Food Drug Offic 18:33–35.

Markowitz G, Rosner D. (1995). The Limits of Thresholds – Silica and the Politics of Science, 1935 to 1990. Am J Public Health 85(2):253–262.

Nielsen GD, Øvrebø S. (2008). Background, approaches and recent trends for setting health-based occupational exposure limits: A minireview. Regul Toxicol Pharmacol 51(3): 253–269.

Paustenbach DJ. (2000) The History and Biological Basis of Occupational Exposure Limits for Chemical Agents. In: Harris RL. Ed. Patty's Industrial Hygiene and Toxicology, 4th ed. Vol 3: part IV. New York: Wiley.

Piney M. (1998). Exposure limits and health risks arguments for a paradigm shift. In: Bal R and Halffman W., eds. The politics of chemical risk. Scenarios for a regulatory future. Dordrecht: Kluwer Academic publishers.

Pohl HR, Abadin HG. (1995). Utilizing uncertainty factors in minimal risk levels derivation. Regul Toxicol Pharmacol 22(2):180–188.

Roach SA and Rappaport SM. (1990). But they are not thresholds: A critical analysis of the documentation of threshold limit values. Am J Ind Med 17(6):727–753.

Schenk L, Hansson SO, Rudén C, Gilek M. (2008). Occupational exposure limits: A comparative study. Reg Toxicol Pharmacol 50:261–270.

SCOEL. (1999). Methodology for the Derivation of Occupational Exposure Limits. Key documentation. EUR 19253;

European Commission. Luxemburg:Office for Official Publications of the European Communities.

SCOEL. (2009) Methodology for the Derivation of Occupational Exposure Limits: Key Documentation (version 6). Available at: http://ec.europa.eu/social/BlobServlet?docId=4526&langId=en (July 1, 2010)

Stouten H, Ott H, Bouwman C, Wardenbach P. (2008). Reassessment of Occupational Exposure Limits. Am J Ind Med 51:407–418.

Vermeire T, Stevenson H, Peiters MN, Rennen M, Slob W, Hakkert BC. (1999). Assessment factors for human health risk assessment: a discussion paper. Crit Rev Toxicol. 29 (5): 439–490.

Critical Reviews in Toxicology Downloaded from informahealthcare.com by (ACTIVE) Karolinska Institutet University Library on 01/12/11
For personal use only.

RIGHTSLINK

View publication stats