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3 **A quantitative comparison of the safety margins in the European indicative occupational**
4 **exposure limits and the derived no-effect levels for workers under REACH.**
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Abstract

The new European Union (EU) REACH legislation requires Derived No-Effect Levels (DNEL) to be calculated for substances produced in quantities above 10 tonnes/year. Meanwhile, the setting of occupational exposure limits (OEL) continues both at the member state and the EU level. According to REACH, Indicative OEL Values (IOELVs) from the Commission may under some circumstances be used as worker-DNELs. On the other hand, worker-DNELs will be derived for several thousand substances, far more than the roughly 100 substances for which IOELVs have been established. Thus, the procedure to set health-based OELs may become influential on that of DNELs and vice versa. In this study, we compare the safety margins of 88 SCOEL recommendations with those of the corresponding worker-DNELs, derived according to the default approach as described in the REACH guidance document. Overall, the REACH safety margins were approximately six times higher than those derived from the SCOEL documentation but varied widely with REACH/SCOEL safety margin ratios ranging by two orders of magnitude, from 0.3 to 58 (n=88). The discrepancies may create confusion in terms of legal compliance, risk management and risk communication. We also found that the REACH guidance document, although encompassing detailed advice on many issues, including default assessment factors for species and route extrapolation, gives little quantitative guidance on when and how to depart from defaults.

Key words: Chemicals regulation, DNEL, IOELV, Occupational Exposure Limit, REACH, SCOEL.

Abbreviations: BOELV: Binding Occupational Exposure Limit values; DNEL: Derived No-Effect Levels; EU: European Union; IOELV: Indicative Occupational Exposure Limit; ISM: Implicit Safety Margin; LOAEL: Lowest Observable Adverse Effect Level; NOAEL: No Observable Adverse Effect Level; OEL: Occupational Exposure Limit; POD: Point of Departure; SCOEL: Scientific Committee on Occupational Exposure Limits; TAAF: Total Adjustment and Assessment Factor.

1 Introduction

1.1 OELs and SCOEL

Limiting the average concentration of certain airborne substances is one of the means authorities have to protect workers from harmful effects from chemicals. Occupational exposure limits (OELs) have been used since the mid 1900's for this purpose, and most industrialized countries have a national authority issuing lists of OELs on a regular basis. A relatively new actor on this arena is the European Union (EU), and since 1991 lists of indicative and binding OEL values are set within the union. Indicative OEL values (IOELV) are only set for substances for which an effect threshold can be identified and such values are claimed to be purely health-based. Binding OEL values (BOELV) are set according to more pragmatic principles including a toxicological evaluation as well as issues of feasibility. As the name implies, the IOELVs are not mandatory and the member states may implement them at higher, equal or lower numerical values in their national legislations. In contrast, the BOELVs must be implemented at the same or a lower level (i.e. providing the same or a higher safety margin). The scientific substantiation of these OELs is produced and documented by the Scientific committee on Occupational Exposure Limits (SCOEL) or, for documents produced before 1995, its predecessor the Scientific Expert Group (SEG). The SCOEL is a multinational group of independent scientific experts from different fields with relevance for the setting of OELs. Substances are selected for evaluation by the SCOEL by the Directorate-General for Employment, Social Affairs and Equal Opportunities. For the priority setting criteria such as availability of data, severity of effects and number of persons exposed are taken into account. A methodological description on how to derive the OEL recommendations was first published in 1998 and has since been updated (SCOEL, 2009a). This "SCOEL Key Document" includes guidelines on data selection, identification of critical effect

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3 and point of departure (POD) and which factors may be taken into account when extrapolating
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5 from a POD to an OEL. According to SCOEL, uncertainty is handled by the application of
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7 uncertainty factors, henceforth called assessment factors (AFs) in concordance with the
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9 nomenclature in the REACH guidance document (ECHA, 2008). The SCOEL guidance gives no
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11 numerical recommendations for AFs but lists a number of aspects of uncertainty that might need
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13 consideration. The SCOEL recommendations should also adhere to a preferred value approach,
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15 i.e. decimals of the integers 1, 2 or 5. The preferred units are ppm for gases and vapors and
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17 mg/m³ for particles (SCOEL, 2009a). The SCOEL's use of uncertainty factors is also discussed
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19 in Schenk and Johanson (2010).
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27 *1.2 REACH and DNELs*

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29 In December 2006 the proposition for the new chemicals legislation within the European
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31 Community was passed by the European Parliament and the Council of the European Union. It
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33 entered into force on the first of July 2007 (European Commission, 2006). REACH, which is the
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35 common name of this new legislation, stands for regulation, evaluation and authorization of
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37 chemicals. Under REACH the burden of proof of ensuring that risk to man and environment is
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39 adequately controlled is transferred from the member states to the industry. This legislation
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41 together with accompanying guidance documents sets a framework on how to perform risk
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43 assessment including recommendations on how to produce basic information about the
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45 chemicals that are on the market today. For substances within the scope of REACH that are
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47 produced or imported in annual quantities above 10 tonnes, a chemical safety report has to be
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49 prepared. One of the requirements of this report is to identify so called Derived No-Effect Levels
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51 (DNELs) for substances that have identifiable threshold effects. DNELs are to be seen as tools
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3 for task-specific risk assessment, to evaluate different exposure scenarios and identify allowable
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5 uses according to REACH. Thus, if the estimated exposure does not exceed the DNEL the risk of
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7 the substance can be considered as adequately controlled. For substances such as genotoxic
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9 carcinogens or sensitizers, which may cause effects with no threshold, or no identifiable
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11 threshold, so-called Derived Minimal Effect Levels (DMELs) are to be derived. A DMEL should
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13 correspond to a risk level “which is considered to be of very low concern”, the cut-off level
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15 between concern and low concern is suggested to be a life time cancer risk in the region of 10^{-5}
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17 and 10^{-6} . Guidelines on how to derive these DNELs and DMELs, including recommended AFs,
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19 are specified in the REACH guidance document chapter R.8 (ECHA, 2008). Workers are
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21 regarded as a subpopulation that requires specific DNELs, and the framework of how to derive
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23 such worker-DNELs is also given in chapter R.8. The most obvious difference compared to the
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25 general population is that the interindividual (intraspecies) variability is considered to be smaller,
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27 hence a default intraspecies AF of 5 is given for workers versus 10 for the whole population.
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36 REACH hence puts another set of actors (producers and importers of chemicals) on the stage of
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38 worker protection. The worker-DNELs show many similarities with national legislative OELs,
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40 which prompts the need for discussions on how national regulations on the work environment
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42 should relate to the REACH legislation. This is of special concern in the hypothetical, but not
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44 unrealistic, case that the OEL for a chemical differs from the worker-DNEL and the exposure
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46 exceeds one of them but not the other. Gromiec (2008) compared the procedure of setting Polish
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48 OELs with the derivation of worker-DNELs and concluded that although the process of
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50 toxicological evaluation are similar the final values might be quite different. While the worker-
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52 DNELs are derived by manufacturers and importers, national OELs are developed by
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3 governmental agencies, thus the source and responsibilities differ significantly. As both selection
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5 criteria and legal demands differ, the number of substances with a worker-DNEL is expected to
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7 exceed by far the number of substances with a national and/or a European OEL in the
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9 foreseeable future. Further, as each registrant is responsible for deriving DNELs, several
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11 different worker-DNELs might be derived for the same substance. Thus, an important task for
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13 national work environment agencies in the near future will be to decide how to relate to worker-
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15 DNELs in their legislation.
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22 There is also a more direct connection between the worker-DNELs and the IOELVs. If a health-
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24 based OEL such as a SCOEL IOELVs exists for a substance and if there is no new scientific
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26 information contradicting that OEL, the industry is not required to perform its own evaluation,
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28 but can use the OEL as a worker-DNEL. Registrants can however not use the binding European
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30 OELs as a worker-DNEL since those are determined with heed to issues of feasibility, but need
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32 to perform their own scientific evaluation for these substances (Appendix 8-13 in ECHA, 2008).
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39 The bases for OEL and worker-DNEL setting follow similar procedures of literature review,
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41 hazard assessment and characterization of dose-effect and dose-response relationships. However,
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43 while OELs are generally based on data published in the scientific literature, the REACH
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45 registrants may use internal, non-published data as a basis for their DNEL derivations. The dose-
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47 response relationship provides a POD from which an exposure limit can be extrapolated. The
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49 POD can take several forms but is a quantification of exposure. This POD might be derived from
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51 epidemiological studies, but more often from animal or, occasionally, human experimental data.
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55 In the latter cases the POD often corresponds to the no observed adverse effect level (NOAEL)
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3 or the lowest observed adverse effect level (LOAEL). In the details there are, however, a number
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5 of significant differences between the processes leading to the setting of an OEL and a worker-
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7 DNEL, respectively. The main difference is the use of specific adjustment and assessment
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9 factors in the REACH framework contrasting the current praxis of case-by case decision among
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11 OEL expert groups such as the SCOEL. In REACH several AFs are combined to cover the
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13 different aspects of uncertainty covered in the framework of ECHA (2008). The guidance
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15 document distinctly presents default values for these AFs, while also stating in more general
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17 terms that chemical-specific assessment factors (CSAF) should be used provided that sufficient
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19 knowledge is available. The praxis among OEL setters varies, but generally the safety margins
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21 seem to be low compared to other regulatory areas (Nielsen and Øvrebø, 2008; Schenk and
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23 Johansson, 2010). Another difference between current OEL and REACH practices is that
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25 between critical effect and leading effect (ECHA, 2008). The OEL hazard assessment basically
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27 aims at identifying the critical effect, i.e. the first adverse effect that appears as dose (or exposure
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29 level) increases. The underlying assumption is that if exposure is kept below the critical effect
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31 level, neither the critical effect, nor other more serious effects will appear. In contrast, in the
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33 derivation of DNELs according to the REACH framework several, endpoint-specific DNELs
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35 have to be calculated, one for each identified adverse health effect and relevant exposure route.
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37 The lowest of the endpoint-specific DNELs for each relevant exposure route is then chosen as
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39 the final DNEL, the corresponding effect being called the leading effect.
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3 general population. Uncertainty can for instance be the lack of knowledge on how observations
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5 in animals translate to humans or how well an experimentally derived dose-response
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7 relationship, with its dependence on dose-spacing and limitations in statistical power, is related
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9 to the true dose-response relationship.
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15 The aim of this paper is to compare quantitatively SCOEL health-based OEL recommendations
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17 and worker-DNELs with respect to the safety margin to the POD as identified by the SCOEL.
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20 21 22 **2 Method** 23

24 The scrutiny covers SCOEL summary documents with recommended health-based OELs
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26 adopted before 2009. The documents were included disregarding whether the recommendations
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28 had yet been included in an EU Directive on IOELVs. Binding OELs were not included as these
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30 are not derived by SCOEL and because registrants will not be able to use them as DNELs. A list
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32 of SCOELs summary documents is available at the SCOEL website (SCOEL, 2009b). In 2009,
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34 125 summary documents had been finally (n=120 of which 5 under revision) or provisionally
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36 (n=5) adopted by SCOEL. In addition, 39 summary documents were under preparation. Some
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38 summary documents cover several substances or isomers, giving rise to similar health effects. If
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40 the POD and the OEL were the same, only one DNEL was derived from such a document. In
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42 some cases (n=20) the SCOEL was unable to recommend a health-based OEL, such documents
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44 could obviously not be used in our study. One document was excluded because it concerned only
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46 a biological limits value (BLV), and an additional 6 documents were not available to the authors.
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49 In total we were able to extract a POD for 88 health-based OEL recommendations from 87
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60 different summary documents. Of these, 10 are not yet represented by an IOELV.

2.1 Calculation of SCOEL implicit safety margins

In many summary documents, the SCOEL does not explicitly define the choice of AFs. An implicit safety margin (ISM) was therefore calculated by dividing the POD with the corresponding OEL. For instance, if a POD was defined at 100 ppm and the recommended OEL was set at 20 ppm, we calculated an ISM of $100/20 = 5$. It should be noted that the ISM is affected not only by implicit or explicit AFs, but may also be slightly influenced by SCOEL's adherence to the preferred value approach.

2.2 Derivation of REACH total adjustment and assessment factors

Apart from the POD itself, additional information is needed to derive the DNELs. These pieces of information, including information about the critical effect, LOAEL or NOAEL, tested species and exposure conditions, were also extracted from the SCOEL summary documents. The POD was then adjusted according to the guidelines on adjustment of the dose-descriptor in ECHA (2008), and AFs applied for extrapolation to the worker-DNEL (table 1).

The aspects considered, briefly described in the following sections, are:

1. Adjustment of the POD, including:
 - Route to route extrapolation
 - Allometric scaling
 - Correction for exposure conditions
 - Correction for differences in respiratory volume
2. Extrapolations, including:
 - Additional interspecies differences

- Intraspecies differences
- Differences in exposure duration
- Issues related to dose-response
- Quality of the database

Route to route extrapolation

The worker-DNEL should address human inhalation exposure. If the POD is from a different exposure route (e.g. oral or dermal) a route to route extrapolation must be performed. A default factor of 2 is introduced to account for differences in absorption between different routes, i.e. assuming 50% absorption for the tested exposure route and 100% absorption for inhalation. As with other defaults, this factor can be set to other values if empirical data so suggest. Other default assumptions on route to route extrapolation for workers are a body weight of 70 kg and a breathing volume of 10 m³ during 8h.

Allometric scaling

Allometric scaling is introduced to account for differences in metabolic rate between species. If the POD is from a human inhalation study, or from an animal inhalation study and the bioavailability can be assumed to be equal in humans and the tested species, no allometric scaling is needed. However, if the POD is from a study with oral or dermal exposure, different adjustment factors are required depending on species, e.g. dog 1.4, rabbit 2.4 and rat 4 (table R.8-3 in ECHA, 2008).

Correction for exposure conditions

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3 In instances where the exposures differ from 8h/day the dose descriptor is to be corrected using
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5 Haber's law: $C^n \times t=k$, where C denotes the concentration, t the duration of exposure and k is a
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7 constant. When adjusting from shorter to longer exposure, for instance 6h/day to 8h/day, n=1 is
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9 used, from longer to shorter, for instance continuous exposure to 8h/day, n=3 is used.
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14 15 *Correction for differences in respiratory volume*

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17 The default lung ventilation during an 8-h shift is 10m³ for workers with light physical activity.
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19 For humans without activity the default in the REACH guidance (ECHA, 2008) is 6.7m³ during
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21 8h.
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27 After adjustment of the POD, AFs were applied for the following extrapolations steps (table 1).
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32 *Additional interspecies differences*

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34 The allometric scaling addresses the metabolic/toxicokinetic part of the interspecies differences
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36 in sensitivity. The remaining (toxicodynamic) differences are suggested to be covered by a factor
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38 of 2.5 in most cases. If the critical effect is a local effect that does not require metabolism of the
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40 substance in question and also not located in the respiratory tract, a factor of 1 is recommended.
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44 For effects in the respiratory tract a factor of 2.5 is recommended.
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48 *Intraspecies differences*

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50 Worker-DNELs are derived for a subgroup of the population (more healthy and excluding the
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52 very young and very old) for which a smaller intraspecies variability is expected. Therefore, a
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3 factor of 5 is recommended for intraspecies extrapolation for workers. This contrasts the factor
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6 10 given for the general population.
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10 *Differences in exposure duration*

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12 In general longer exposure durations can be expected to result in more frequent and/or more
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14 severe toxic effects and hence lead to lower NOAELs and LOAELs. Table R.8-5 in the REACH
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16 guidance (ECHA, 2008) gives advice on AFs addressing differences in exposure duration. An
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18 AF of 6 is set for subacute (28 days) to chronic (1.5-2 years) extrapolation. This AF can be
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20 divided in factors of 3 for subacute to subchronic (90 days) and 2 for subchronic to chronic
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22 extrapolations. No recommendations are given for extrapolation of acute exposure data (less than
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25 8 h) to chronic exposure (corresponding to long-term worker-DNEL).
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32 *Issues related to dose-response*

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34 This heading covers several aspects of the dose-response relationship. If the worker-DNEL is
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36 derived from a LOAEL instead of a NOAEL a factor of 3 is recommended in the majority of
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38 cases, but also it is mentioned that it might be suitable with higher factors (up to 10). With
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40 respect to bench-mark doses (BMD), BMD5 (the lower confidence limit of the dose that
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42 produces a response of 5%) is preferred over BMD10, but no specific recommendations are
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44 given on the extrapolation from BMD10 to BMD5. According to the guidance, additional factors
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46 may be needed even when the POD is a NOAEL, depending on the shape of the dose-response
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48 curve, or issues related to study quality and statistical uncertainty. Again, no specific advice on
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50 magnitude of the AF is given for such cases.
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Quality of the database

A factor covering issues with the quality of the whole database (not covered by the previous aspects) may be justified, for instance if data are contradictory or lacking. However, the default recommendation is a factor of 1.

Subsequent to the assignment of different AFs for each substance, according to the above schemes, we multiplied the individual AFs to obtain an overall AF. In case the POD had not already been adjusted by SCOEL in the same manner as outlined in the REACH guidance (ECHA, 2008), we also multiplied the overall AF with a dose adjustment factor to obtain a total adjustment and assessment factor (TAAF). This exercise was undertaken to achieve comparability with the SCOEL ISMs. The adjustment factor is calculated by dividing the original POD, as defined in the SCOEL summary document, by the dose-adjusted POD. For instance if the POD used by SCOEL without additional modification is 100 ppm and taken from a study where rats were exposed 6 h/day, this needs to be adjusted according to the REACH guidance because workers are exposed 8 h/day. Using Haber's law as described above leads to an adjusted POD of 75 ppm, hence the adjustment factor is $100 \text{ ppm} / 75 \text{ ppm} = 1.33$. This adjustment was only included in the TAAF when not already performed by SCOEL.

Examples of the derivation of TAAFs are given in the Results section (table 2), it should be noted that both the ISM and the TAAF calculated by us represent the safety margin between the limit value (OEL or worker-DNEL) and the POD for the critical effect *as defined by SCOEL*. Meanwhile, the final TAAF should, according to the REACH guidance, be based on the leading effect. The final TAAF may thus be equal to (leading effect=SCOEL critical effect) or higher

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3 than (leading effect \neq SCOEL critical effect) the TAAF calculated by us. The SCOEL critical
4 effect was used in order to make the TAAF comparable with the ISM for the same substance.
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6 Thus, while the ISM represents the safety margin between the POD and the OEL, as defined in
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8 the SCOEL summary document, the TAAF represents the safety margin between the same POD
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10 and the worker-DNEL.
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18 The following assumptions and simplifications were made:

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20 1. When correcting for exposure routes, oral and dermal absorption in animals was set to 50%
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22 whereas the inhalation uptake in humans as well as animals were set to 100%.
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26 2. For a number of substances the POD was derived from very short-term exposures, ranging
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28 from a few minutes to 8h. If the critical effect was sensory irritation the AF for duration of
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30 exposure was set to 1. When POD was derived from short-term data, but more long-term
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32 data supported the conclusions, i.e. no other effects were found after longer exposures, the
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34 choice of AF for duration of exposure was based on the supporting data with longer
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36 exposure duration.
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40 3. Irritation effects affecting eyes and/or skin only were classified as local effects not requiring
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42 metabolism of the substance (AF=1).
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46 4. A factor of 3 for extrapolation to a NOAEL was applied to all substances where the POD
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48 was a LOAEL.
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52 5. The quality of the database was deemed to be acceptable for all substances (AF=1).
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55 For the purpose of this paper of DNEL versus OEL comparisons, the TAAFs calculated herein
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57 were derived according to the framework for protection from long-term effects. Thus, according
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3 to REACH terminology, the full label for the resulting DNELs, herein referred to as worker-
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5 DNEL, should be “worker-DNEL long-term for inhalation route-systemic” or “worker-DNEL
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7 long-term for inhalation route-local”.
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10 11 12 **3 Results**

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15 When applying the REACH guidance (ECHA 2008) it becomes obvious that a lot of important
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17 information on how to correctly derive the DNELs is to be found in the text. However, the
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19 summarizing tables and figures only present default values for the different AFs. Moreover,
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21 these defaults are often the lowest values of a suggested range, while higher AFs are described as
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23 needed for exceptional cases. For instance, the default AF for issues related to the reliability of
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25 the dose-response relationship, including extrapolation from LOAEL to NOAEL is 1 (table R.8-
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27 6, ECHA, 2008). Meanwhile, the body text reads: “it is suggested to use an assessment factor
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29 between 3 (as minimum/majority of cases) and 10 (as maximum exceptional cases)”. Such
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31 discrepancies are likely to result in arbitrary choices of AFs. Thus one assessor, reading only the
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33 table, might apply an AF of 1 whereas another assessor, reading also the text, might apply an AF
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35 of 3, or perhaps even 10, depending on how reliable the data are considered to be.
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44 Six examples of the derivation of the TAAF are given in table 2. First of all, it should be noted
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46 that for triethylamine, sodium azide and 2-(2-methoxyethoxy)ethanol and with strict adherence
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48 to the REACH guidance, the critical effect indentified by the SCOEL would not be the leading
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50 effect, as other endpoints (liver and lung damage, increased relative liver weight and reduced
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52 spleen weight) presented in the SCOEL summary documents would result in lower worker-
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55 DNELs.
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6 For triethylamine, the AF for duration of exposure to was set to 1 because data suggest that the
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8 effect is transient and that the substance acts locally on the corneal epithelium. The AF was set to
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10 1 also for 2-(2-methoxyethoxy)ethanol, as the effect is developmental toxicity and the exposure
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12 covered the whole relevant period , namely the embryonic phase.
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18 The SCOEL ISMs range from 0.8 to 71.4, whereas the TAAFs calculated according to our
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20 interpretation of the REACH guidance range from 5 to 234 (table 3, figure 1). On average, the
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22 TAAFs are six-fold higher than the SCOEL ISMs, as illustrated by the geometric mean of the
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24 TAAF-ISM ratios of 6.0 (median 5). The lowest TAAF-ISM ratio of 0.3 is seen for hydrogen
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26 selenide, and the highest (58.6) is seen for ethanolamine. For 28 of the 88 substances the TAAF
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28 is 10 times higher or more than the ISM. For substances where SCOEL has not used any AF
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30 (ISM 0.8-1.4, deviations from unity are due to the preferred value approach) the TAAF ranges
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32 from 5 to 35.
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39 The ISMs take on their highest values for PODs being animal NOAELs, while the REACH
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41 TAAFs follow the expectation of the highest safety margins applied for animal LOAELs. The
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43 magnitude of the ISMs and the TAAFs, obey the expected trend of lower AFs for less severe and
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45 effects not requiring metabolism such as local irritants (figure 1, table 4)
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50 Figure 2 shows a comparison of REACH TAAFs and SCOEL ISMs. For four substances out of
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52 88 (4.5 %) the ISMs were higher than the TAAFs calculated according to our interpretation of
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3 the REACH guidance documentation (i.e. TAAF:ISM ratio below 1). These substances are listed
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5 in table 5.
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10 A closer scrutiny of the TAAFs for these four substances suggests that our simplification to
11 always use AF=1 for quality of database may be a questionable simplification. For *2-butanone*
12 the POD was a subchronic NOAEL; SCOEL applies a factor of 10 because of lack of long-term
13 data, while the REACH guidance recommends an AF of 2 (extrapolation subchronic to chronic).
14 For *heptan-2-one* SCOEL considered a factor of 20 appropriate due to lack of human data and
15 limited animal data. Also for *heptan-3-one* SCOEL found that the available database was limited
16 and recommended an AF of 20. The rounding down of the value for the recommended OEL, to
17 adjust to the preferred value approach, led to an ISM of 30. For these two substances, adherence
18 to the REACH guidance would favour the use of an AF for quality of database higher than 1, due
19 to the lack of data. For *hydrogen selenide* the POD was irritation effects in workers after several
20 minutes of exposure, the SCOEL recommendation was also supported by data on long-term oral
21 exposure to selenium. The SCOEL recommended an AF of 20 to account for limitations in the
22 reporting of the POD study, adjustment for the preferred value approach resulted in an ISM of
23 15. In contrast, under the assumption that the irritation is local and concentration driven, the
24 TAAF is 5. On the other hand, assuming a dose driven effect and applying Haber's law for time
25 scaling, a TAAF of 48-96 (assuming "several minutes" means maximum 10 and minimum 5
26 minutes) would be obtained. In conclusion, the TAAF should be higher than presented here for at
27 least these three substances, however, no specific numerical advice is given in the guidance
28 (ECHA, 2008) on the issues of concern.
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4 Discussion

In this study, we compare safety margins derived using the REACH framework for worker-DNELs with those apparently used by the SCOEL expert committee of the European Commission for 88 different chemicals. We have calculated worker-DNELs as best we could in accordance with the REACH guidance. Such DNELs are required, or will be required in the near future, for most chemicals on the European market. For comparison, we wanted to use safety margins applied by the SCOEL, however these where in most cases was not explicitly stated in the summary documents. We therefore calculated implicit safety margins by dividing the POD by the 8-h OEL recommended by the SCOEL.

Three major conclusions may be drawn from our exercise. First, it suggests that worker-DNELs will generally be considerably lower than the OELs recommended by the SCOEL. This is illustrated e.g. by the six-fold higher TAAFs compared to ISMs (geometric mean 6.1). The deviations are, partly, explained by differences in the adjustment of the POD and, mainly, by differences in choice of AFs.

Second, our exercises indicate that the procedures used to handle dose adjustment, variability and uncertainty differ between REACH and SCOEL. This is illustrated by the large variability in TAAF: ISM ratios, spanning from 0.3 to 58.6, i.e. over two orders of magnitude.

The third conclusion concerns the degree of quantitative advice given in the SCOEL Key Document (SCOEL, 2009) and the REACH guidance document (Chapter R.8, ECHA, 2008). As pointed out earlier, the former document gives only qualitative and no quantitative advice on the

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3 choice of AFs and emphasises the use of expert judgement and case-by-case decisions. The
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5 latter, on the other hand, gives quantitative advice on a number of issues including dose-
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7 adjustments, allometric scaling, time scaling, route and species extrapolation etc. Still, as
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9 discussed in more detail below, it often remains unclear under which specific circumstances and
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11 by how much one may depart from the default AFs.
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17 ECETOC (2010) has made a similar exercise to calculate long-term worker-DNELs for 21
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19 substances based on the SCOEL summary documents. Of these 21 chemicals, 19 were also
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21 included in our assessment. We were unaware of the ECETOC effort at the time when we carried
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23 out our exercise. In view of the difficulties in interpreting the REACH guidance, our choices of
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25 individual AFs were strikingly similar to those by ECETOC. Only marginal differences were
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27 obtained, mainly related to the modification of the POD.
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34 In the near future, worker-DNELs will be defined for many more substances than health-based
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36 OELs set by SCOEL or regulatory agencies. This leads to the question on whether further work
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38 on deriving OELs really is needed. As the results from the comparisons in this paper show the
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40 safety margins of the worker-DNELs are higher in a majority (95.5%) of cases compared to the
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42 SCOEL OEL recommendations. Had we applied non-default AFs for deficiencies in the quality
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44 of database this percentage would have been even higher (99-100%). However the larger safety
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46 margins in the REACH guidance should not be interpreted as the worker-DNELs necessarily are
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48 over-protective or even sufficiently protective. For one, the safety margins have traditionally
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50 always been low concerning hazardous chemicals and occupational hygiene. The safety margins
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52 explicitly or implicitly used by the SCOEL are remarkably low compared to the total AFs
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3 generally recommended for the general population , as also noted previously (Nielsen and
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6 Øvrebø, 2008; Schenk and Johanson, 2010). This suggests that the magnitude of the AFs in the
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8 REACH guidance should perhaps not be calibrated against the assessments made by the SCOEL.
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15 The recommended AFs in the REACH guidance document have already been subject to some
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17 criticism. Malkiewicz et al. (2009) investigated the empirical data behind the recommendations
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19 in the REACH guidance concerning subchronic to chronic exposure, and concluded that the
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21 default AF of 2 corresponds to the 50th percentile while. It was further argued that for a
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23 conservative approach, it would not be unreasonable use the 90th or a higher percentile. The
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25 investigated data have however not been corrected for effects of dose-spacing in the investigated
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27 studies, which might affect the observed ratios between subchronic and chronic NOAELs.
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34 Another critique pointing in the opposite direction, voiced by ECETOC (2010) is that the
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36 multiplication of several AFs will lead to overly conservative TAAFs. Kalberlah and Schneider
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38 (1998) suggested that in order to not get too overprotective AFs when multiplying several
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40 extrapolation steps some steps could be less conservative but these should be compensated by
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42 other more conservative steps. However, had this been the view of the REACH guidance
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44 document it should have been clearly stated in the guidance text (Chapter R.8, ECHA, 2008).
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46 ECETOC recommends that the AFs should be further investigated and reconsidered as new
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48 knowledge becomes available, as some of the default AFs in ECHA (2008) were found to “be
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50 unjustified by the current state of scientific knowledge”. Further, the AFs of 2.5 for interspecies
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3 differences remaining after allometric scaling and 5 for intraspecies among the workers are
4 questioned. ECETOC has previously recommended an AF of 3 for the latter (ECETOC, 2010).
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10 The framework for the derivation of worker-DNELs presented in Chapter R.8 (ECHA, 2008) is
11 well needed, however, we believe that it might be further improved and have the following
12 suggestions. A first and obvious note on the derivation of any DNEL is that it is not sufficient to
13 apply the quantitative guidance given in the tables, as many qualifiers are found in the text. To
14 this end, it is problematic that some of the default AFs presented in the tables represent the lower
15 end of a range, implying that a special motivation is required to select higher values even if still
16 within the range. One example is the AFs related to dose-response, including LOAEL/ NOAEL
17 extrapolation. For both this AF, a default of 1 is given in table R.8-6 (ECHA, 2008), albeit with a
18 footnote that states that deviations from the default are described in the text. Yet the body text
19 recommends a factor of 3 in the majority of these cases, while it might be suitable with higher
20 factors of up to 10. A more cautious approach would be to set the tabular default AFs at the
21 upper rather than the lower end of the intended range.
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41 Although we tried to strictly adhere to the framework given in the guidance (ECHA, 2008), the
42 selection of the AFs was in some instances quite equivocal. An issue that is not presently fully
43 addressed in the REACH guidance is that of time scaling. For instance when the POD is an
44 extremely short-term human volunteer study, the guidance lacks advice on how to use this dose
45 descriptor for the derivation of a long-term-DNEL. There is however specific guidance on how
46 to derive DNELs for acute toxicity in Appendix 8-8. In the present study we tentatively used the
47 guidance concerning adjustment of the dose-descriptor for exposure conditions other than 8
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3 h/day, i.e. we used Haber's law for extrapolation up to 8 h. This approach does, however, not
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5 solve the issue of extrapolation to long term exposure, i.e. a full working life as the guidance
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7 only gives AFs for extrapolation from subacute to chronic data. Again, we had to use a tentative
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9 approach to be able to complete our exercise. Thus, we searched the SCOEL summary
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11 documents for data supporting that no other effects (than the short-term effect) are to be expected
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13 after long-term exposures. If the absence of other effects was supported by chronic data, we did
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15 not use any additional factor to account for duration of exposure. If, on the other hand, the
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17 supporting data were subchronic or subacute, we applied AFs of 2 and 6, respectively.
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25 The difference between expert judgment and the expected variability of the toxicological
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27 knowledge of the registrants' representatives deriving the worker-DNELs should also be taken
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29 into account. It might be warranted to apply an even larger safety margin in the REACH
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31 guidance system, since there is an additional factor of uncertainty concerning the experience and
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33 knowledge of the producers and importers.
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39 The default AFs given in table R.8-6 in ECHA (2008), and also presented in table 1 of this paper,
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41 are 1 for two of the five aspects covered, namely issues related to dose-response and quality of
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43 database. Under issues related to dose-response for instance also LOAEL to NOAEL
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45 extrapolation and severity of the effect are to be covered. As the framework prescribes selection
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47 of the effect leading to the lowest DNEL as leading effect, an AF for severity of effect could
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49 have a substantial impact. Quantitative suggestions on issues related to dose-response are
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51 however only given for the extrapolation from LOAEL to NOAEL. Under quality of database,
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53 issues like data completeness, reliability and consistency are to be considered, however, only
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3 qualitative guidance is given in ECHA (2008). The guidance document would benefit from more
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5 examples, including numerical advice, for those cases where the default AF is inappropriate. A
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7 more extensive set of criteria for the quality of the database would also be valuable, for instance
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9 on how to decide when the data are sufficient to conclude that more sensitive end points than
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11 those already documented are unlikely to occur.
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17 As the framework stands now, the selection of leading effect could lead to confusion regarding
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19 the toxicity of a substance. Consider two substances, A and B, both have the same industrial
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21 application and both cause the same severe effect, but at different doses, so that B is less toxic
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23 than A. However, B also has an additional effect, a mild irritation which occurs at considerably
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25 lower doses. B will therefore obtain get a lower critical DNEL, possibly leading to more
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27 restrictions concerning B than A. The lower DNEL of substance B may promote a shift in use
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29 from B to A, in spite of A being, in essence, more toxic. This would be contrary to the general
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31 rule that one should aim at reducing the use of chemicals with potentially severe effects as much
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33 as possible.
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41 Confusion may also arise if the worker-DNELs appearing in the near future turn out considerably
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43 lower than the corresponding OELs, as indicated by the present study. The differences in the
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45 safety margin between worker-DNELs and national OELs and can lead to significant
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47 interpretation and risk management problems. Assume that substance C has no OEL, and is less
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49 toxic than substance D, which already has a European IOELV. However, for substance C
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51 compliance with the frame-work in ECHA (2008) leads to the derivation of a relatively low
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53 worker-DNEL. The first point of potential confusion is that according to REACH the European
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3 IOELV can be used instead of deriving an own worker-DNEL. As our comparison has shown,
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5 IOELVs will probably be significantly higher than the corresponding worker-DNELs. Hence,
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8 substance C (worker-DNEL) might be perceived as more harmful than substance D (IOELV),
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10 and will be subject to more extensive risk management measures. This could lead to the use of D
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12 increasing at the expense of C, although the former is more toxic.
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17 An obvious alternative for the registrant would be to derive a worker-DNEL also for D,
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19 following the same REACH guidance as for C. Now substance D does have a lower DNEL than
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21 substance C. Then another problem arises, namely that D has at two different exposure limits,
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23 one worker-DNEL, one European IOELV (and perhaps a third, national OEL as well). For
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25 employees and other stakeholders this lead to the question of which of the values to trust or give
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27 priority to. It is therefore important for European and national work environment authorities to
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29 clearly communicate the relation between OELs and worker-DNELs and give guidance on how
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31 to handle potential conflicts between different OEL values.
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39 Indeed, the European Commission has published a guidance for employers which describes the
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41 relation between IOELVs and worker-DNELs (European Commission, 2010). The guidance
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43 states: “Although both DNELs and IOELVs are health-based, they are not necessarily set in the
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45 same way. The primary duty is to comply with risk management measures and good control
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47 practice. This should also mean compliance with relevant exposure reference levels.” The
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49 guidance further states that both OELs and DNELs are “useful in establishing what is needed to
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51 secure adequate control of exposure”. However, with regards to dissimilar national OELs and
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53 worker-DNELs, the European Commission (2010) merely states that the employers are
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3 “responsible for the protection of their employees, and should seek to resolve the situation with
4 their suppliers and, as appropriate, with the relevant national authorities”.
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10 The worker-DNELs are not equivalent to regulatory OELs, and it should not be expected that the
11 DNELs will be enforced in the same manner as one can expect national or EU-level OELs to be.
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14 Nonetheless, there are parallels and connections between worker-DNELs and OELs. The most
15 notable is that the EU IOELVs under some circumstances are allowed to be used as a
16 replacement for worker-DNELs. The main function of the worker-DNEL is to evaluate different
17 exposure scenarios, i.e. defining uses that correspond to an adequate control of risks to workers.
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20 An adequate control of risks in this context equals exposures below the relevant worker-DNELs.
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23 This is in essence not so far from measuring the levels at a work-place to see if the current
24 practices are in compliance with an OEL. Reasonably, practices aiming at deriving health-based
25 OELs (or similar exposure limits) should be in accord with each other concerning the results, to
26 ensure fairness of different risk estimates for groups of workers covered by different systems.
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29 We find the development of frameworks such as the one in the REACH guidance document
30 (ECHA, 2008) an important step in this direction. However, more specific, numerical
31 suggestions on ranges of AFs would significantly improve the user-friendliness of the guidance
32 and probably also the reliability and consistency of the worker-DNELs derived by registrants.
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48 According to the SCOEL Key Document (SCOEL, 1999; 2009) AFs (termed uncertainty factors
49 by SCOEL) should be used for the extrapolation from POD to IOELV. However, when
50 scrutinizing SCOEL summary documents, we found that only 44 out of 75 IOELVs examined
51 were derived using explicit AFs (Schenk and Johanson, 2010). We further found that the safety
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3 margins (calculated as OEL/POD) were on average twice as high for chemicals where the AFs
4 applied had been explicitly stated compared to chemicals with no such statements. Furthermore,
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6 and contrary to expected, the average safety margins for irritation were similar to those for more
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8 severe systemic effects. The kind of information that was used as the point of departure (NOAEL
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10 vs. LOAEL, animal vs. human data) affected the safety margins only slightly and less than
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12 expected. Contrary to expected, PODs based on longer exposure duration resulted in higher
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14 safety margins. The safety margins showed a weak but significant negative correlation with the
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16 amount of available toxicological data, whereas SCOEL statements on data sufficiency had no
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18 influence. In summary, we concluded that the use of AFs by SCOEL is neither very transparent
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20 nor consistent and is less transparent than stated in the SCOEL Key Document (SCOEL, 1999;
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22 2009). We therefore recommended that SCOEL should develop and adhere to a more articulate
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24 framework for their use of AFs (Schenk and Johanson, 2010).
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34 The comparison of SCOEL ISMs with the REACH TAAFs, as done in the present paper, does
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36 not imply that any one of the two approaches gives a more accurate view of uncertainty or risk
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38 than the other. There are strengths and limitations with either one. The safety margins from
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40 SCOEL and the REACH guidance document differ markedly in their origin. Thus, the REACH
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42 guidance gives a numerical framework for dose adjustment and choice of AFs for different
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44 aspects of uncertainty that are combined into one TAAF. In contrast, the SCOEL safety margins
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46 are not a result of such a framework but depend more or less entirely on case-by-case “expert
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48 judgment”. The major strength of a case-by-case approach is that it addresses chemical specific
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50 aspects and thus acknowledges that every chemical is unique. On the other hand, there is an
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52 increased risk that uncertainties in the assessment are treated in an inconsistent manner. Another
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3 limitation of the case-by-case approach is that it is very time consuming and that it has,
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5 historically, resulted in a relatively low output of OEL values. A framework approach, such as
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7 that for worker-DNELs, allows for spreading the effort of derivation among several actors, a
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9 factor that may significantly increase the number and speed of derived values.
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15 For several reasons, however, we still believe that, in spite of the efforts invoked by the REACH
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17 legislation, there will be a continued need for OELs developed by independent expert groups.
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20 First, the full implementation of the REACH legislation will take several years. Second, there are
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22 harmful exposures in the workplace, such as dusts and exhaust fumes, that are not directly
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24 related to chemical products and hence do not fall under the requirements of REACH. Third,
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26 there is often an open or hidden cost-benefit (i.e. potential health risks versus economic benefits
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28 or other advantages of the chemical) conflict in toxicological risk assessment, underlining the
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30 need for independent experts. Expert group assessments will also be essential when developing
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32 and improving future frameworks, including the REACH guidance document.
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39 In conclusion, by comparing the safety margins of SCOEL recommendations with those of
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41 worker-DNELs derived according to the REACH guidance document, we find: (1) that the safety
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43 margins implicitly used by the SCOEL are markedly lower than those recommended in the
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45 REACH guidance, (2) that the safety margins vary widely with poor correlation between the two
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47 systems, (3) that these discrepancies may create confusion in terms of legal compliance, risk
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49 management and risk communication, and (4) that that the REACH guidance document,
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51 although encompassing detailed advice on many issues, including default assessment factors for
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3 species and route extrapolation, gives very little quantitative guidance on when and how to
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5 depart from defaults.
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10 **Conflicts of interest statement**

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12 Gunnar Johanson is a member of the SCOEL.
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18
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Figure captions

Figure 1 Comparison of SCOEL Implicit Safety Margins (ISM, \triangle and \circ) and REACH Total Adjustment and Assessment Factors (TAAF, \blacktriangle and \bullet) for 88 substances, sorted by nature of point of departure. Triangles (\triangle and \blacktriangle) represent effects not requiring metabolism of the substance and circles (\circ and \bullet) indicate effects requiring metabolism.

Figure 2 Total Adjustment and Assessment Factors (TAAF) according to the REACH guidance versus SCOEL's Implicit Safety Margins (ISM). Each point represents one substance ($n=88$). All ISMs are over or close to 1, i.e. on the right side of the vertical line. Nearly all TAAF:ISM ratios are higher than 1, i.e. above the diagonal line.

Table 1 Default assessment factors given in the REACH guidance document chapter R.8 (adapted from table R.8-6, ECHA, 2008)

Assessment factors – accounting for differences in:	Default values		Range of assessment factors specified in the guidance text ^a
	Systemic effects	Local effects	
Interspecies differences	Correction for differences in metabolic rate per body weight	Allometric scaling	1-7
	Remaining differences	2.5	1-2.5 <i>1 -no metabolism</i> <i>2.5 - on respiratory tract or via local metabolism</i>
Intraspecies differences	Workers	5	5
	General population	10 ^b	10 ^b
Differences in duration of	Subacute → subchronic	3	3 – <i>respiratory tract</i>
	Subchronic → chronic	2	2– <i>respiratory tract</i>

1 2 3 4 5 6 7	exposure	Subacute → chronic	6	6– <i>respiratory tract</i>	
8 9 10 11 12 13 14 15 16	Issues related to dose- response	Reliability of the dose- response, including severity of effect	1 ^b	1 ^b	-
17 18 19 20 21 22 23	Quality of whole database	Completeness and consistency of available data Reliability of alternative data	1 ^b	1 ^b	3-10 ^d - -

^aThe guidance document gives preference to chemical specific factors when available data allow, these examples only cover the numerical suggestions given in the text of the guidance document section R8.4.3.1 “Assessment factors relating to the extrapolation procedure”

^bAdditional qualitative guidance on deviations from the defaults is given in the text of ECHA, 2008

^cA higher factor than 10 is suggested when the resulting DNEL is to encompass very young or unborn children (not applicable to worker-DNEL)

^dNumerical suggestions for the extrapolation from LOAEL to NOAEL are given in the text: “3 (as minimum/majority of cases) to 10 (as maximum/exceptional cases)”

Table 2 The derivation of Total Adjustment and Assessment Factors.

Substance	<i>triethylamine</i>	<i>Sodium azide</i>	<i>2-(2-methoxyethoxy)ethanol</i>	<i>pyrethrum</i>	<i>1,1,1-trichloroethane</i>	<i>ethanolamine</i>
	Visual		Developmental		Behavioural	Behavioural
Critical effect	disturbance ^d	Hypotension	toxicity	liver damage	effects	effects
Point of departure	NOAEL 2.4 ppm	LOAEL 0.3 mg/m ³	NOAEL 50 mg/kg bw	NOAEL 10 mg/kg bw	LOAEL 175 ppm	LOAEL 50 ppm
Exposure duration	8 h	5 to 30 years	Gestational days 6 to 18 ^e	2 years	3.5 h	2-3 weeks continuous
Exposure route	Inhalation	Inhalation	Dermal	Oral	Inhalation	Inhalation
Species	Human (V)	Human (W)	Rabbit	Rat	Human (V)	Rat
<i>ADJUSTMENT OF DOSE DESCRIPTOR</i>						
Route to route ^a	1	1	2	2	1	1
Exposure conditions ^b	1	1	1	1	2.29	0.69
Respiratory volume ^c	1 ^d	1	1	1	1.49	1.49
Allometric scaling	1	1	2.4	4	1	1
<i>REACH ASSESSMENT FACTORS</i>						

Interspecies	1	1	2.5	2.5	1	2.5
Intraspecies	5	5	5	5	5	5
LOAEL-						
NOAEL	1	3	1	1	3	3
Duration of exposure	1 ⁴	1	1 ^e	1	2	6
Quality of data base	1	1	1	1	1	1
<i>TOTAL ADJUSTMENT AND ASSESSMENT FACTOR</i>						
	5	15	60	100	102.6	234

(W) workers (V) volunteers

^aCorrection for differences absorption between different routes, assuming 50% absorption for dermal and oral exposure and 100% absorption for inhalation.

^bCorrection using Haber's law $C^n \times t = k$, where C = concentration, t= duration of exposure, k=constant. When adjusting from shorter to longer exposure, n=1 has been used, from longer to shorter n=3 has been used.

^cCorrection for difference in respiratory volume during rest and light activity; 6.7 m³ / 10m³ (1/0.67 = 1.49).

^dLocal effect, data suggest this effect is transient and not causing permanent eye-damage. Thus no adjustment for respiratory volume and no assessment factor for differences duration of exposure is needed.

^eAuthors consider this exposure chronic as it occurred during the whole of the embryonic phase

Table 3 Comparison between SCOEL's Implicit Safety Margins (ISM) and the Total Adjustment and Assessment factors (TAAF).

Point of departure	No	Lowest	Highest	Median
<i>ISM – TAAF – TAAF/ISM</i>				
Animal LOAEL	14	2 – 37.5 – 3.9	12.5 – 234 – 46.8	5 – 52.4 – 11
Animal NOAEL	37	1 – 5 – 0.8	71.4 – 149 – 49.7	4 – 25 – 6.25
Human LOAEL	15	1 – 15 – 2.5	6 – 102.6 – 58.6	2 – 15 – 7.5
Human NOAEL	22	0.8 – 5 – 0.33	15 – 37.3 – 17.3	1.2 – 5 – 5
All point of departures	88	0.8 – 5 – 0.33	71.4 – 234 – 58.6	2.5 – 17.5 – 5

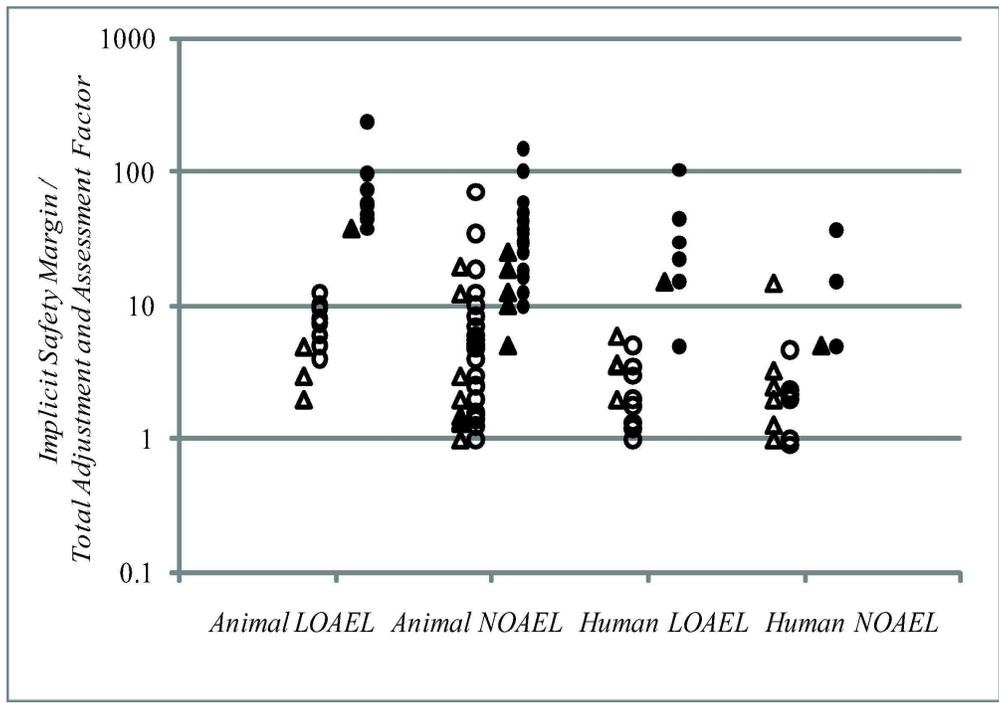
Table 4 Comparison of SCOEL Implicit Safety Margins (ISM) and REACH Total Adjustment and Assessment Factors (TAAF), sorted by nature of point of departure and nature of effect.

	<u>Effect requiring metabolism</u>					<u>Effect not requiring metabolism</u>				
	<i>SCOEL ISM</i>		<i>REACH TAAF</i>			<i>SCOEL ISM</i>			<i>REACH TAAF</i>	
	No	Range	Median	Range	Median	No	Range	Median	Range	Median
Animal LOAEL	10	4-12.5	6.75	37.5-98	66.9	4	3-5	2.5	37.5-37.5	37.5
Animal NOAEL	29	1-71.4	4.75	10-100	30.6	8	1-20	1.75	5-25	12.5
Human LOAEL	10	1-4.7	2	15-102.6	15	5	2-6	3.6	15-15	15
Human NOAEL	11	0.9-2.3	1.2	5-37.25	5	11	0.8-15	1.3	5-5	5

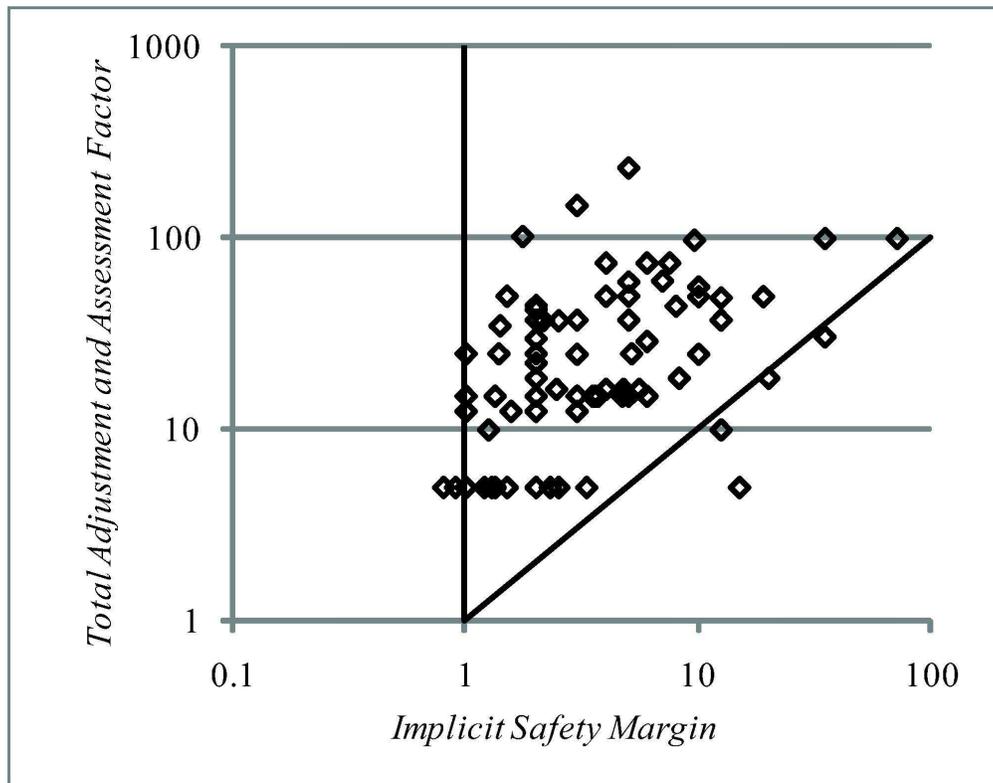
Table 5 Substances for which the SCOEL Implicit Safety Margin (ISM) is higher than the REACH Total Adjustment and Assessment Factor (TAAF).

CAS No.	Substance	TAAF	ISM
78-93-3	2-butanone	10	12.5
110-43-0	Heptan-2-one	18.6	20
106-35-4	Heptan-3-one	30.6	35
7783-07-5	Hydrogen selenide	5	15

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100x70mm (600 x 600 DPI)



85x66mm (600 x 600 DPI)

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