Derivation of occupational exposure limits for airborne chemicals - Comparison of methods and protection levels

Klaus Schneider[1], Eva Kaiser[1], Valerie Rebhahn[1], Ulrike Schumacher-Wolz[1], Karin Heine[1], Heidi Ott[2], Claudia Drossard[2]

baua: Focus

The BAuA Research project F2437 on "Derivation of occupational exposure limits for airborne chemicals - Comparison of methods and protection levels" analysed the currently used methods to derive occupational exposure limits (OELs) and analogue values in the EU and at national level in Germany. At an international workshop at the BAuA in Dortmund on 5 April 2022 (organised as hybrid event with the possibility to participate online) the authors from FoBiG (Forschungs- und Beratungsinstitut Gefahrstoffe GmbH) presented the project outcome and discussed with more than 190 participants results and conclusions. One of the major observations was that large differences exist between currently used methods for deriving such values. Discussions focused on ways to implement steps towards harmonisation of methods for deriving OELs.

Content

1 Introduction

The derivation of occupational exposure limits (OELs) is an important component of the risk assessment and risk management of chemicals in different national as well as international processes. At the EU level, harmonisation of airborne exposure limits is a current issue, because for some substances different exposure limits for workplaces were yielded by occupational safety and health legislation on the one hand and by chemicals legislation on the other hand. Important steps in the process of setting OELs or analogue values are the determination of a point of departure (POD) based on adverse effects reported in toxicological studies and the application of assessment factors to bridge data gaps (regarding studies with different exposure duration, differences between species and variability in sensitivity between humans).

[1] Research and Advisory Institute for Hazardous Substances (FoBiG), Freiburg, Germany

[2] Federal Institute for Occupational Safety and Health (BAuA)

baua: Federal Institute for Occupational Safety and Health

The objective of research project F2437 was to analyse and disclose the differences between the current methods for deriving exposure limits and the resulting differences in protection levels. To achieve this, methodologies proposed or used at EU level and at national level in Germany were analysed and compared. Data were compiled and distributions for assessment factors used for deriving exposure limits were derived from the data. With these distributions and their combinations, levels of protection achieved by the various methodologies and the reasons for differences were analysed. Further, important instruments and methods for deriving exposure limits were investigated: Dose-response modelling with the benchmark dose approach to determine the point of departure; probabilistic approaches to describe probabilities and uncertainties of exposure limits; and, last not least, methods for the modelling of kinetics of aerosols in the respiratory tract to describe respective interspecies differences and for determining a human equivalent concentration (HEC). The overarching aim was to develop a common understanding of the necessary methodological steps for setting exposure limits and in this way to support harmonisation of the derivation of occupational exposure limits in the EU. The project methodology and results are described in detail in the project report (Schneider et al., 2022b). Further, two peer-reviewed publications summarise the main results (Dilger et al., 2022; Schneider et al., 2022a).

In order to disseminate the project outcome, to present the results for discussion in the scientific community and to identify steps towards harmonisation of methods for deriving OELs an international workshop was held at the BAuA in Dortmund on 5 April 2022. More than 190 scientists participated either in Dortmund or attended online.

2 Content of the workshop

The workshop focussed on the following main parts of the project:

- the analysis of the existing methodologies to derive OELs and analogue values,
- the compilation of new data to derive distributions for extrapolation steps
- and the analysis of protection levels achieved by the currently used methodologies.

After an introduction held by Rüdiger Pipke of BAuA and an overview on the project objectives from BAuA perspective provided by Claudia Drossard, the topics enumerated above were presented by Klaus Schneider and Eva Kaiser of FoBiG. Their colleagues Karin Heine and Ulrike Schuhmacher-Wolz moderated the workshop and led through the discussions. The workshop closed with final conclusions by Thomas Gebel of BAuA. The workshop agenda and all presentations are available online[3].

The analysis of existing methodologies addressed various regulatory areas:

- EU-wide OELs as proposed by the European Chemicals Agency's (ECHA) Committee for Risk Assessment (RAC) and formerly by the Scientific Committee on Occupational Exposure Limits (SCOEL)
- derived-no-effect-levels (DNELs) under REACH (according to ECHA Guidance and following proposals by the European Centre for Ecotoxicology and Toxicology, ECETOC),
- health-based values derived for biocides under the EU Biocidal Products Regulation and for pesticides under the EU Plant Protection Products Directive and
- OELs in Germany (by MAK Commission and by the 'Ausschuss für Gefahrstoffe' (AGS)).

[3] International workshop on BAuA research project F 2437 on methods for derivation of occupational exposure limits on 05 April 2022; *www.baua.de/EN/Service/Events/Proceedings/Hazardous-substances/F2437-Workshop.html*

Relevant methodological differences, which might lead to numerical differences in OELs, were identified at all steps of the derivation process. Differences in default values for assessment factors used were recognized as being of special quantitative importance. Recommendations were given for increasing transparency by providing detailed guidance documents and steps requiring harmonisation were identified.

In a further part of the project the empirical databases for assessment factors were evaluated and improved by compiling new data. For time and interspecies extrapolation, data from studies of the US National Toxicology Program (NTP) as well as REACH registration data were analysed. For intraspecies extrapolation published human studies with regard to variation of susceptibility due to differences in toxicokinetics and -dynamics were evaluated. Distributions describing the probability that a certain value of an assessment factor covers the uncertainty resulting from substance-to-substance variability were derived from the data compiled. Based on these distributions the probability achieved by currently used default values for assessment factors was derived, as well.

In the final part of the project the distributions derived previously were used to analyse the protection level provided by the existing methodologies. In a first step the overall assessment factors in use were compared to the combined distributions for the individual extrapolation steps (probabilistic Monte-Carlo analysis was used to combine distributions). In a second step, for two example substances a full probabilistic assessment was performed, including a description of the uncertainty introduced by the point of departure. Large differences in the probability with which the existing methodologies cover the OEL uncertainties were identified (i.e., large differences in the protection levels achieved). Based on these results, recommendations for steps towards harmonisation were presented.

All presentations were followed by discussion sections, where the present audience as well as online participants (via the chat function) had the possibility to comment and present questions. Further, a plenary discussion took place at the end of the afternoon session, taking up all aspects raised in the presentations. The discussions are summarised in the following section with the two major topics

- methodological approach taken in the project and
- possibilities to implement steps towards harmonisation.

3 Workshop discussions

3.1 Methodological approach taken in the project

3.1.1 Time and interspecies extrapolation

Several questions concerned the way how dose ratios used for time and interspecies extrapolation were derived in the project.

Although dose-response modelling is the preferred and recommended way to derive a point of departure (POD) and although it also has advantages when deriving dose ratios, e.g., for describing differences in effect levels due to different exposure duration, the project team derived ratios by comparing NOAELs („no observed adverse effect level“) from the NTP studies on 256 substances and from the REACH data due to restrictions in time and budget of the project. Also, in the case of the REACH data, dose-response modelling was not applicable as the full set of dose-response data is not available from the registration dossiers.

NOAEL ratios were not calculated from study pairs, where either both NOAELs or both LOAELs („lowest observed adverse effect level“) were missing. As explained in detail in the

project report (Schneider et al., 2022b), ratios were calculated from LOAELs when the NOAEL was missing in one out of two studies but was available for the second study (i.e. three out of four N/LOAELs from a study pair were available).

As longer-term studies often include larger groups of animals, thereby increasing the statistical power, the project team took care to compare similar endpoints only. For example, with the 14-day NTP studies, only body weight was assessed as an endpoint and 10% difference in body weight between dosed and control animals were considered relevant in these and longer-term studies. However, a certain influence of the size of dose groups cannot be completely ruled out in these evaluations for the various endpoints evaluated.

A further question was whether dose spacing could have negatively affected the ratios calculated from NOAELs. Dose spacing is expected to increase the variability in the calculated ratios, as it adds to the uncertainty associated with the ratios. However, as it is assumed that these errors tend towards both directions, average or median values are not expected to be affected to a large extend, considering the large number of ratios calculated. This is supported by the fact, for example, that the ratios could adequately distinguish between oral and inhalation studies with regard to interspecies extrapolation (with expected values of 0.59 and 1, respectively).

In the analysis of NTP and REACH data it was not possible to stratify according to solubility. Therefore, no conclusion could be drawn as to whether readily water-soluble substances show a different behaviour compared to poorly soluble ones. A subset of substances evaluated concerned metal compounds. They showed a higher-than-average toxicity in inhalation studies with rats compared to mouse studies. It is known that inflammatory responses in the lungs after particle exposure can be more pronounced in rats than in mice (Carter et al., 2006; Elder et al., 2005).

The evaluations showed that NOAELs of locally acting substances decrease with increasing exposure duration in a similar way as systemically acting substances. It can be concluded that effects of locally acting substances in repeated-dose studies are not concentration-driven. The situation is less clear for short exposure durations (hours) which are relevant with regard to adapting exposure conditions in the experimental inhalation studies (typically 6 hours per day) to the occupational scenario (8 hours exposure per day).

In the discussions, several proposals were made to further improve the database, especially with regard to the inclusion of study designs typically used for industrial chemicals. Such an evaluation should include studies of the following types:

- OECD TG 407 (Repeated dose 28-day oral toxicity study)
- OECD TG 408 (Repeated dose 90-day oral toxicity study)
- OECD TG 422 (Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test).

Furthermore, it should yield ratios for both, comparable endpoints and the lowest overall no effect level found in each of the studies (the second also considers differences in investigation depth between the study types) and, ideally, the ratios should be derived using dose-response modelling to identify the adequate dose descriptors to calculate the ratios.

3.1.2 Intraspecies extrapolation (toxicokinetics)

With regard to the human studies evaluated for variation in toxicokinetics, the project team explained that published data from peer-reviewed publications with both, industrial chemicals and pharmaceuticals were included in the assessment. No definite explanation is available

for the lower variation observed in inhalation studies compared to that in oral studies. This should be addressed by expanding the database on toxicokinetic variation.

In many of these studies a limited number of volunteers participated. This adds an aspect of uncertainty to the variation observed in the individual studies. As volunteer studies with large numbers of participants are scarce, a solution would be to increase the number of evaluated studies. However, as the description of variation (log GSD) is derived from values such as mean and standard deviation and not from extreme percentiles of the observations, the impact of this source of uncertainty might be limited.

Many publications on toxicokinetic variability in humans emphasize the role of polymorphically expressed xenobiotics metabolising enzymes for variation in toxicokinetics. It is reasonable to assume that inter-individual differences in the capacity of these enzymes play a major role for the partly large variation observed in toxicokinetic parameters in vitro.

3.1.3 Intraspecies extrapolation (toxicodynamics)

For describing variation with regard to toxicodynamic reasons the in vitro data created by Abdo et al. (2015) were used in our project. The advantages and disadvantages of these data were addressed in the presentation and in the discussion. Because Abdo et al. (2015) performed replicate measurements, they were able to correct their ratios for the measurement error in their experiments. Median values were substantially reduced from 7.02 to 3.04 and from 3.24 to 1.95 for the ratios median versus 1th percentile and median versus 5st percentile, respectively.

Limitations of using a single endpoint (cytotoxicity, measured as intracellular ATP concentration) as well as using immortalised cell lines were discussed. One participant proposed to use primary respiratory cells instead. However, difficulties could arise in obtaining such cells from a large number of individuals.

3.2 Steps towards Harmonisation

Various aspects of the derivation process were addressed by discussion participants. One participant asked how the use of the benchmark approach could be supported. In response to that the project team recommended to include a detailed description of how to use it in all guidance documents. These details should include, inter alia, information on tools, on how the benchmark response should be determined, whether BMD or BMDL should be used as POD and how the method can be applied to human data.

Another contribution addressed the problem arising from the use of the benchmark approach in case of limited dose-response data (e.g., only controls and two dose groups, resulting both in high incidences). The benchmark approach in such cases will produce PODs with high uncertainty, but this uncertainty is inherent to the data (and not to the method) and will only be made transparent by the modelling.

A participant proposed to add a confidence assessment to the derivation of OELs, referring to the example of “occupational biomonitoring levels”[4], OBL, as discussed in an OECD working group. Confidence in the assessment is expressed in three categories (low, medium, high), depending on the data quality and uncertainty of the derivation steps.

[4] OECD, Environment Directorate Chemicals and Biotechnology Committee, Working Party on Hazard Assessment; Draft Occupational Biomonitoring Guidance Document, NV/CBC/HA(2022)2; 11 March 2022

In one of the presentations the use of sensory irritation (effects caused by stimulation of nerves such as the trigeminus nerve) for OEL derivation in Germany was addressed. A participant commented that no agreement exists internationally on how to deal with these observations. This was recognized as another potential reason for differences in OELs.

Judgements on (non-)adversity of observations was identified as another source of differences. It was noted that respective case-by-case decisions and application of expert judgement is unavoidable but can be made transparent by a detailed justification document explaining the decisions taken in the derivation of a substance-specific OEL.

Time since the last update of a substance-specific assessment was identified as another potential reason for differences. Requirements for updates might vary between regulatory areas.

In another contribution to the discussion, concerns were raised that probabilistic tools could lead to lower acceptance and transparency of OELs because they are difficult to understand. This was acknowledged. However, probabilistic modelling is currently not proposed to be used on a daily basis for deriving OELs, but rather as a means to compare methods and make their protection levels transparent. The Monte-Carlo tool provided on EFSA's platform[5] is easy-to-use in a transparent way and the project team encouraged workshop participants to gather experiences. A participant pointed to another ready-to-use tool, APROBA[6], which was developed in the frame of an WHO IPCS project (WHO, 2014) and is also discussed in the project report (Schneider et al., 2022b).

Several discussion contributions focussed on the way how individual assessment factors could be derived (e.g., at which percentile of the distribution). How could an agreement on protection levels be achieved? In response to these questions the project team's perspective was that the overall protection level an OEL is aiming at should be decided upon first

- With regard to the percentage of the target population (workers) to be covered
- With regard to the uncertainty (probability) which is considered acceptable.

As these decisions are risk management decisions, decision makers should be included in the discussions at an early stage. Such decisions would certainly require a comparison with the situation of current OELs and to check whether conservatism of the OELs increases with the decisions taken.

Following these decisions, a coherent system with individual assessment factors could be established.

For the probabilistic examples of 1,1,2,2-tetrachloroethane and benzoic acid, the quantitative difference between using the distribution covering 95% or 99% of the target population was approximately factor 2. Regarding the probability with which the uncertainties of the OEL should be considered, the occupational safety provisions at the workplace might be seen as an argument to accept lower probabilities compared to health-based values for the general population.

One discussion contribution proposed establishing a platform for providing databases, distributions and tools to make them freely available. This was seen as a way to increase transparency and harmonisation and to trigger discussions on the most suitable datasets.

[5] *https://r4eu.efsa.europa.eu/*

[6] Available at *www.who.int/publications/i/item/9789241513548*

Socio-economic arguments are considered in setting binding occupational exposure limit values (BOELV) in the EU. However, the project team recommended to deal with the scientific justification for deriving OELs and the socio-economic aspects in a two-step procedure, to keep the process transparent.

Implementing steps towards harmonisation (which was considered a desirable objective by the participants) would require activities at various levels, among them

- Discussion of suitable databases for extrapolation steps
- Discussion of methodological details, e.g., with regard to locally acting substances and particles in the respiratory tract; or regarding the use of the benchmark approach or allometric scaling
- Discussion of protection levels and associated risk management decisions.

The further discussion focussed on the practical process: should these efforts start at the national level, to allow for fast progress or better at EU or international level? No conclusion was taken here, but several participants representing internationally operating companies advocated for international efforts. Such activities could potentially be placed with the OECD, whose Working Party on Hazard Assessment recently issued a report on "Establishing Occupational Exposure Levels".[7] However, starting activities at more than one level was considered an option as well. A further participant proposed to give the Europeans Chemicals Agency (ECHA) a general mandate to derive (harmonised) OELs. Another comment asked for implementing a board of appeal to be called in case of strongly deviating OELs.

Thomas Gebel in his concluding remarks pointed out that the discussion on harmonisation of OELs fitted perfectly in the EU Chemicals Strategy, which strongly advocates for the principle of "one substance - one assessment").

4 Conclusions

Large differences between existing frameworks for deriving OELs and analogue values were observed in the research project F2437. There was a general agreement among workshop participants that harmonisation of methods to derive OELs is a worthwhile objective.

Several important activities were identified:

- Although the project substantially improved the database for extrapolation steps there are possibilities to further improve the empirical database, by
  - Evaluating studies according to OECD TG 407/408/422 design (by comparing no effect levels for the same type of effect and at the level of the lowest no effect level per study)
  - Investigating concentration- or time-dependency of locally acting substances over short time periods (to conclude on the need for exposure scenario adaption for this group of substances
  - Enlarge the database for inter-individual differences regarding toxicokinetics (to elucida te potential differences between the oral and inhalation route)
  - Improve the database for toxicodynamic variation with regard to shortcomings of the data from Abdo et al. (2015).

[7] OECD, Environment Directorate Chemicals and Biotechnology Committee; Establishing Occupational Exposure Limits; Series on Testing and Assessment, No. 351; 17 June 2022;
www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/cbc/mono(2022)6&doclanguage=en

- Differences in methodological procedures were identified, requiring harmonisation, for example
  - Modelling of deposition and clearance of particles in the respiratory tract (“Human equivalent concentration approach”, HEC)
  - Dealing with data on sensory irritation
  - Use of the benchmark approach
  - Use of allometric scaling.
- Steps towards harmonisation should be implemented organisationally, either
  - at national, EU- or international level, or in parallel
  - such bodies should address how to conclude on risk-management decisions on the percentage of the target population covered and the probability with which uncertainty is addressed.

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