

RESEARCH ARTICLE

Derivation of occupational exposure limits: Differences in methods and protection levels

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Funding information

Federal Institute for Occupational Safety and
Health, Grant/Award Number: F2437

Abstract

Frameworks for deriving occupational exposure limits (OELs) and OEL-analogue values (such as derived-no-effect levels [DNELs]) in various regulatory areas in the EU and at national level in Germany were analysed. Reasons for differences between frameworks and possible means of improving transparency and harmonisation were identified. Differences between assessment factors used for deriving exposure limits proved to be one important reason for diverging numerical values. Distributions for exposure time, interspecies and intraspecies extrapolation were combined by probabilistic methods and compared with default values of assessment factors used in the various OEL frameworks in order to investigate protection levels. In a subchronic inhalation study showing local effects in the respiratory tract, the probability that assessment factors were sufficiently high to protect 99% and 95% of the target population (workers) from adverse effects varied considerably from 9% to 71% and 17% to 87%, respectively, between the frameworks. All steps of the derivation process, including the uncertainty associated with the point of departure (POD), were further analysed with two examples of full probabilistic assessments. It is proposed that benchmark modelling should be the method of choice for deriving PODs and that all OEL frameworks should provide detailed guidance documents and clearly define their protection goals by stating the proportion of the exposed population the OEL aims to cover and the probability with which they intend to provide protection from adverse effects. Harmonisation can be achieved by agreeing on the way to perform the methodological steps for deriving OELs and on common protection goals.

KEYWORDS

assessment factors (AFs), distributions, occupational exposure limits (OELs), probabilistic hazard assessment, protection level, uncertainty

1 | INTRODUCTION

Occupational exposure limits (OELs) are important tools for controlling and managing exposures to hazardous substances at the workplace. Various bodies at national and international level set OELs.

Within the European Union (EU), the Scientific Committee on Occupational Exposure Limits (SCOEL) proposed OELs, until the Committee for Risk Assessment (RAC) at the European Chemicals Agency (ECHA) took over this task in 2019. At the national level in Germany, two committees are engaged in the derivation of health-based OELs:

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the Committee on Hazardous Substances (Ausschuss für Gefahrstoffe, AGS) and the Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (the MAK Commission) of the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG). However, health-based guidance values for the workplace are not only established in the context of occupational safety and health legislation but also in other regulatory areas. Under the EU chemicals legislation REACH (EC, 2006), derived no-effect levels (DNELs) are used as part of the chemical safety assessment in registration dossiers prepared by registrants, and acceptable exposure levels (AELs) and acceptable operator exposure levels (AOELs) for active substances are derived under the EU Biocidal Products Regulation (BPR) (EU, 2021) and the EU Plant Protection Products (PPP) Directive (EC, 2021), respectively. These latter values will be referred to here as 'OEL-analogue values'.

In principle, the approaches used to derive an OEL or analogue value are similar in the different regulations or committees: Typically, a point of departure (POD) is derived from a toxicological study, which is then extrapolated to a working-life exposure scenario, taking into account exposure duration, interspecies differences and intraspecies variability by applying assessment factors (AF). However, as assessors follow different guidelines that, for example, provide different default values for AF, it is not surprising that quantitative differences are observed for workplace exposure limits derived for the same substance in the different regulatory areas. In particular, differences observed between DNELs and OELs have generated discussion (Kreider & Spencer Williams, 2010; Nies et al., 2013; Schenk et al., 2014, 2015; Schenk & Johanson, 2011; Tynkkynen et al., 2015).

To analyse the different methodologies used for deriving health-based OEL or OEL-analogue values and the reasons for variation,

especially with respect to the protection levels achieved by the exposure limits, a project was initiated by the German Federal Institute for Occupational Safety and Health (Bundesanstalt für Arbeitsschutz und Arbeitsmedizin, BAuA). This project aimed to improve the empirical database for extrapolation steps (time, interspecies and intraspecies extrapolation) forming part of the OEL derivation process (Dilger et al., 2022) and, by means of this analysis, to contribute to transparency and harmonisation of the approaches for deriving OELs or similar values in the various regulatory areas in the EU. The analysis was restricted to long-term exposure limits via inhalation for substances thought to act via a threshold mechanism.

Further aspects of OEL derivation were discussed in this project, for example, differences between species regarding deposition and clearance of particles and the derivation of human equivalence concentrations. Interested readers are referred to the project report (Schneider et al., 2022). Here, we describe the outcome of the comparison and analysis of methodologies in use in Europe (for the scope, see Table 1), investigate the protection levels achieved by the various frameworks and discuss steps for increasing transparency and harmonisation of the approaches. Two examples of probabilistic assessments provide further insight into the uncertainties and variability associated with the various steps of OEL derivation.

2 | METHODS

2.1 | Comparison of methods

Methods used to set OELs on a national level in Germany as well as OELs and analogue values in various regulatory areas at the EU level

TABLE 1 Occupational exposure limits (OEL) and analogue values analysed

Type of value	Organisation	Guidance/documentation
German OELs (AGW, Arbeitsplatzgrenzwerte, legally binding)	Committee on Hazardous Substances (AGS)	AGS (2010, 2018)
MAK values (proposals for German OELs, not legally binding)	MAK Commission (Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area of the DFG)	DFG (2020)
OELs on behalf of European Commission	Scientific Committee on Occupational Exposure Limits (SCOEL)	SCOEL (2013, 2017)
OELs on behalf of European Commission	Committee for Risk Assessment (RAC)	ECHA (2019)
Derived no-effect levels (DNELs) (workplace, inhalation)	European Chemicals Agency (ECHA)/ REACH registrants	ECHA (2012)
Derived no-effect levels (DNELs) (workplace, inhalation) with regard to REACH	European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC)	ECETOC (2003, 2010)
Acceptable exposure levels (AEL values) for biocidal products with regard to BPR	ECHA/BPR applicants	ECHA (2017)
Acceptable operator exposure levels (AOEL values) for active substances with regard to the EU plant protection products (PPP) directive	Authorities/PPP applicants	EC (2006)

were analysed and compared. The types of values, organisations and documentation included in the analysis are given in Table 1. Only long-term health-based values for the inhalation route were compared.

Available guidance documents were evaluated in respect of the following topics: (1) data search and evaluation (including the following aspects: requirements for information searches, assessment of data quality, identification of critical effects and key studies, application of read-across and quantitative structure–activity relationships (QSAR), use of human vs. animal data, consideration of severity of effects, requirements for updates, documentation requirements), (2) methodology for deriving exposure limits for systemic effects (including type of POD used and ways to select the POD, route-to-route extrapolation, POD modification, use of AF and deviation from default values) and (3) methodology for deriving exposure limits for local effects on the respiratory tract (with the additional aspects: consideration of sensory irritation, and deposition and clearance of aerosols in the respiratory tract). For more details, see Schneider et al. (2022) (Report 1: Comparison of Methods for Deriving OELs).

2.2 | Evaluation of protection levels

In the OEL frameworks discussed, it is current practice to multiply the values of the different AF. The OEL is then obtained by dividing the POD by the total AF (deterministic approach). The term protection level here refers to the probability with which the deterministic total AF is protective for a certain effect (level), as calculated with the probabilistic model below.

As part of this project, we compiled and analysed data for improving the empirical database for different extrapolation steps. From these data, we derived distributions describing the substance-to-substance variability of dose descriptor ratios (e.g. no observed adverse effect level [NOAEL] ratios) for large sets of chemicals, described in detail by Dilger et al. (2022). In short, we calculated ratios using NOAELs (or lowest observed adverse effect levels [LOAELs] in the absence of NOAELs) from subacute, subchronic and chronic studies with rats and mice for 256 substances carried out by the US National Toxicology Program (NTP). To derive distributions for time extrapolations, we calculated ratios by dividing the NOAEL (or LOAEL, under specific conditions) of the shorter study by that of the longer study (subacute/subchronic, subacute/chronic, subchronic/chronic). Care was taken to compare NOAELs for similar endpoints. So, for example, only NOAELs and LOAELs for the endpoint body weight were extracted from subacute studies to avoid inconsistencies due to differences in investigation depths between the studies of different exposure duration. Details on the procedures are given in Dilger et al. (2022) and in Schneider et al. (2022) (Report 6: Time Extrapolation; section 2: Methods).

The same NOAELs and LOAELs from the NTP study data were used to calculate ratios for the interspecies comparison (rat/mouse), with two objectives: to check the agreement of the data with the predictions made by the concept of allometric scaling according to the basal metabolic rate and to describe the substance-to-substance variability. The latter was used to establish a distribution to describe the remaining interspecies

variability after applying allometric scaling factors. By comparing the obtained variability with that obtained by Bokkers and Slob (2007), the variability was adjusted for the additional uncertainty introduced by using N(L)OEL ratios instead of benchmark dose ratios (for more detailed explanations, see Dilger et al., 2022, or Schneider et al., 2022; Report 10: Synthesis report; section 2.4: Interspecies extrapolation).

For describing inter-individual variability due to differences in toxicokinetics and toxicodynamics, two different sets of human data were used. To describe toxicokinetic variability, 68 toxicokinetic studies with adult humans (oral or inhalation exposure) were identified by literature searches and evaluated. These contained quantitative kinetic measures (area under the curve, AUC, or maximum plasma concentration, C_{max}) and a measure of the inter-individual variability (individual data given, standard deviation [SD], variation coefficient [CV] or geometric mean [GM] plus 95th confidence interval or 25th and 75th percentile). All data were assumed to be lognormally distributed, and \log_{10} GSD (standard deviation of the logarithmic data) was calculated for each dataset, in accordance with WHO (2014). From the distribution of \log_{10} GSD values, two distributions were obtained for the protection goals to include 95% or 99% of the target population.

To describe toxicodynamic inter-individual variability, data as reported by Abdo et al. (2015) were used. These authors provided information on the variability in the in vitro cytotoxicity of 179 chemicals in immortalised human lymphoblastoid cell lines derived from 1086 individuals representing nine different populations from five different continents ('1000 Genomes Project'). EC10 values (effective concentration, 10th percentile) were determined by these authors for each substance in each cell line, and variability between cell lines was described by percentiles of the obtained empirical distributions of EC10 values. In addition, factors were calculated for each dataset describing the difference between the 1st (or 5th percentile) and the median, reflecting the difference in response of the 1% (or 5%) with the lowest EC10 (highest susceptibility) and the median, corrected for sampling variability (variation between replicate measurements). We used these reported factors to establish distributions describing toxicodynamic differences with the protection goals to include 95% or 99% of the target population.

The distributions for toxicokinetic and toxicodynamic variability for each protection goal were combined by Monte Carlo simulation to obtain two distributions for intraspecies extrapolation for the 95% and 99% protection goals, respectively. Methodological details are given in Dilger et al. (2022) and Schneider et al. (2022) (Report 8: Intraspecies extrapolation; section 2: Evaluation of literature data on inter-individual variability).

The distributions resulting from these analyses are given in Table 2.

The distributions for time and interspecies extrapolation describe the uncertainty as to whether a specific substance behaves like the substances used in the empirical dataset. For example, using a 90th percentile of the distribution leads to the conclusion that there is a 90% probability that the behaviour of the substance to be assessed falls within this range. In other words, there is a 90% probability that the OEL derived is sufficiently protective. The distributions for intraspecies extrapolation include the substance-to-substance uncertainty

TABLE 2 Distributions for extrapolation steps as derived by Dilger et al. (2022)

Extrapolation step	μ	σ	Median	75% percentile	95% percentile
Time: sa/c	1.31	1.05	3.71	7.52	20.85
Time: sc/c	1.04	0.99	2.83	5.53	14.49
Interspecies	0.02	0.75	1.02	1.69	3.49
Combined (TK and TD) intraspecies at 1% incidence	-	-	7.25	12.53	34.26
Combined (TK and TD) intraspecies at 5% incidence	-	-	3.56	5.15	10.37

Abbreviations: c, chronic; sa, subacute; sc, subchronic; TD, toxicodynamic; TK, toxicokinetic; μ , location parameter; σ , shape parameter of lognormal distribution.

TABLE 3 1,1,2,2-Tetrachloroethane: relative liver weights in male and female rats (daily oral exposure for 14 weeks) (NTP, 2004)

Dose (mg/kg bw/d)	Relative liver weight (mean) (mg/g bw)	Relative liver weight (SEM) (mg/g bw)	N (# animals in group)	Sex
0	34.79	0.42	10	m
20	36.72	0.44	10	m
40	41.03	0.85	10	m
80	45.61	0.52	10	m
170	44.68	0.45	10	m
320	52.23	1.42	10	m
0	35.07	0.56	10	f
20	36.69	0.36	10	f
40	37.84	0.51	10	f
80	44.2	0.27	10	f
170	48.03	0.89	10	f
320	58.4	1.42	10	f

Abbreviations: bw, body weight; f, female; m, male; SEM, standard error of the mean.

but in addition describe the inter-individual variability. To derive an OEL with this distribution, a decision on the percentage of the target population (workers) to be protected needs to be taken. Without the intention to set a precedent, for the calculations here, 95% (5% incidence) and 99% of the target population (1% incidence) are used.

These distributions were multiplied by Monte Carlo simulation (10^7 samples) using base functions from the software R (Version 4.0.3) (R Core Team, 2021), resulting in a distribution representing the probabilistic model of the combined assessment steps. For two exemplary scenarios, subacute oral study and subchronic inhalation study, the total deterministic AF for each of the OEL frameworks in Table 1 was determined and compared with the respective probabilistic model. That is, for each total AF, the probability was read from the distribution. The protection level is given as the probability achieved by a specific total AF. The protection levels for all types of combinations of factors are given in Schneider et al. (2022) (Report 10: Synthesis report; section 3: Comparison of distributions with currently used default values).

2.3 | Probabilistic evaluation of example substances

For two substances, for which OELs were recently derived in Germany and which represent examples for continuous

(1,1,2,2-tetrachloroethane) as well as quantal data evaluations (benzoic acid), benchmark doses were calculated with the web-based PROAST-EFSA tool at <https://r4eu.efsa.europa.eu/> (PROAST Version 67.0 for quantal data and Version 69.0 for continuous data), applying model averaging. For both substances, we combined data from both sexes. We performed probabilistic modelling for the two substances using the Monte Carlo tool as provided by the European Food Safety Agency (EFSA) (<https://r4eu.efsa.europa.eu/>) with the distributions given in Table 2 (for details, see Schneider et al., 2022, Report 10: Synthesis Report; section 5: Probabilistic assessment of two example substances).

The critical study chosen for deriving an OEL for 1,1,2,2-tetrachloroethane is an NTP subchronic continuous feeding study (NTP, 2004): Adult rats were dosed with 1,1,2,2-tetrachloroethane 7 days/week for 14 weeks via feed (Table 3). A BMDL and BMDU (lower and upper bound of the one-sided 95% confidence interval of the benchmark dose, BMD) were calculated with a benchmark response (BMR) of 20% change in relative liver weight. Assuming a lognormal shape, a distribution of the benchmark dose was calculated and then modified as proposed by the MAK Commission (Hartwig, 2020): A difference in absorption rates in rats (95% oral absorption) versus humans (60% absorption after inhalation), 7- versus 5-day exposure of rats compared with workers, an allometric scaling factor of 4, 70 kg body weight and 10 m^3 breathing

volume per workday were considered. For the probabilistic modelling, the distributions for subchronic to chronic extrapolation, interspecies extrapolation and intraspecies extrapolation (at the 1% and 5% incidence level) were used, as given in Table 2, together with the distribution for the benchmark dose.

In the case of benzoic acid, the key study is an unpublished 4-week inhalation toxicity study in rats, reported by Hartwig and MAK Commission (2018), in which interstitial inflammation of the lungs was observed. Concentration–response data are shown in Table 4. Assuming a lognormal shape, a distribution of the benchmark dose was calculated and was divided by a factor of 2 to account for differences in exposure time per day (6 h in the experimental study vs. 8 h per day at the workplace) and physical activity (breathing volume: 10 m³ for light activity vs. 6.7 m³ at rest; see ECHA, 2012).

For the probabilistic modelling, the distributions for subacute to chronic extrapolation, interspecies extrapolation and intraspecies extrapolation (at the 1% and 5% incidence level) were used, as given in Table 2, together with the distribution for the benchmark dose.

3 | RESULTS

3.1 | Key observations regarding differences between methodologies

The analysis of available guidance documents revealed various reasons for qualitative and quantitative differences in OEL derivation. The guidance given on methodology and performance of specific tasks (e.g. how to perform data searches, how to weigh human vs. experimental animal data, how to identify key studies and their reliability, how to define a POD, recommendations for default AF) varies considerably between the frameworks assessed. For example, in contrast to others, the REACH guidance (ECHA, 2011) and the methodology of SCOEL (SCOEL, 2017) provide detailed guidance on how to perform data searches, and only the REACH guidance uses a systematic approach to evaluate data quality (so-called Klimisch scores) (ECHA, 2011). Although all frameworks emphasise the importance of

(high-quality) human data and careful consideration to identify the key study, in practice, OELs are often derived from human data (Schenk & Johanson, 2010), whereas in the REACH, BPR or PPP context experimental animal data are often used. This is at least partly explained by the fact that OELs are derived for fewer, more data-rich substances, whereas for the latter frameworks, specific information requirements exist, sometimes leading to differences in the available database and a tendency to use information from the set of required studies. Also, there are differences regarding consideration of newly emerging toxicological information. Only the REACH guidance (ECHA, 2012) and SCOEL (SCOEL, 2017) explicitly call for an update of the evaluation in the event that relevant new information becomes available. At all these steps, differences might occur and might lead to differences in the key study and the POD selected and the numerical value of the OEL (for details, see Schneider et al., 2022, Report 1: Comparison of Methods for Deriving OELs; section 2.2: Data search and evaluation).

All types of exposure levels under analysis share a similar definition: They aim at identifying doses or concentrations, at or below which no detrimental effects in exposed workers are expected, including sensitive individuals or subpopulations. However, a detailed analysis reveals distinct differences (Table 5). In contrast to other values, AEL and AOEL values for operators derived for active substances in biocidal products or plant protection products focus on systemic effects, and values are given as systemic doses (mg substance per kg body weight and day). Although consideration of local effects in the respiratory tract is not excluded, little information is given on how to use such data for deriving AEL or AOEL values. Furthermore, these values are intended to be used to assess the risks to professionals handling the products, but they are applied equally for assessing the risks to bystanders and non-professional users. In contrast, OELs as derived by SCOEL, RAC, AGS or the MAK Commission are given as air concentrations (mg/m³) and are specifically intended for workers. Local effects in the respiratory tract (including sensory irritation) are a major consideration here.

A major quantitative difference in OELs may result from the (non-)consideration of specific endpoints, such as respiratory sensitisation and developmental toxicity. For example, in Germany, a workplace

TABLE 4 Benzoic acid: incidences of interstitial inflammation ('generalised') of the lungs in male and female rats (unpublished inhalation study, exposure at 6 h/d, on 5 d/w for 4 w, reported by Hartwig and MAK Commission, 2018)

Concentration (mg/m ³)	Effect (# affected animals) ^a	N (# animals in group)	Sex
0	0	10	m
25	3	10	m
250	4	10	m
1200	8	10	m
0	0	10	f
25	0	10	f
250	5	10	f
1200	9	10	f

Abbreviations: d, day; f, females; h, hour; m, males; w, week.

^aFor each concentration group, affected animals classified to show 'generalised' signs of interstitial lung inflammation were counted (all grades combined).

TABLE 5 Key characteristics of occupational exposure limits (OEL) and analogue values derived in different regulatory frameworks

	REACH regulation (DNELs for workers)	RAC OEL methodology (OELs at EU level)	SCOEL (OELs at EU level)	AGS (German OELs)	DFG MAK (German OELs)	ECETOC (DNELs for workers)	Plant Protection Products Directive (AOELs for bystanders and residents)	EU Biocidal Products Regulation (AELs/AECs for non-professional users)
Target populations	Workers only	Workers only	Workers only	Workers only	Workers only	Workers only	Workers (operators) and others	Workers (professional) and others
Unit	mg/m ³ or ppm (for workplace inhalation exposure)	mg/m ³ or ppm (for workplace inhalation exposure)	mg/m ³ or ppm (for workplace inhalation exposure)	mg/m ³ or ppm (for workplace inhalation exposure)	mg/m ³ or ppm (for workplace inhalation exposure)	mg/m ³ or ppm (for workplace inhalation exposure)	mg/kg body weight/day (absorbed dose from all routes)	mg/kg body weight/day (absorbed dose from all routes), mg/m ³ (for AECs for route-specific effects)
Developmental toxicity quantitatively considered?	Yes	Yes	(Yes) ^a	No—pregnancy group notation	No—pregnancy group notation	Yes	Yes	Yes
Respiratory sensitisation quantitatively considered?	Considers only qualitative assessment possible	Yes, plus sensitisation notation	If data allow, plus sensitisation notation	No, sensitisation notation	No, sensitisation notation	Not mentioned	Not mentioned	Considers only qualitative assessment possible
Default AF for time extrapolation	sa – c: 6 sa – sc: 3 sc – c: 2	sa – c: 6 sa – sc: 3 sc – c: 2	No	sa – c: 6 sa – sc: 2 sc – c: 2	In practice, same factors applied as AGS	sa – c: 6 sa – sc: 3 sc – c: 2	sc – c: 2	sa – c: 6 sa – sc: 3 sc – c: 2
Allometric scaling for interspecies extrapolation	Yes, exponent 0.75	Yes, exponent 0.75	Yes, exponent 0.75	Yes, exponent 0.75	Yes, exponent 0.75	Yes, exponent 0.75	No	No, but can be used to replace default interspecies AF
Default AF for interspecies extrapolation	2.5	2.5	No default provided	5 (combined factor for interspecies and intraspecies extrapolation)	2 (combined factor for interspecies and intraspecies extrapolation)	1	10	10
Default AF for intraspecies extrapolation	5	5	> = 1			3	10	10

Abbreviations: c, chronic; sa, subacute; sc, subchronic.

^aPregnant women in scope in latest guidance (SCOEL, 2017), but older evaluations might not comply.

limit value of $7 \mu\text{g}/\text{m}^3$ ($3.4 \mu\text{g}$ isocyanate [or NCO] groups/ m^3) was proposed for toluene diisocyanates, based on irritating effects in the respiratory tract (Hartwig and MAK Commission, 2021). Respiratory sensitisation was not considered quantitatively, but a notation indicating hazards for this endpoint was assigned. In contrast, the Health Council of the Netherlands (HCN) based its recommendation for an OEL for di- and triisocyanates on consideration of asthma risk. According to this evaluation, the recommended value of $0.1 \mu\text{g}/\text{m}^3$ (measured as the sum of NCO groups) corresponds to an extra risk for asthma of 1% (HCN, 2018). In line with this approach, ECHA's RAC developed an exposure–response relationship for the risk of respiratory sensitisation as a basis for deriving an EU-wide OEL (RAC, 2020), which indicates excess risk of up to 5% at concentrations below $1 \mu\text{g}$ NCO groups/ m^3 .

Similarly, there are differences between the methodologies with respect to the endpoint developmental toxicity: For derivation of AOELs and AELs for pesticides and biocides as well as OELs and DNELs at the European level, data on developmental toxicity are included to provide protection of the unborn child, whereas in Germany notations are used to warn that OELs may not provide this protection. As a reference DNEL for authorisation of bis (2-methoxyethyl)ether (diglyme) applications, RAC derived an inhalation DNEL for workers of $1.68 \text{ mg}/\text{m}^3$, based on reproductive and developmental toxicity (ECHA, 2015). The German OEL is $5.56 \text{ mg}/\text{m}^3$, accompanied by notation Z, indicating that a risk for the unborn cannot be excluded at the OEL (AGS, 2021).

Although many frameworks recommend using BMD or BMDL as the POD, little detailed guidance on its application is available. Often NOAELs or even LOAELs, when no dose or concentration without effect could be identified, are used as the POD, with the high associated uncertainty for estimating a no adverse effect level from the LOAEL. For example, guidance is required for setting benchmark response levels (the effect size associated with the BMD) for dose–response data measured on a continuous scale (such as body weight or transaminase activity in blood). Respective recommendations are given in the recently updated chapter 5 of the Environmental Health Criteria document 240 (WHO, 2020). Modifications to adapt PODs to the occupational exposure scenario are another potential source of differences. For example, the REACH guidance, in the absence of substance-specific data, assumes a lower absorption via the oral route (50%) compared with inhalation (100%) (ECHA, 2012), whereas the MAK Commission by default uses the same absorption for oral and inhalation exposure (see Schneider et al., 2022, Report 1: Comparison of Methods for Deriving OELs; section 3: Methodology for deriving limit values for systemic effects).

A major reason for quantitative differences is that AFs differ between the frameworks (Table 5). Considerable differences exist for time extrapolation for substances acting locally in the respiratory tract. In contrast to most other methodologies, European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) (2010) assumes that such effects do not increase with prolonged exposure. In an up-to-date, comprehensive review, ECETOC cited studies showing a decrease of NOAELs for local effects with increasing exposure

duration similar to systemic effects (ECETOC, 2020), however without proposing specific values for the time AFs. Our analysis of data from the US NTP studies and REACH data confirmed that the effect on NOAELs of prolonged inhalation exposure is similar for systemic and local effects (Dilger et al., 2022). A recent evaluation found that higher values for time extrapolation factors are required in cases of local compared with systemic effects (Mangelsdorf et al., 2021).

Considerable differences are also observed in default values used in various frameworks for intraspecies extrapolation, ranging from 1 to 10. This is certainly caused by the scarcity of empirical data for this step. As part of our project, the results of which are reported elsewhere (Dilger et al., 2022), we compiled new data for intraspecies variability, including human data on toxicokinetic differences after inhalation exposure, which is especially relevant for workplace exposure situations.

For pesticides and biocides, allometric scaling is not usually applied for interspecies extrapolation, in contrast to all other methodologies. Allometric scaling means that differences in basal metabolic rate due to body size are compensated for by species-specific scaling factors (Kenyon, 2012; Schneider et al., 2004). Whereas the interspecies factor of 10 applied for pesticides and biocides is numerically identical to a scaling factor of 4 for rat studies plus an additional factor of 2.5 ($4 \times 2.5 = 10$), as proposed, for example, by the REACH guidance (ECHA, 2012), quantitative differences result for species other than rats.

3.2 | Protection levels

The distributions provided in Table 2 for time and interspecies extrapolation represent the results from our recent and comprehensive evaluation of NTP studies (Dilger et al., 2022). In addition, new empirical distributions covering both aspects of toxicokinetic and toxicodynamic differences were derived from 68 human studies, including 31 inhalation studies, on toxicokinetic differences. For quantifying toxicodynamic differences, the analysis of Abdo et al. (2015) was used (for details see Dilger et al., 2022, and Schneider et al., 2022, Report 8: Intraspecies extrapolation).

It is noteworthy that no clear quantitative difference was observed between systemic toxicity and local effects in the respiratory tract when analysing the empirical databases for time and interspecies extrapolation. Hence, the same distributions are proposed for systemic effects and local (irritating) effects in the respiratory tract.

To investigate the protection levels achieved (i.e. the probability that the combined AFs provide protection against effects as defined by the POD) by the various OEL frameworks, two exemplary cases were used: Case A: a subacute oral rat study reporting systemic effects and Case B: a subchronic inhalation rat study reporting local effects in the respiratory tract.

The protection levels achieved (or probability) as given in Table 6 (Case A) and Table 7 (Case B) describe the probability with which 95% or 99% (for the incidence levels 5% and 1%, respectively) of the target population are protected against an effect as described by the POD,

TABLE 6 Protection levels achieved (probability) by default assessment factors (AF) proposed in various occupational exposure limit (OEL) frameworks (point of departure [POD] from subacute oral rat study)

OEL framework	Proposed AF (time, inter, scaling, intra)	Total AF proposed	Incidence for intraspecies extrapolation	Probability at total AF
EU BPR	6, 10, -, 10	600	1%	85.6%
			5%	95.0%
REACH/RAC	6, 2.5, 4, 5	300	1%	73.3%
			5%	88.0%
AGS	6, -, 4, 5 ^a	120	1%	51.0%
			5%	70.3%
MAK	6, -, 4, 2 ^a	48	1%	28.0%
			5%	45.3%
ECETOC	6, 1, 4, 3	72	1%	37.7%
			5%	56.8%

^aCombined factor for inter- and intraspecies extrapolation.

TABLE 7 Protection levels achieved (probability) by default AFs proposed in various OEL frameworks (POD from subchronic inhalation study reporting local effects in the respiratory tract)

OEL framework	Proposed AF (time, inter, intra)	Total AF proposed	Incidence for intraspecies factor	Probability at total AF
EU BPR	2, 2.5, 10	50	1%	70.8%
			5%	86.7%
REACH/RAC	2, 2.5, 5	25	1%	53.3%
			5%	73.0%
AGS	2, -, 5 ^a	10	1%	29.5%
			5%	47.7%
MAK	2, -, 2 ^a	4	1%	12.1%
			5%	23.1%
ECETOC	1, 1, 3	3	1%	8.5%
			5%	17.1%

^aCombined factor for inter- and intraspecies extrapolation.

when the OEL is derived using the total AF as proposed in a specific framework. For example, with a total AF of 300, as proposed in the REACH guidance, there is a probability of 73.3% that 99% of the target population is protected by the limit value (incidence level 1%), when starting from a subacute oral rat study, whereas it is only 37.7% in case of the total AF of 72 proposed by ECETOC. The default AFs recommended by the various organisations for the two cases are also given in Tables 6 and 7.

For an oral rat study reporting systemic effects, an allometric factor of 4 would be used by all organisations applying basal metabolic rate scaling (exponent 0.75). In the case of REACH/RAC, this is combined with a factor of 2.5 to allow for remaining uncertainties. Instead of the scaling factor, a high interspecies factor of 10 is used in the EU BPR system, which leads to the same combined interspecies factor for rat studies (4×2.5). The BPR methodology results in the highest combined factors, due to a high intraspecies factor of 10 (600 for the subacute oral study, 50 for the subchronic inhalation study). The EU PPP guidance does not provide an AF for subacute to chronic

extrapolation and therefore is not included in the case description above. However, a similar outcome can be assumed as for BPR. The lowest combined AFs result from the ECETOC recommendations: 72 (subacute oral rat study)/3 (subchronic inhalation study) and the German MAK: 48/4. The other systems are in between (ECHA/RAC: 300/25; German AGS: 120/10).

Table 6 shows that for Case A, with a subacute oral rat study as key study, probabilities achieved range from 28% (MAK) to 86% (BPR) for the incidence level of 1% and from 45% to 95% for the incidence level of 5%. For Case B (subchronic inhalation study, local respiratory effects; Table 7) the differences between frameworks are even larger: Probabilities range from 9% (ECETOC) to 71% (BPR) and 17% (ECETOC) to 87% (BPR) for the 1% and 5% incidence level, respectively.

Figure 1 visualises the cumulative probability distribution for Case B for the 1% incidence level. Vertical lines represent the combined AF used by the various organisations from which the probabilities achieved by these factors can be read.

3.3 | Probabilistic OEL derivation

3.3.1 | 1,1,2,2-Tetrachloroethane

1,1,2,2-Tetrachloroethane was recently re-evaluated by the MAK Commission, and an OEL of 14 mg/m³ was derived (Hartwig, 2020). The critical study was a subchronic continuous feeding study by NTP with rats. Dose–response data used are given in Table 3. The MAK Commission determined a NOAEL of 20 mg/kg bw/d based on increased relative liver weight in both sexes and decreased sperm motility in males. They modified the POD for differences between rats and the exposure scenario for workers (for details, see Section 2) and arrived at a concentration of 77.6 mg/m³. We used the same POD modifications with all approaches (ECHA/RAC, EU BPR, ECETOC) to maintain comparability. With a factor of 2 for time extrapolation and a factor of 2 for inter- and intraspecies differences, the MAK Commission derived an OEL of 14 mg/m³ (19.4 mg/m³ or 2.8 ppm, leading to an OEL of 2 ppm (or 14 mg/m³), according to the ‘preferred value

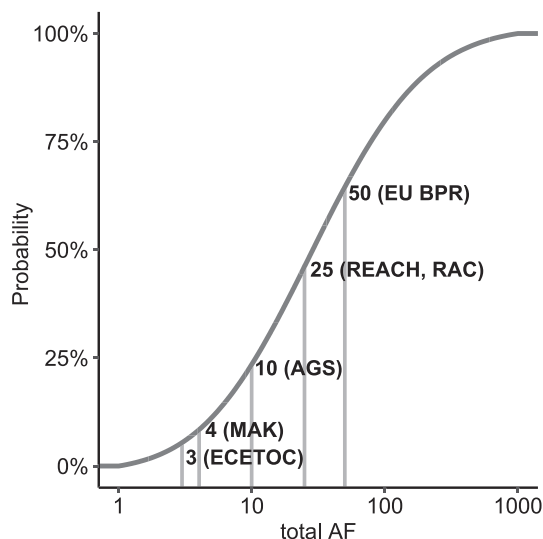


FIGURE 1 Cumulative distribution of the probability that the incidence is not higher than 1% (POD derived from subchronic inhalation study showing local effects) and probabilities achieved by the total AFs applied in various OEL frameworks (vertical lines)

TABLE 8 Assessment factors used, resulting OELs or OEL-analogue values and protection levels according to the probabilistic model for 1,1,2,2-tetrachloroethane

Framework	Proposed AF (time, interspecies, intraspecies)	Total AF	OEL or OEL-analogue value	Probability at OEL according to probabilistic model	
				5% incidence	1% incidence
RAC/REACH	2, 2.5, 5	25	3.1 mg/m ³	92.7%	80.7%
AGS	2, 5, -	10	7 mg/m ³	80.9%	62.9%
MAK	2, 2, -	4	(rounded) 14 mg/m ³	64.5%	44.5%
ECETOC	2, 1, 3	6	12.9 mg/m ³	66.7%	46.9%
EU BPR	2, 2.5 ^a , 10	50	1.5 mg/m ³	97.5%	90.7%

^aAn allometric factor of 4 was used in the POD modification; to allow comparison, the interspecies factor is reduced to 2.5.

approach’ used by MAK Commission). The OELs and OEL-analogue values that follow from the other frameworks are given in Table 8.

We performed benchmark dose modelling with the dose–response data in Table 3 and a BMR of 20% change in relative liver weight. We chose this rather high response level to distinguish adaptive responses from initial liver toxicity, following the conclusions of German committees for this endpoint based on Hall et al. (2012). This yielded a BMDL of 49.3 mg/kg bw/d, which is higher than the NOAEL (for details, see Schneider et al., 2022, Report 10: Synthesis Report; section 5: Probabilistic assessment of two example substances). The BMD distribution is assumed to be lognormal, resulting in the parameters $\mu = 4.16$ and $\sigma = 0.16$ used for the probabilistic modelling, with 49.3, 64.1 and 83.2 mg/kg bw/d for BMDL, BMD and BMDU (upper bound of the one-sided 95% confidence interval of the BMD), respectively.

Figure 2 shows the probability distribution obtained by probabilistic modelling with the BMD distribution combined with the distributions for subchronic to chronic, inter- and intraspecies extrapolation (see Table 5). Relatively high probabilities are achieved by all systems, which is due to the BMD distribution being less conservative in this case than the NOAEL identified.

3.3.2 | Benzoic acid

Benzoic acid serves as a case study for using quantal (also called dichotomous) data. The MAK Commission identified interstitial inflammation and fibrosis of the lungs in a 4-week inhalation study in rats. The rats were exposed for 6 h on 5 days per week. Effects were observed at the lowest concentration in this study (25 mg/m³), but a NOAEC of 12.6 mg/m³ was derived from a second study, which did not reveal effects at the highest concentration tested (12.6 mg/m³) (Hartwig and MAK Commission, 2018).

The MAK Commission used a modified POD of 6.3 mg/m³, as a factor of 2 was applied to adjust for differences in exposure time per day and physical activity. The same POD was used for AGS, as they follow the same approach. With a factor of 6 for time extrapolation and a combined inter-/intraspecies factor of 2, an OEL of 0.5 mg/m³ was derived by the MAK Commission (Hartwig and MAK

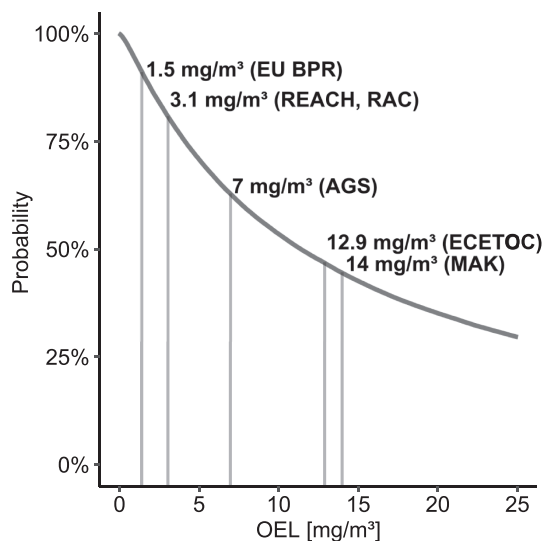


FIGURE 2 Example 1,1,2,2-tetrachloroethane: probability distribution (for incidence level 1%) obtained by Monte Carlo simulation; vertical lines: deterministic OELs

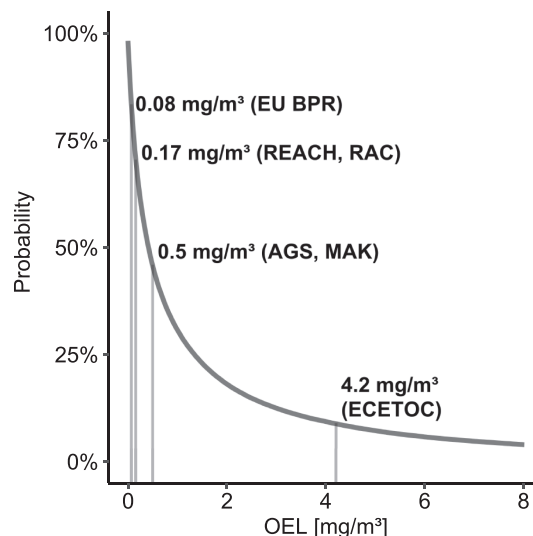


FIGURE 3 Example benzoic acid: Probability distribution (for incidence level 1%) obtained by Monte Carlo simulation; vertical lines: deterministic OELs

TABLE 9 PODs, assessment factors, resulting OEL and protection levels (probability) according to the probabilistic model for benzoic acid

Framework	Modified POD (NOAEC = 12.6 mg/m ³)	Proposed AF (time, interspecies, intraspecies)	Total AF	OEL or OEL- analogue value	Probability at OEL according to probabilistic model	
					5% incidence	1% incidence
RAC/ REACH	12.6 mg/m ³	6, 2.5, 5	75	0.17 mg/m ³	84.1%	70.1%
AGS	6.3 mg/m ³	6, 2, -	12	0.5 mg/m ³	63.3%	46.1%
MAK	6.3 mg/m ³	6, 2, -	12	0.5 mg/m ³	63.3%	46.1%
ECETOC	12.6 mg/m ³	1, 1, 3	3	4.2 mg/m ³	16.4%	9.0%
EU BPR	12.6 mg/m ³	6, 2.5, 10	150	0.08 mg/m ³	92.7%	83.1%

Commission, 2018). AGS supported this value and adopted it as the official workplace limit in Germany (AGS, 2020).

For the deterministically derived OEL-analogue values according to RAC/REACH, ECETOC and EU BPR (column 'OEL or OEL-analogue value' in Table 9), we used the NOAEC of 12.6 mg/m³ as the POD. This was necessary in order to be consistent with the RAC/REACH methodology: The relevant ECHA guidance document (ECHA, 2012) requires that, in the case of local effects, a time dependency of effects needs to be shown to adjust for differences in exposure time per day. As the biocidal products framework is referring to the ECHA guidance, we used the same POD for EU BPR. The probability distribution of the OEL for the workplace scenario obtained by probabilistic modelling with the BMD distribution is presented in Figure 3.

In our evaluations (Dilger et al., 2022), no clear difference in time dependency was observed between systemic and local effects. Therefore, in the probabilistic modelling, we used POD modifications as proposed by the MAK Commission to consider differences in exposure duration and physical activity. We applied benchmark dose

modelling with the dose–response data in Table 4 and a BMR of 10% incidence (both sexes combined, model averaging; for details, see Schneider et al., 2022, Report 10: Synthesis Report; section 5: Probabilistic assessment of two example substances). A BMDL10 of 6.4 mg/m³ was obtained (BMD: 24.2 mg/m³, BMDU: 92.0 mg/m³, modelled by a lognormal distribution with $\mu = 3.18$ and $\sigma = 0.81$).

Considerable differences in protection levels (probabilities achieved) were observed, ranging from 9% to 83% at the 1% incidence level. This variation is mainly due to the wide range of AF used. However, the example also shows that modification of the POD is an important step in the evaluation, which can lead to quantitative differences.

4 | DISCUSSION

In this study, the existing OEL frameworks in the EU and on the national level in Germany were compared systematically. Our analysis

revealed that differences can occur at every individual step of the derivation process, that is, data searches and selection of data for evaluation, prioritisation of information (e.g. by weighing human vs. animal data) and selection of key studies, determination and adjustment of the POD (e.g. with regard to path-specific absorption, if an oral study is used as key study) and the determination of numerical values of AF (with the example of benzoic acid, we showed how different assumptions regarding time dependency of irritating effects lead to numerical differences in OELs). Similar conclusions were previously drawn by other authors (Deveau et al., 2015; Schenk & Johanson, 2010, 2018).

In recent years, several analyses investigating reasons for heterogeneity in derived OELs have been published. Schenk and Johanson (2010, 2018) analysed existing OELs derived by SCOEL and observed that a higher margin of safety resulted when individual factors accounting for uncertainty and variability were explicitly discussed and numerically defined. The methodological differences between OELs as set by SCOEL in previous years and REACH DNELs were also the subject of many investigations. DNELs were found to be consistently lower when derived strictly following the ECHA guidance, but not when DNELs derived by companies submitting registration dossiers were compared with OELs (Kreider & Spencer Williams, 2010; Nies et al., 2013; Schenk et al., 2014, 2015; Schenk & Johanson, 2011; Tynkkynen et al., 2015). Schenk et al. (2015) observed a high variability in DNELs from registration dossiers, when comparing these values with Swedish OELs and with DNELs for 20 substances derived by the authors themselves, based on the ECHA guidance document.

Availability of detailed guidance was identified by us and others as a precondition for avoiding divergent assessments (Maier et al., 2015; Schenk & Johanson, 2010). Therefore, to achieve transparency and harmonisation, OEL frameworks need clear definitions of their protection goals: Are specific endpoints such as developmental toxicity or respiratory sensitisation quantitatively considered when deriving OELs? To what extent do OELs aim to protect susceptible individuals or groups within the workers' population?

With regard to the latter question, probabilistic methods can help to make frameworks more transparent and comparable, as suggested recently by ECETOC (2020). As shown above, distributions can be used to describe the uncertainty inherent to each extrapolation step, but also the variability in susceptibility between individuals (intraspecies extrapolation). If a decision is taken as to what extent inter-individual variability should be considered (by deciding on the percentage of the population to be protected), a probability distribution for the OEL can be derived by probabilistic methods. Deterministic point values can be obtained from this distribution for each selected level of accepted uncertainty.

As shown above, considerable variation exists in the default values of AFs used for the different extrapolation steps. Therefore, for each deterministic factor, the database and the probability aimed at (i.e. the percentile of the underlying distribution) need to be communicated. Without this information, factors proposed are difficult to interpret and to use in a framework together with other extrapolation steps.

To improve the empirical database for AF, we derived distributions for time, interspecies and intraspecies extrapolation, as described by Dilger et al. (2022). Distributions obtained for time extrapolation are based on studies for a large set of chemicals (NTP studies for 256 substances) and cover all three discrete steps (subacute to subchronic and to chronic, subchronic to chronic), which allows for checking of their consistency. A disadvantage is that ratios of NOAELs were used. Compared with ratios based on benchmark doses, this adds uncertainty inherent to the determination of NOAELs to the distributions. However, the observed variability of the NOAEL ratios in our dataset was similar to the variation reported by Bokkers and Slob (2005). These authors reported a GSD of 2.9 for a dataset of 31 subchronic to chronic comparisons based on benchmark modelling of NTP studies. In our evaluation of ratios of NOAELs from subchronic and chronic NTP studies, the GSD was 3.04, indicating a similar level of variability.

We observed a rather low variability in our dataset of NOAEL ratios comparing NTP rat versus mouse studies (95th percentile 3.49). A substantially higher interspecies variability (95th percentile 7.04) was reported in a previous evaluation, which used data from various species including humans (differences in body size were taken into account by allometric scaling factors) (Schneider et al., 2004). The higher variability observed in this older evaluation might reflect higher substance-specific differences between rodent species and humans. However, it might also have been impacted by the higher uncertainty of estimates of subacute toxicity of antineoplastic agents used in that evaluation. Considering these older data, the use of the interspecies distribution derived here may err on the less conservative side.

No methodology has yet been devised for deriving OELs using a data-based AF for intraspecies extrapolation. The distribution proposed here includes, for the first time, a substantial number of human inhalation studies to quantify toxicokinetic variability. The *in vitro* data created by Abdo et al. (2015) that were used to describe toxicodynamic variability cover a large set of substances and cells from more than a thousand individuals. However, there is concern that the only and simple endpoint used (cytotoxicity) might underestimate toxicodynamic variability in more complex organ systems. The observed variability is, although slightly lower, similar to that used by WHO (2014) for a probabilistic model for the general population (for details, see Dilger et al., 2022). This lower inter-individual variability would fit with the general assumption that intraspecies variability is lower in the group of adult healthy workers compared with the general population, which includes children. However, polymorphisms in xenobiotic metabolising enzymes, which are relevant for both workers and the general population, are more likely drivers of inter-individual variability in many cases than age or impaired health. In summary, the proposed distribution for intraspecies extrapolation agrees with current knowledge but might tend slightly to underestimate toxicodynamic variability.

Our probabilistic analysis of AFs used and the level of protection achieved revealed considerable differences between frameworks. Overall, the following order of frameworks ranked by decreasing

probability to achieve the protection goals was observed (see Tables 6 and 7):

$$\text{BPR} (\approx \text{PPP}) > \text{RAC/REACH} > \text{AGS} > \text{MAK} \approx \text{ECETOC}$$

Two major sources of variation were the differences in AFs used in the case of substances causing local irritations in the respiratory tract and the factors used for intraspecies extrapolation. Our data analysis did not detect large differences with regard to exposure time and intraspecies extrapolation between locally and systemically acting chemicals (Dilger et al., 2022). Recently, ECETOC (2020) noted a lack of progress in the relevant empirical databases. With the improved data for intraspecies extrapolation described by Dilger et al. (2022), which comprises human inhalation studies, protection levels of OELs can now be better characterised. With the advent of easy-to-use and freely available tools such as the Monte Carlo tool provided by the EFSA (<https://r4eu.efsa.europa.eu/>), probabilistic approaches can also be used to analyse combinations of extrapolation steps for frameworks to derive OELs and DNELs, as suggested by ECETOC (2020). So far, probabilistic assessments for the workplace are limited (see, e.g. Schneider et al., 2006) and tools were mainly developed for health-based guidance values for the general population (WHO, 2014). Although it is unlikely that they will be used as a standard procedure for deriving OELs soon, they can be used to adjust and harmonise deterministic procedures.

Judging which effect (level) is to be considered adverse and, consequently, deciding on an appropriate POD is another source of difference between evaluations. The method used to derive the POD may have a significant impact on protection levels. This is demonstrated by the two example substances where lower protection levels are determined for benzoic acid (where the BMDL is below the NOAEL) than for tetrachloroethane (where the BMDL is significantly higher than the NOAEL).

The advantage of using benchmark doses over NOAELs has repeatedly been discussed (EFSA Scientific Committee et al., 2017; Haber et al., 2018). However, not only is the NOAEL still often used, but (highly unreliable) extrapolation from LOAELs to no adverse effect levels is also still practised. In contrast, the benchmark approach not only allows for derivation of a better POD, but it also enables characterisation of the associated uncertainty and hence, a full probabilistic approach, which has been demonstrated above with two examples. Detailed guidance on the use of the benchmark dose method is lacking in all frameworks. Particular attention should be given to how to determine the BMR for continuous data. According to the newly updated chapter 5 of the Environmental Health Criteria document, 240 toxicological criteria should be decisive for setting the BMR (WHO, 2020). Benchmark dose modelling should be used as the standard procedure to derive a POD.

In conclusion, our analysis of OEL frameworks confirmed the existence of methodological differences, which potentially lead to considerable quantitative differences between exposure limits derived and the protection levels achieved by these limits. We propose here a complete set of distributions (including a data-based distribution for

intraspecies extrapolation), which can be used to perform probabilistic assessments, allowing comparison and refinement of existing methodologies. Existing uncertainties in the distributions should be addressed in further investigations, for example, the uncertainty introduced by using NOAEL ratios for establishing distributions for time extrapolation. The database for toxicokinetic differences after inhalation exposure would benefit from an increased number of datasets, and the relevance of the in vitro data on toxicodynamic differences in humans for covering various endpoints needs further discussion. Also, more experience needs to be gathered with the probabilistic assessment of OELs, which are derived from human data.

As a means of improving transparency, we propose that OEL frameworks should clearly define their protection goals by stating the fraction of the exposed population the OEL aims to cover and the probability with which they seek to provide protection from adverse effects. Harmonisation can be achieved by agreeing on how to carry out the methodological steps discussed in our analysis and on common protection goals.

ACKNOWLEDGEMENTS

We would like to thank Dr Werner Wosniok, University of Bremen, for his support in statistics, Prof Dr Thomas Gebel, BAuA, for the valuable comments provided throughout the project and Barbara Hauck and Alan Macmillan for linguistic proofreading. The project 'Derivation of occupational exposure limits for airborne chemicals – Comparison of methods and protection levels' was funded by the German Federal Institute for Occupational Safety and Health (Bundesanstalt für Arbeitsschutz und Arbeitsmedizin, BAuA) (project number F2437).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available at <https://www.baua.de/EN/Tasks/Research/Research-projects/f2437.html>.

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How to cite this article: Schneider, K., Dilger, M., Drossard, C., Ott, H., & Kaiser, E. (2022). Derivation of occupational exposure limits: Differences in methods and protection levels. *Journal of Applied Toxicology*, 42(5), 913–926. <https://doi.org/10.1002/jat.4307>