Full paper

ECETOC TRA Worker tool v3.1: a review and update of the tool based on an extensive comparison of measured and modelled inhalation and dermal exposure data

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Trefwoorden: exposure assessment, exposure model, targeted risk assessment, REACH, evaluation.

Samenvatting

Het ECETOC Targeted Risk Assessment (TRA) instrument wordt sinds 2009 veelvuldig gebruikt bij zogeheten 'Tier-1' risicobeoordelingen van chemische stoffen in het kader van de REACH regelgeving. Het instrument bevat 3 modules voor blootstellingsschatting, namelijk voor milieu ('TRA Environment'), consumenten ('TRA Consumer') en werknemers ('TRA Worker'). De module voor het schatten van blootstelling op de werkplek ('TRA Worker') levert conservatieve schattingen voor inhalatoire en dermale blootstelling voor een aantal gestandaardiseerde arbeidsactiviteiten, de zogeheten 'Process Categories' (PROC's).

Het conservatieve karakter van de TRA Worker wordt bevestigd in een reeks van validatiestudies die sinds 2010 zijn uitgevoerd. Echter in een aantal studies concluderen onderzoekers dat TRA Worker mogelijk niet conservatief genoeg is voor alle werksituaties. Dit heeft geleid tot de instelling van een ECETOC 'Task Force', een groep van deskundigen op het gebied van beoordeling van blootstelling aan chemische stoffen. Deze Task Force heeft deze validatiestudies opnieuw beoordeeld met als doel het conservatieve karakter van de TRA Worker te evalueren en mogelijke verbeteringen van het instrument te identificeren. Om meer zekerheid te krijgen over de daadwerkelijk hoogte van de gemeten blootstelling, heeft de beoordeling zich beperkt tot rapporten en artikelen over werkplekblootstelling met datasets van tenminste zes metingen per blootstellingsscenario. Daarnaast diende per scenario een duidelijke en goede beschrijving van de operationele omstandigheden en beheersmaatregelen op de werkplek beschikbaar te zijn als basis voor een blootstellingsschatting met de TRA Worker. Deze zoektocht naar goed gedocumenteerde blootstellingsmetingen heeft geresulteerd in de constructie van drie databases, namelijk voor inhalatoire blootstelling (8-uur gemiddeld en 15-minuten gemiddeld) en dermale blootstelling (8-uur gemiddeld).

Deze drie databases met blootstellingsgegevens en daarbij behorende TRA blootstellingsschattingen zijn visueel geanalyseerd met behulp van plots alsook met regressieanalyse en analyse van zogeheten 'residuals' (verschil tussen gemeten en voorspelde blootstelling). De resultaten van deze analyse laten zien dat voor werknemers in zogeheten professionele

Abstract

Since 2009 the ECETOC Targeted Risk Assessment (TRA) tool has been widely used in Europe for Tier-1 risk assessments of chemical substances under REACH. The TRA tool contains three modules for estimating exposure, i.e., for the environment ('TRA Environment'), consumers ('TRA Consumer') and workers ('TRA Worker'). The module dealing with occupational exposure ('TRA Worker') provides conservative estimates for both inhalation and dermal exposure for a series of standardised worker activities, called Process Categories (PROCs).

The conservative nature of the 'TRA Worker' has been confirmed in several validation studies conducted since 2010. However, in a number of studies researchers have concluded that the tool might not be sufficiently conservative in all occupational scenarios. Therefore, ECETOC has set up a ECETOC Task Force to review these published performance studies with the objective to evaluate the TRA Worker performance and to identify potential tool improvements. The review focussed on measurement reports with more substantive data sets as these provided more certainty about the existing exposure levels and allowed to create high-quality curated databases. Three databases have been created for long-term (full-shift) and short-term (15 minutes average) inhalation exposure and long-term dermal exposure. Each database consists of data sets of six or more measurements from workplace assessments with sufficiently detailed information on operating conditions and risk management measures to derive TRA exposure estimates.

The three databases with exposure situations and corresponding TRA Worker exposure predictions were analysed using plots, regression analysis and analysis of residuals (difference between predicted and measured level). The results show that for professional workers no underestimation for inhalation exposure occurred. For industrial workers some underestimates were identified for certain exposure scenarios, indicating that in those cases the TRA Worker is not sufficiently conservative. Analysis of residuals demonstrated that for inhalation exposure underestimates for these exposure scenarios are associated with input

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omstandigheden (professional setting) het instrument de gemeten inhalatoire blootstelling niet onderschat. Echter voor werknemers in meer industriële omstandigheden (industrial setting) komt voor bepaalde blootstellingssituaties onderschatting van de gemeten blootstelling wel voor. Uit de nadere analyse blijkt dat de onderschatting van de inhalatoire blootstelling voor bepaalde scenario's (PROC's) wordt veroorzaakt door een te lage basisschatting in een bepaalde vluchtigheidscategorie, of door overschatting van de parameter 'lokale afzuiging'. Onderschatting van de dermale blootstelling lijkt samen te hangen met een te lage basisschatting van TRA worker voor bepaalde scenario's (PROC's).

Aangezien slechts voor een beperkt aantal combinaties van PROC's, vluchtigheid van de chemische stof en werkplekomstandigheden data beschikbaar waren, is een volledige beoordeling van de prestaties van de TRA Worker niet mogelijk. Desalniettemin is deze analyse van beschikbare data een goede basis voor aanpassingen aan het instrument voor wat betreft de basisschatting van enkele van de PROC's en de efficiency van de parameter 'lokale afzuiging'. De implementatie van deze aanpassingen leidt tot een aanzienlijke reductie van de onderschatting door de TRA Worker en daarmee tot een verbetering van de prestaties ervan als conservatief instrument. Voor het overgrote deel van de onderzochte scenario's lijkt de TRA Worker voldoende conservatief te zijn en daarmee geschikt als screeningsinstrument voor schatting van blootstelling aan gevaarlijke stoffen op de werkplek, zowel bij het opstellen van REACH dossiers voor chemische stoffen als bij beoordeling van arbeidssituaties in de praktijk. Deze conclusie wordt ondersteund door de analyse van zogeheten 'fout negatieven' bij de beoordeling van veilig gebruik van een chemische stof op de werkplek. De kans op een onjuiste beslissing over veilig gebruik op basis van een schatting met de TRA Worker is erg laag.

parameters as (medium) fugacity and Local Exhaust Ventilation. For dermal exposure underestimation could be linked to the base estimate of the PROC for certain scenarios.

An overall assessment of the performance of the TRA Worker is not possible, as data are only available for a limited number of all potential combinations of PROCs, substance fugacity and workplace conditions. However, the current analysis on the available data provides a sufficiently solid base for updating the TRA Worker with adjustments for base estimates for certain PROCs and efficiency of the Local Exhaust Ventilation modifier. Implementing these adjustments results in a significant reduction of underestimations and thereby improvement of the performance of the tool. For the majority of the scenarios investigated the TRA Worker appears to be sufficiently conservative and hence suitable as a screening tool for occupational exposure estimation in the preparation of REACH dossiers for chemical substances as well as for evaluation of exposure in existing workplaces. This conclusion is supported by the analysis of 'false negatives' when assessing safe use. The probability of an incorrect decision on safe use when using the TRA Worker is very low.

Introduction

In 2004 the European Centre of Ecotoxicology and Toxicology of Chemicals (ECETOC) released the first version (ECETOC, 2004) of its Targeted Risk Assessment (TRA) tool with the aim to support companies in preparing REACH registrations dossiers within the context of the Registration, Evaluation, Authorization and restriction of CHemicals (REACH) legislation (ECHA, 2016). A second (TRAv2 (ECETOC, 2009)) and third (TRAv3 (ECETOC, 2012)) version of the tool were released in 2009 and 2012 respectively. The tool is a so-called first tier tool, meant to generate sufficiently conservative screening level estimates of human and environmental exposures to hazardous chemical substances under normal circumstances of intended use or reasonable worst-case estimates, where conditions of use are variable across a market segment. If in such a risk assessment at the screening level, the estimated exposure exceeds the established exposure limit value, then the assessor is typically expected to resort to higher, more complex exposure estimation tools or measured data sets. The tool has been very widely used for that purpose since 2010. Because of its relative ease of use and transparent approach, the module dealing with occupational worker estimation (TRA Worker module version 3.1, further referred to as 'TRA Worker') is also finding application in workflows to meet regulatory obligations under Occupational Safety and Health (OSH) legislation around the world.

The TRA Worker covers 26 different conditions of workplace use (so-called Process Categories, termed PROCs; ECHA, 2016) of chemicals and starts with a base exposure estimate for liquids and solids depending on fugacity and type of setting (industrial/professional). This base estimate can be further refined using modifiers for operational conditions (e.g., activity duration, concentration in preparations) and risk management measures (e.g., general ventilation, local exhaust ventilation (LEV), use of personal protection equipment (PPE)). The tool provides estimates for long-term (full-shift 8-hour) inhalation and dermal exposure, as well as estimates for short-term (peak) inhalation exposure (typically 15 minutes). The model was derived from the exposure estimates at the upper end of interquartile bands originally described in the UK HSE EASE model (Tickner et al., 2005; Creely et al., 2005), and hence the 75th percentile of the exposure distribution for a use group, which consequently provides a historical link to the regulatory decisions made in previous EU chemicals regimes (European Commission, 1996). As for all models, the outcome of the TRA Worker tool is highly dependent on the selected input parameters by the assessor based on experience and knowledge of the tool as well as the degree of information on the scenario to assess.

In the decade since 2010 a number of research groups have undertaken validation studies of the tool estimates for worker inhalation exposures and reported these in the literature. Typically, these studies have utilised measured workplace exposure data along with contextual information on the tasks and workplace settings and then constructed corresponding TRA estimates for comparison. While a wide variety of results have been published, the most prominent study is the ETEAM study coordinated by the German Federal Institute for Occupational Safety and Health (BAuA), where several exposure estimations tools for inhalation exposure were compared against 2098 exposure measurements (van Tongeren et al., 2017).

Additionally, the Cefic Long-Range Research Initiative funded a research project (Cefic LRI B16 study, cited in Marquart et al. (2017)) which addressed the dermal exposure prediction by the tool.

As the validation studies on inhalation exposure show mixed results on the performance of the TRA Worker tool and questions were raised on the validity of the tool as conservative screening tool (refer to Savic et al. (2023) for a discussion on the various results), ECETOC has assembled an expert Task Force to review the presented results and conclusions in these studies and propose adjustments to tool settings or improvements to user guidance, where considered relevant.

The Task Force has reviewed the different validation studies and projects in detail in view of the quality and quantity of data used, the coverage of TRA Worker's applicability domain, and the validity of the published research. An overview of the available material for inhalation exposure as well as the adopted review and analysis approach has been published previously (Urbanus et al., 2020). The review focussed on measurement reports with more substantive data sets as these provided more certainty about the existing exposure levels and also presented the possibility to create a high-quality, pooled database for future studies. Using a selection of the higher quality data sets in the published materials, three curated databases (full shift (long-term) inhalation, short-term inhalation, full shift (long-term) dermal exposure) were constructed. Each database consists of data sets of six measurements or more from workplace assessments with sufficiently detailed operating conditions and risk management measures to derive a TRA estimate and for which the 75th percentile was calculated from the measurements for comparison. The results of the review of validation studies for full shift inhalation exposure have been reported in ECETOC TR report 140 (ECETOC, 2022). The results of the performance assessment of the TRA Worker tool for inhalation exposure has been published in the peer-reviewed scientific literature (Savic et al., 2023). The results of the performance assessment for short-term inhalation and dermal exposure will be published shortly in ECETOC TR report 141 (ECETOC, 2023).

This manuscript, written by the Dutch members of the Task Force, provides the overall results of the review of the performance assessment. Based on these results adjustments have been defined to some of the base estimates and the efficiency of one of the modifying factors (i.e., LEV). These adjustments will be implemented in an updated version of the TRA Worker. The effect of these adjustments on the performance of the tool in general and in REACH risk assessment are evaluated.

Methodology

Collection of exposure data

The occupational inhalation and dermal exposure data were obtained from previous validation studies that investigated the performance of the TRA Worker tool. This process was conducted by the Task Force in teams of two reviewers per data source. All reviewers are exposure scientists/occupational hygienists with at least 20 years of experience. All measurement data available were verified and assessed using state-of-the-art approaches from the field of occupational hygiene for the characterisation of an exposure profile of a similar exposure group (SEG) in a particular location or situation. Exposure situations or scenarios with less than six individual measurements were not regarded as valid for a detailed analysis and discarded, as a lower number of measurements would not reflect the existing workplace exposure with sufficient confidence. Each exposure scenario represents a single line in the assembled databases (see available supplementary material). The technical quality of the data for each exposure scenario was systematically scored using the criteria in Table 1, based on a similar system developed in another study (Franken et al., 2020). Each exposure scenario had to represent personal exposure measurements covering a single activity or several similar activities and have clear indications of duration of exposure as well as duration of the measurements. Exposures had to be occurring as part of normal routine operations, covering activities that could be assigned unequivocally to a single process category (PROC).

Coding of input parameters for calculation of the TRA estimate

For each exposure scenario the required information on input parameters for calculation of the TRA estimate were extracted by the review teams from the original publications, their corresponding supplementary material or underlying documentation. Where the required infor-

Table 1: Criteria for evaluating and assigning reliability scores to exposure data and input data for generating TRA estimates (based on Franken et al., 2020)

Score	Adequacy assignment	General criteria	Examples
1	Adequate without restriction	Data of good technical and contextual adequacy is available	Completely documented measurement studies, performed with validated measurement methods (published by renowned institutes) and with all information on each data point in annexes. Full and unambiguous data to select TRA input parameter settings.
2	Adequate with restrictions	Data of at least acceptable technical adequacy and information on contextual adequacy is available or can be evaluated based on the expert judgement and reasonable assumptions	Well documented measurement studies, performed with validated measurement methods (published by renowned institutes) or methods that resemble such methods closely and for which sufficient information on validity, accuracy, precision, and boundaries is available; sufficient description of context to either directly know the values for relevant factors or to make informed and justified expert judgement on a number of factors; activities may need to be categorized, based on descriptions, assumptions on scale and setting may need to be based on expert judgement, data on substance and product characteristics may need to be found in other sources or estimated.
3	Useful as supporting evidence	Data of limited technical adequacy	Measurements with undocumented sampling techniques; statistical summaries of data (vapour pressure of measured substances, concentrations of substances in products or largely different settings) that are not stratified; studies in which only the jobs of sampled workers are indicated without any indication of activities being sampled.
4	Not adequate	Data for which the technical adequacy cannot be evaluated or that are described too insufficiently to allow evaluation of several factors related to contextual adequacy	Studies in which the sampling method is not described (e.g. no reporting of whether respirable dust, inhalable dust or total dust has been measured); the method for measuring solid/liquid aerosols is not described; studies in which no information is given on e.g. the use or no use of localized control measures, the concentration of measured substances in articles, the duration of activities within shift-based measurements, the containment of sources, etc.

mation could not be collected, the authors were directly contacted to provide the raw exposure information and the input parameters they had used to calculate the estimates. Scenarios for which the required information could not be retrieved were excluded from the database ('non valid scenarios').

Based on the information retrieved and/or received, a verification of the coding of input parameters in the validation studies was conducted independent of the authors of these studies. Two reviewers performed the review independently to minimize individual bias. For a number of the exposure scenarios the reviewers had reason to disagree with the coding of the input parameters by the authors of the validation studies. Each identified disagreement was discussed internally in the Task Force until consensus was achieved and, where justified, the coding was corrected. The reason for disagreement has been documented in appendices in the ECETOC Technical Report 140 (ECETOC, 2022) and Technical Report 141 (ECETOC, 2023).

For publications where the validation of the TRA Worker tool was not based on own measurements by the original authors, the changes in coding were not discussed with the original authors.

For publications where the validation of the TRA Worker tool was based on measurements by the original authors, an attempt was made to discuss the changes in coding with the original authors. Where possible, the changes in input values were agreed with the original authors, however the final decision on changes was made by the Task Force.

The TRA Worker allows for a reduction of the exposure estimate when dermal protection (i.e., chemical protective gloves) is used (ECETOC, 2012). The reduction is limited to two levels (80 % and 90 % effectiveness) for professional users, and three levels for industrial users (80 %, 90 % and 95 % effectiveness). 80 % effectiveness should be applied when chemically resistant gloves are used, 90 % effectiveness, when chemically resistant gloves are used in combination with 'basic' employee training. 95 % effectiveness should only be applied for industrial users, wearing chemically resistant gloves in combination with specific activity training. As the Task Force did not have information on the training level of users, we have used 80 % effectiveness for professional users and 90 % effectiveness for industrial users (assuming that in an industrial setting workers receive training on use of chemical protective gloves).

Construction of databases
From the reviewed studies with information on long-term (full shift) inhalation exposure a database was constructed containing, in total, 129 exposure scenarios, i.e., 119 for liquid substances and 10 for solid substances, covering 2272 measurements. For detailed information on the selection and review process, refer to ECETOC TR report 140 (ECETOC, 2022). Next to the already mentioned ETEAM study, other research groups that have validated the inhalation exposure part of the TRA Worker for a large number of exposure scenarios are Hesse et al. (2018), Ishii et al. (2017), Kupczewska-Dobecka, Czerczak & Jakubowski (2011), Lee, Lee & Kim (2019), and Lee et al. (2019).

A subset of these reviewed studies contained datasets with information on short-term exposure with sufficiently detailed operating conditions and risk management measures to derive a TRA short-term inhalation estimate, typically required for chemicals with a Derived No Effect Level (DNEL) or Short-Term Exposure Limit (STEL) for acute effects. Using these datasets, a second database was constructed consisting of in total 38 exposure scenarios, i.e., 36 exposure scenarios for liquids and 2 exposure scenarios for solids, covering 399 measurements. For detailed information on the selection and review process, refer to ECETOC Technical Report 141 (ECETOC, 2023).

For full shift (long-term) dermal exposure only two studies have been identified to evaluate the performance of the TRA worker tool, the Cefic LRI B16 study (cited by Marquart et al. (2017)), and the Cefic LRI B20 study (cited by Franken et al. (2020)). Following a similar selection process as for the inhalation exposure data, a third databases was constructed consisting of in total 82 exposure scenarios, covering 1719 measurements. For detailed information on the selection and review process, refer to ECETOC Technical Report 141 (ECETOC, 2023).

The three assembled databases are available as supplementary material (supplementary datafile; in this datafile the first table contains the database on inhalation long-term exposure (ILT), the second table the database on inhalation short-term exposure (IST) and the third table the database on dermal long-term exposure (DLT)).

Statistical calculations
For each exposure scenario the 75th percentile (P75) was calculated either directly from the geometric mean (GM) and standard deviation (GSD) if these were available or if all individual measurement results were available, or (in a limited number of exposure scenarios) from the arithmetic mean (AM) and standard deviation (SD) of the data set.[5] Equation 1 was applied to calculate the 75th percentile for the measured exposure, using a z-score of 0.674.

Equation 1: $P75 = GM \times GSD^z$

For the dermal data from the Cefic B16 study insufficient information was available to recalculate the 75th percentile. Therefore the 75th percentile as calculated by the original authors has been used.

Regression: A linear regression model was established to estimate intercept (a), slope (b) and R-squared between the measured and the modelled estimates. Since occupational exposure usually follows a lognormal distribution (Leidel, Busch & Lynch, 1977), the log-transformation was applied on the 75th percentile calculated from the measurements (P75) and the modelled (TRA) exposure estimate. These data points were plotted to illustrate how they follow the established regression line. In an ideal situation, the linear regression line should go to zero and have a slope of 1, meaning that the model calculates the same exposure value as given by the measurement data. The R-squared was evaluated to show how much variance in the measurements the TRA could explain.

$Delta_{TRA}$: This parameter was calculated to aid visualisation of local trends between the measured and modelled exposure. As shown in Equation 2, a residual (termed '$delta_{TRA}$' in the publication of Savic et al. (2023)) is calculated as a difference between the logarithms of the modelled (TRA) value and its corresponding 75th percentile of measured values (P75). While positive $delta_{TRA}$s indicate overestimation, negative values indicate an underestimation of the measurements by the model.

Equation 2: $delta_{TRA} = logTRA – logP75$

To investigate the effect of input parameters on underestimation by the TRA Worker, the $delta_{TRA}$ was plotted against each of the input parameters (e.g., PROC, type of setting (industrial or professional), general ventilation, LEV).

Since for short-term inhalation exposure only a limited number of datasets was available (n=38), no analysis was conducted on the effect of input parameters on underestimation by the TRA Worker.

Mean Absolute Error (MAE): The mean of the absolute differences between the modelled and measured exposure in Equation 3 defines another performance measure called Mean Absolute Error (Walther & Moore, 2005). While $delta_{TRA}$ is calculated for all data points, MAE is calculated as a single value. This parameter shows how far, on average, the modelled estimates are away from the measured values for a data set with a number (n) of exposure scenarios.

Equation 3: $MAE = (1/n)\sum_{i=0}^{n} |logTRA-logP75|$

[5] *GM and GSD were estimated from AM and SD using the following formulas:*
$GM = AM^2/\sqrt{(AM^2 + SD^2)}$
$GSD = exp(\sqrt{(ln(^1 + SD^2/AM^2))})$

Table 2. Number of exposure scenarios and measurements per constructed database

Databases	Liquid substances	Solid substances	Solid substances in liquid	Non valid scenarios
Long-term inhalation				
# exposure scenarios	119	10	n.a.	10
# measurements	2171	101	n.a.	60
Short-term inhalation				
# exposure scenarios	36	2	n.a.	3
# measurements	356	43	n.a.	29
Long-term dermal				
# exposure scenarios	21	25	36	1
# measurements	881	284	554	14

If, for example, MAE equals 1.0, this would mean that the modelled and measured values differ on average by one order of magnitude or a factor of ten since the difference is on the log scale.

All statistical calculations and the visualization of the obtained results were conducted in Excel.

Results

Constructed databases

Table 2 summarizes the number of exposure scenarios and measurements per constructed database. For the two databases on inhalation exposure the majority of exposure scenarios are scenarios for liquid substances. For the database on dermal exposure the scenarios are more evenly spread, although the larger part consists of scenarios for solid substances. Table 2 also shows the number of exposure scenarios for which we were not able to receive the required information for a good comparison between measurements and TRA Worker estimates ('Non valid scenarios').

Coverage of PROCs

Figure 1 shows the coverage of PROCs by exposure scenarios per database. For most of the PROCs no or only a limited number of exposure scenarios are available. PROCs covering at least 5 % of the exposure scenarios in one of the three databases are PROC5, PROC7, PROC8a, PROC8b, PROC10, PROC11, PROC13 and PROC15. A short description of these PROCs can be found in ECHA's Guidance on Information Requirements and Chemical Safety Assessment Chapter R.12: Use description (ECHA, 2015). The majority of exposure scenarios are covered by PROC7, PROC8a, PROC8b and PROC10 (at least 10 % of all scenarios in the three databases).

Correction of input parameters

A verification was conducted of the input parameters coded by the authors of the published studies on validation of the TRA (PROC, type of setting (industrial versus professional), general ventilation, LEV, fugacity, duration of activity, concentration of the substance, Personal Protective Equipment). This review confirmed that the majority of the original TRA

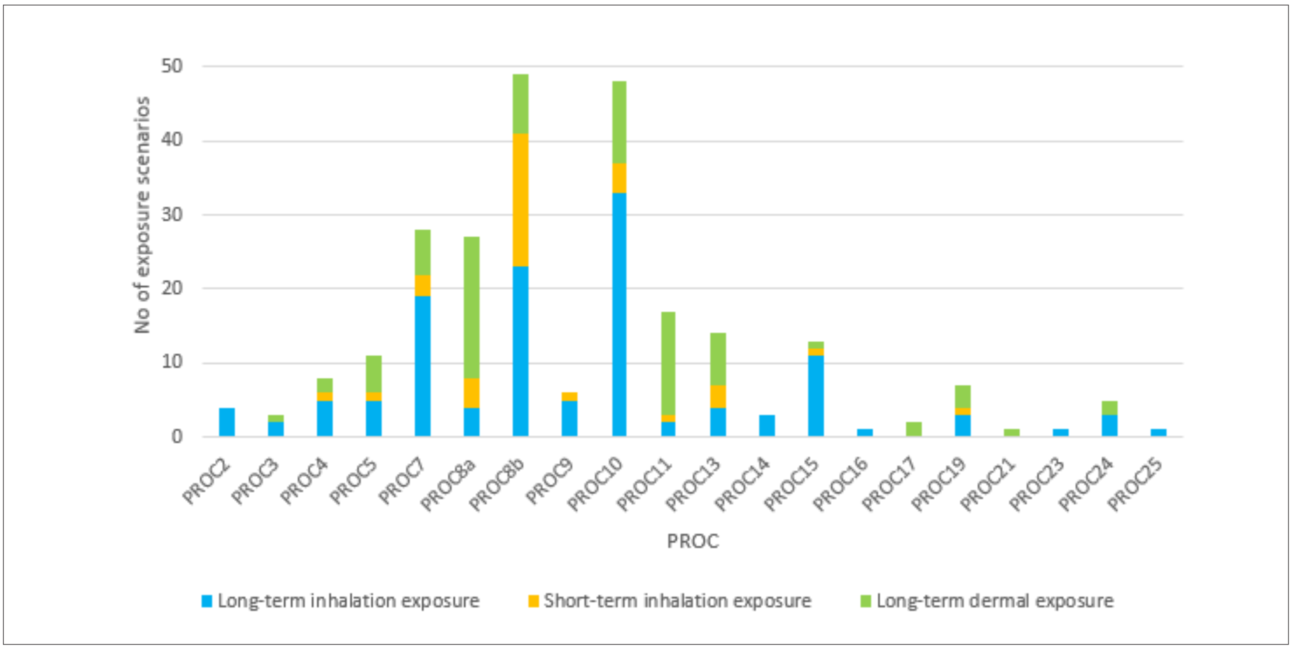

Figure 1. Coverage of PROCs by exposure scenarios per database

input parameter selections were correct, however, for a number of the exposure scenarios the Task Force disagreed with the input parameters selected by the authors of the validation studies. Table 3 provides an overview of the correction of input parameters as applied by the Task Force.

In the long-term inhalation exposure database, the PROC assignment for an activity was corrected for 25 % of the exposure scenarios. Examples for these corrections include a change from PROC 2 to PROC 4 because the described activity was not a continuous process, a change from PROC10 to PROC7 for an activity described as spraying, and a change from PROC13 to PROC15 for activities with small quantities of substance (less than one litre), typical for laboratory activities. General ventilation status was corrected in 16 % of the exposure situations, in particular when available data on room size and air volume exhausted by fans allowed the calculation of the actual number of air changes per hour (ACH) to align with the TRA definitions of basic (1-3 Air Changes per Hour (ACH)), general (3-5 ACH) and enhanced ventilation (>5 ACH).

In the short-term inhalation exposure database, the percentage of corrections in input parameters was high for general ventilation status (39 %) and LEV (37 %). In a significant number of datasets from the same facility and for the same substance and activity, LEV was coded to 'yes' (Angelini et al., 2016). However, after discussion with the authors of the paper, it became clear from the description of the type of LEV used and from the author's data on the effectiveness of their LEV, that the effectiveness was significantly lower than the 95 % efficiency as assigned to the related activity (PROC) in the TRA Worker module. Therefore, it was agreed with the original authors to change the input parameter for LEV to 'no' and the input parameter for general ventilation to 'enhanced ventilation' instead of 'no ventilation', as this better reflected the workplace conditions.

Long-term inhalation exposure: analysis of data

Figure 2 illustrates the relation between the 75th percentile of measured exposure (P75) and the modelled (TRA) exposure (including regression coefficients and R-squared). The analysis has been performed on the scenarios for liquid

Table 3. Percentage correction of input parameters applied to original materials for generation of TRA exposure predictions

Parameter	Correction of input parameters (%)		
	Long-term inhalation database	Short-term inhalation database	Long-term dermal database
PROC	25	16	2
General ventilation status	16	39	n.a.
Local exhaust ventilation	8	37	6
Setting (industrial, professional)	6	0	n.a.
Application of duration factor	5	n.a.	0
Concentration substance in product	3	0	0
Substance fugacity	1	11	n.a.
Personal protection equipment	8	13	2

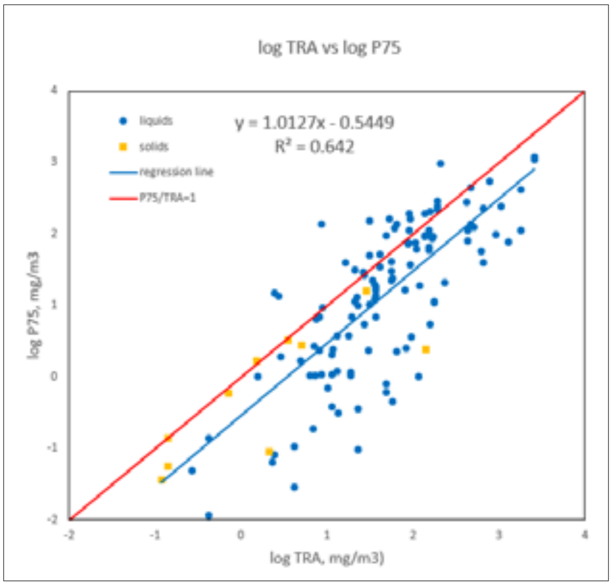

Figure 2. 75th percentile of measured exposure (P75) versus modelled exposure (TRA) for solid substances and liquid substances (long-term inhalation exposure)

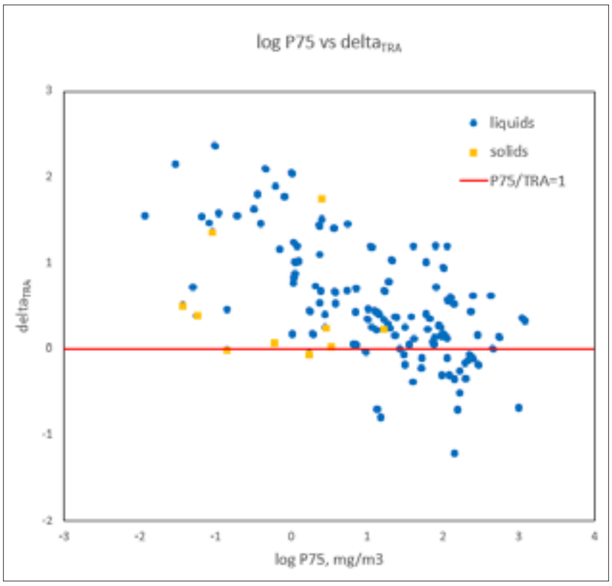

Figure 3. Delta$_{TRA}$ versus 75th percentile of measured exposure (P75) for long-term inhalation exposure

(n=119) and solid (n=10) substances combined. The variance in measured exposure explained by modelled exposure (R-squared) is 64 %. For the liquid and solid substances scenarios separately the R-squared is 61 % and 64 % respectively. The slope of the regression line is almost 1.0, while the intercept is negative, implying that on average the 75th percentile of the measured exposure was lower than the modelled estimates. For the majority of scenarios (81 %) the TRA estimate is higher than the 75th percentile of measured exposure. For 25 out of 129 scenarios (19 %) the TRA estimate is lower than the 75th percentile of measured exposure.

Figure 3 shows the $delta_{TRA}$ versus the 75th percentile of measured exposure. The calculated $delta_{TRA}$s indicate a tendency of the TRA to underestimate exposure at higher exposure levels. The Mean Absolute Error (MAE) is 0.65, which means that the TRA estimates on average differ a factor 5 from the 75th percentile of the measured long-term inhalation exposure. By plotting the $delta_{TRA}$ per PROC, the effect of the PROC on underestimation by the TRA Worker is demonstrated (figure 4). Of the PROCs covering at least 5 % of the exposure scenarios, particularly PROC7 (industrial spraying) and PROC10 (roller application or brushing) underestimate exposure more than the other PROCs.

In addition, the effect of variables as fugacity, concentration of the substance, duration of the activity, type of setting (industrial/professional), general ventilation and presence of LEV on underestimation was investigated. No underestimation was found for professional type of setting. Higher tendencies for underestimations were

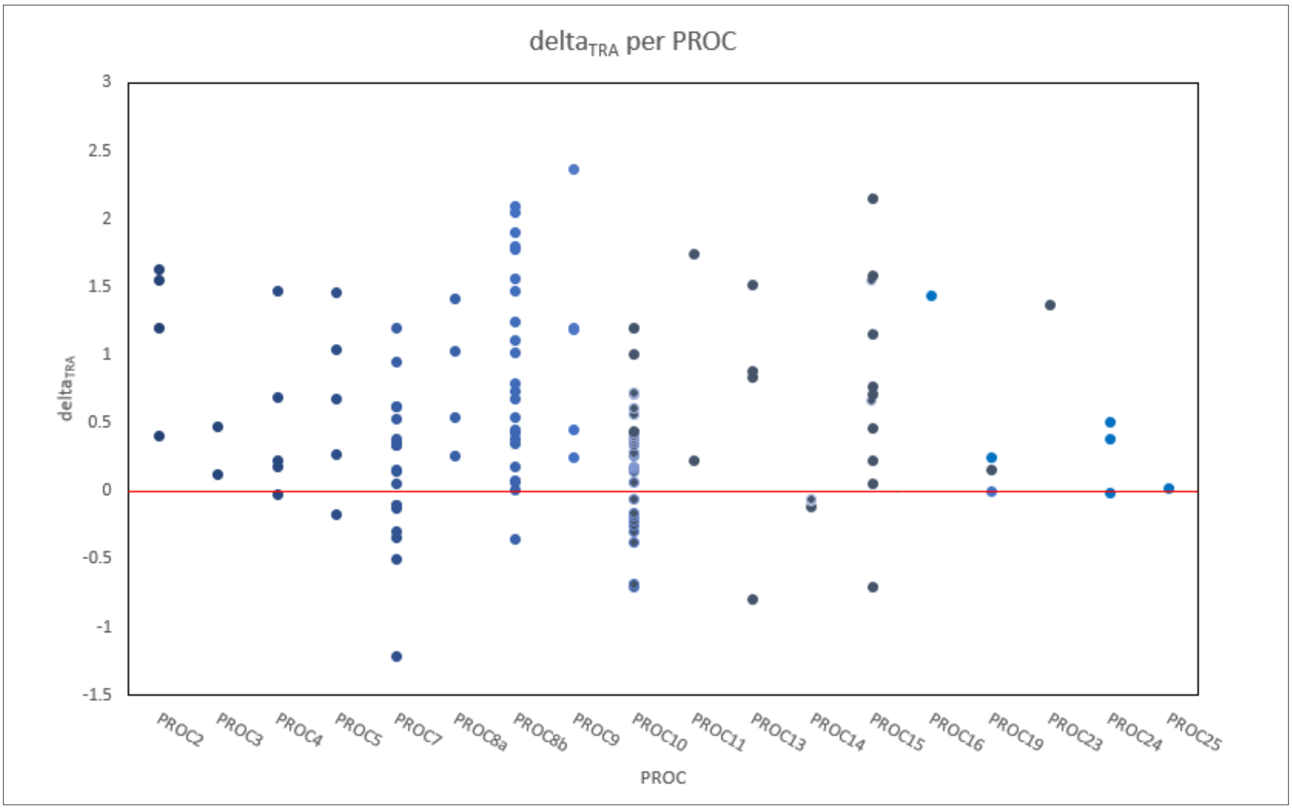

Figure 4. $Delta_{TRA}$ per PROC for long-term inhalation exposure

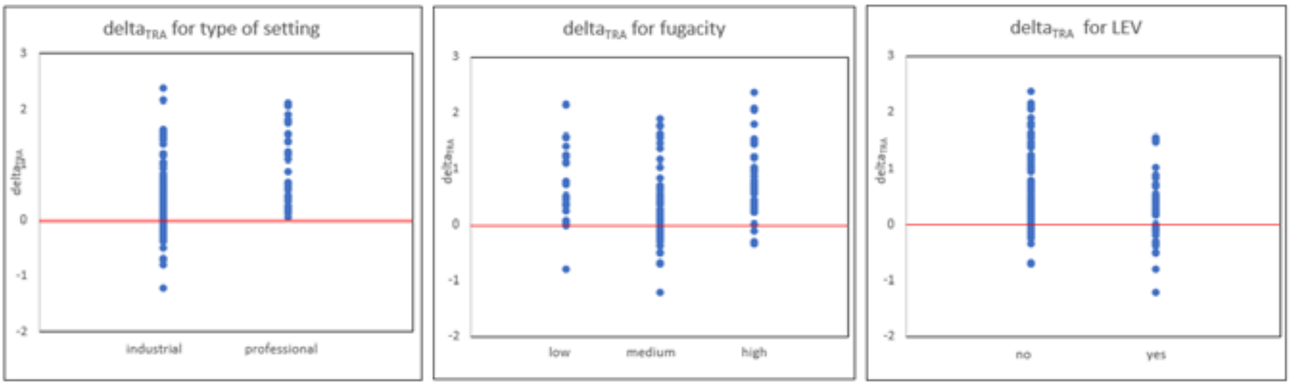

Figure 5. $Delta_{TRA}$ for type of setting (industrial/professional), fugacity and presence of LEV (long-term inhalation exposure)

noticed for medium fugacity and for exposure scenarios where LEV was present (figure 5). With respect to the variable's concentration of the substance, duration of the activity and general ventilation underestimations in certain categories were found, however no clear trends for underestimation could be identified (data not shown).

As most of the underestimations occurred for PROC7 and PROC10 scenarios, for these PROC scenarios $delta_{TRA}$ was plotted against fugacity and presence of LEV (figure 6 and 7). Only scenarios in an industrial setting were selected, as no underestimation occurred for professional scenarios. Furthermore note that the PROC7 and PROC10 scenarios only contained scenarios for substances with medium and high fugacity. Figure 6 seems to indicate that the underestimation in PROC7 scenarios is more related to presence of LEV than to the category of fugacity (medium or high). Figure 7 shows that the underestimation in PROC10 scenarios tends to be more related to the category of fugacity (medium or high) than to the presence of LEV.

Overall, for long-term inhalation the percentage of underestimated situations by the TRA Worker amounts to 19 % (table 4).

Short-term inhalation exposure: analysis of data

Figure 8 illustrates the relation between the 75th percentile of measured exposure and the modelled (TRA) exposure for the short-term inhalation data (including the regression coefficients and R-squared). The analysis has been performed on the scenarios for liquid (n=36) and solid substances (n=2) combined. The slope of the regression line is almost 1.0, while the intercept is negative, implying that on average the 75th percentile of measured exposure was lower than the modelled estimates. The TRA explained 39 % of the variance in the measurements. For the majority of all scenarios the TRA estimate is higher than the 75th percentile of measured exposure (87 %). For 5 scenarios (13 %) the TRA estimate is lower than the 75th percentile of measured exposure.

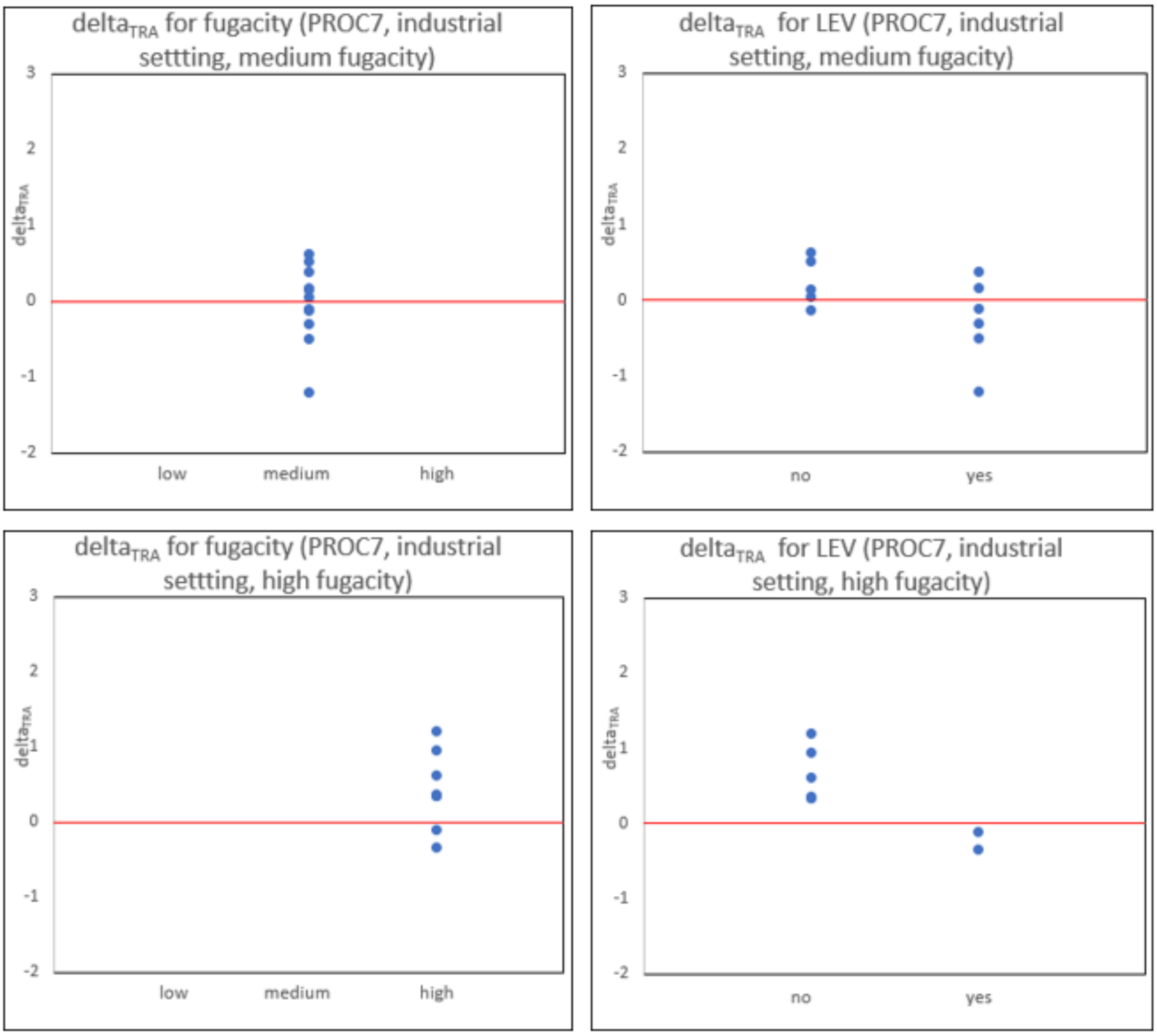

Figure 6. $Delta_{TRA}$ for PROC7 scenarios (industrial setting) plotted against fugacity and presence of LEV (long-term inhalation exposure)

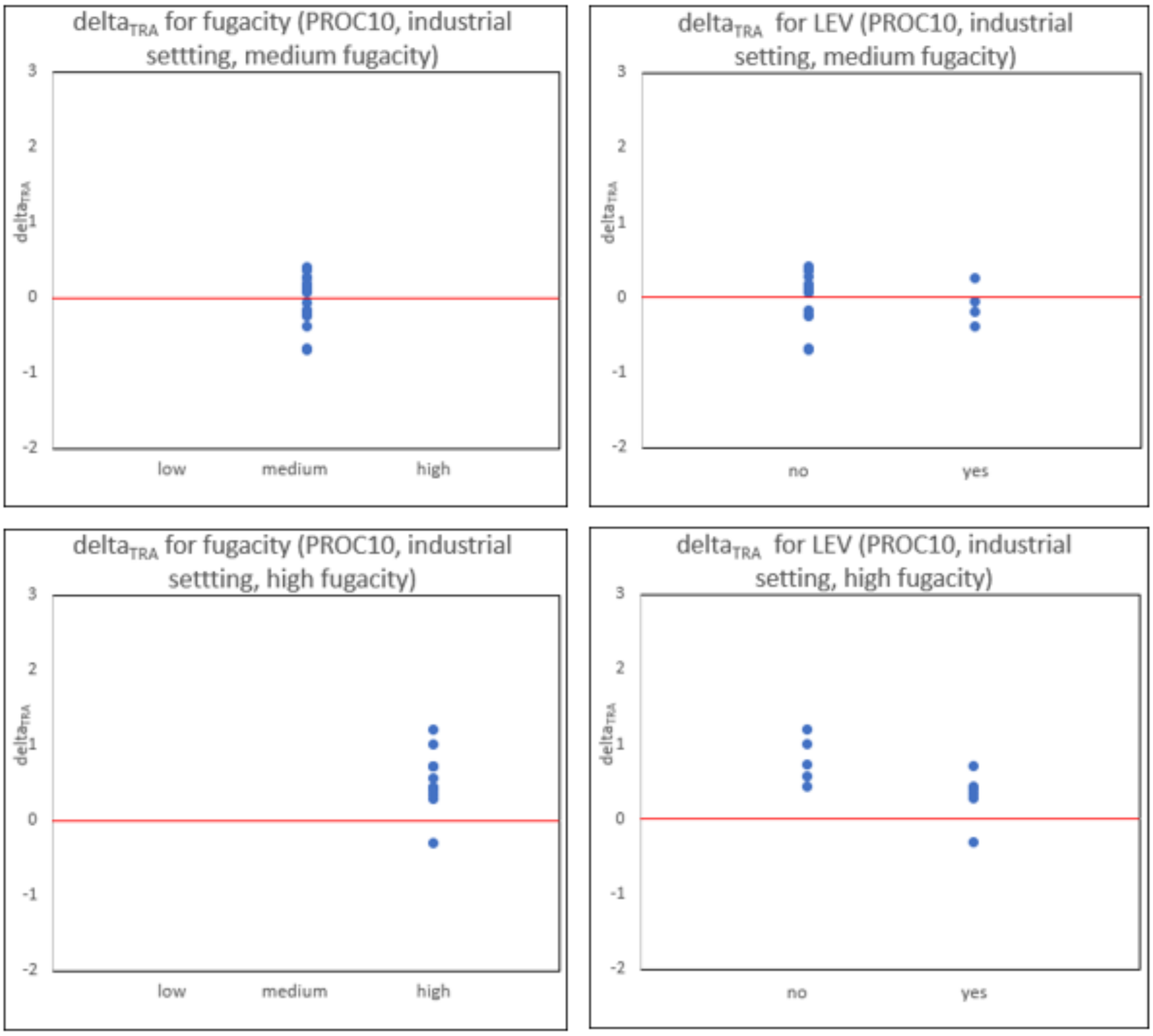

Figure 7. Delta$_{TRA}$ for PROC10 scenarios (industrial setting) plotted against fugacity and presence of LEV (long-term inhalation exposure)

Table 4. Effect of planned changes on underestimation by the ECETOC TRA Worker tool

Exposure route/duration	Underestimates before changes	Underestimates after changes
Long-term inhalation	19 %	13 %
Short-term inhalation	13 %	8 %
Long-term dermal	18 %	13 %

When plotting the deltaTRA versus the 75th percentile of measured exposure (figure 9), as for the long-term inhalation exposure, the calculated delta$_{TRA}$s indicate a tendency of the TRA to underestimate exposure at higher exposure levels. The Mean Absolute Error (MAE) is 1.29, indicating that the TRA estimates on average differ approximately a factor 20 from the 75th percentile of measured short-term inhalation exposure.

By plotting the delta$_{TRA}$ per PROC the effect of the PROC on underestimation by the TRA Worker was investigated (figure 10). Only a few underestimates were found, i.e., for PROC8b (dedicated transfer of chemicals), PROC10 (roller application or brushing) and PROC13 (treatment of articles by dipping or pouring).

Overall, for short-term inhalation the percentage of underestimated situations by the TRA Worker amounts to 13 % (table 4).

Long-term dermal exposure: analysis of data

Figure 11 illustrates the relation between the 75th percentile of measured exposure and the modelled

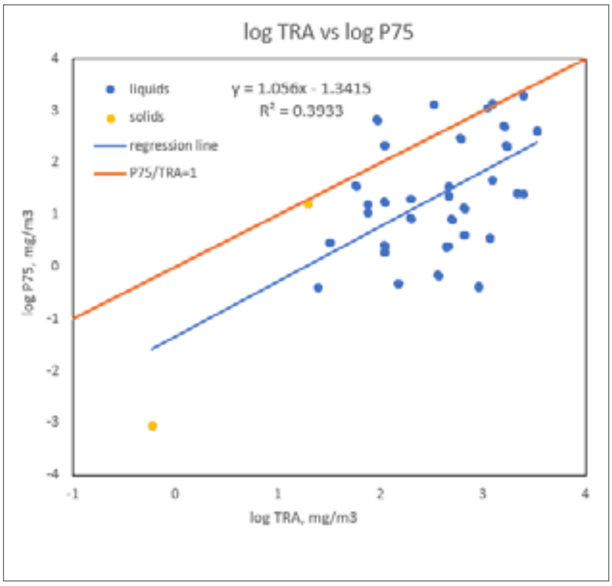

Figure 8. 75th percentile of measured exposure (P75) versus modelled exposure (TRA) for solid substances and liquid substances (short-term inhalation exposure)

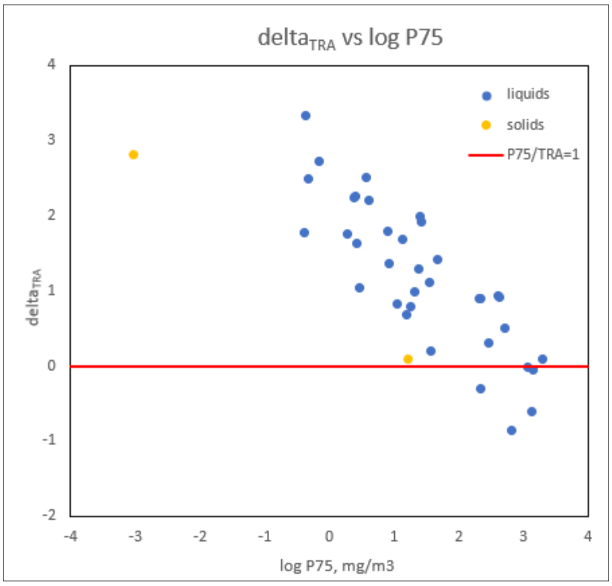

Figure 9. Delta$_{TRA}$ versus 75th percentile of measured exposure (P75) for short-term inhalation exposure

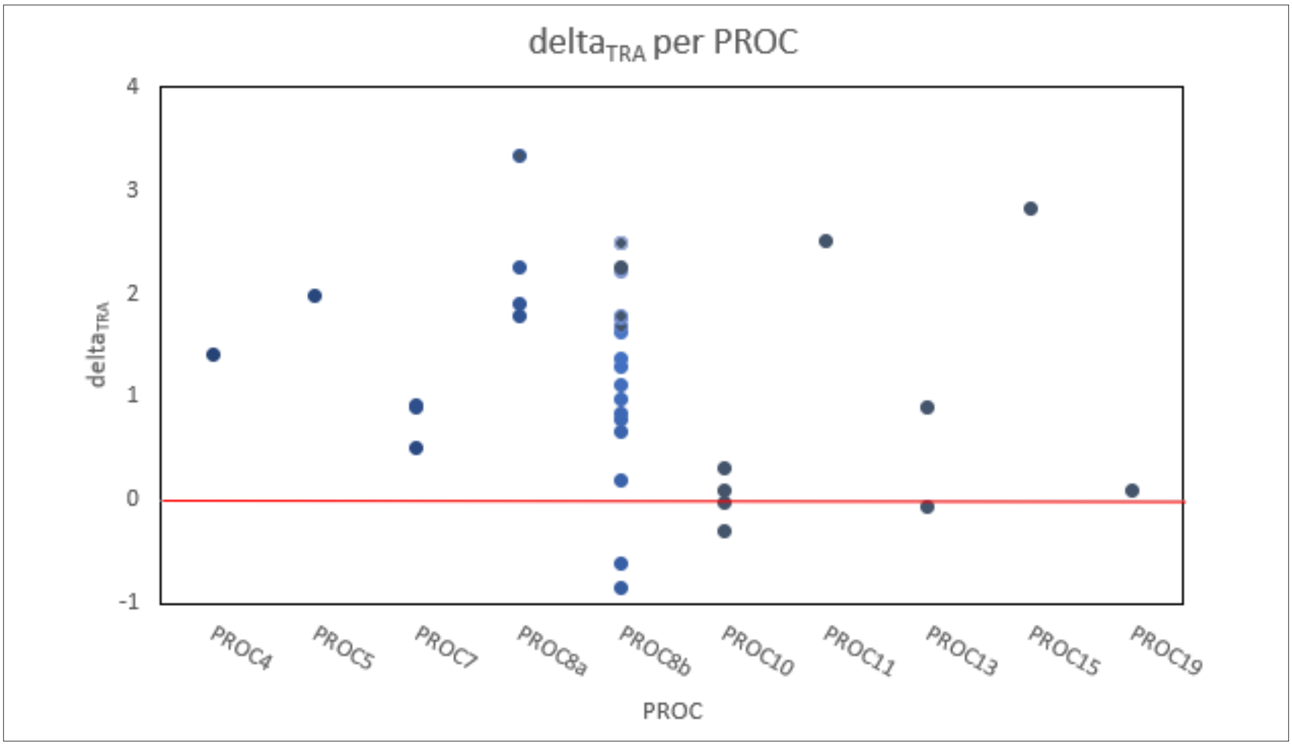

Figure 10. Delta$_{TRA}$ per PROC for short-term inhalation exposure

(TRA) dermal exposure for the three categories (solid substances, liquid substances and solid substances in liquid) as well as the corresponding regression coefficients and R-squared. In the Cefic LRI B16 study a significant number of exposure scenarios for solid substances used in a liquid matrix (e.g., solvent) were identified. Although the TRA does not cover solids in liquids, it was decided to include these exposure scenarios as a separate category solid-in-liquid (Marquart et al., 2017). For these datasets the substance was always considered to be a liquid with negligible vapour pressure, in line with the approach for dermal exposure assessment for periods shorter than 8 hours as described in ECETOC Technical Report 114 (paragraph 2.3.3; ECETOC, 2012).

The Worker TRA explained 35 % of the variance in the measurements. The R-squared varied to some extent per category (e.g., 44 %, 43 % and 31 % for liquid substances, solid substances in liquids (solids-in-liquids) and solid substances respectively). The slope of the regression line

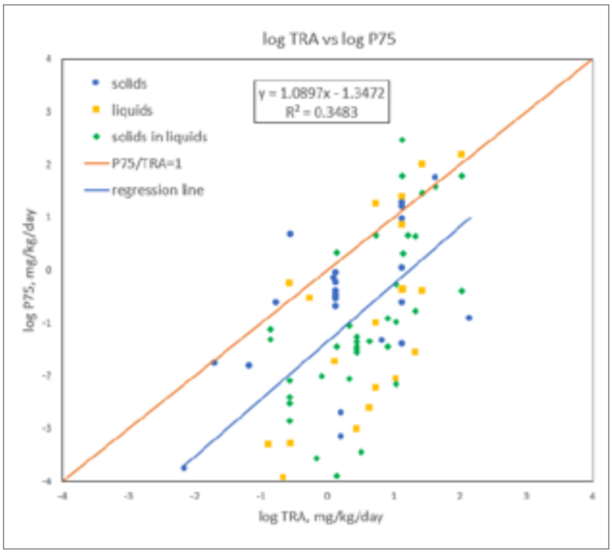

Figure 11. 75th percentile of measured exposure (P75) versus modelled exposure (TRA) for solid substances, liquid substances and solid-in-liquid substances for long-term dermal exposure

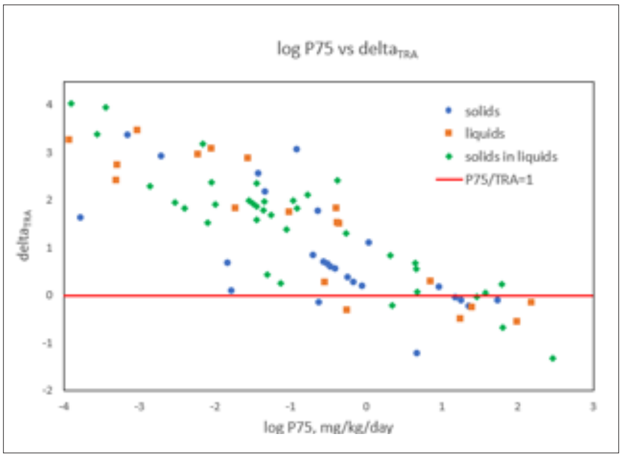

Figure 12. Delta$_{TRA}$ versus 75th percentile of measured exposure (P75) for long-term dermal exposure

is close to 1.0, however, due to the negative value of the intercept, on average the 75th percentile of measured exposure was lower than the modelled estimate within this range of exposures. For the majority of exposure scenarios, the TRA estimate is higher than the 75th percentile of the measured dermal exposure (82 %). For 15 out of 82 exposure scenarios (18 %) the TRA estimate is lower than the 75th percentile of measured dermal exposure.

Figure 12 shows the delta$_{TRA}$ versus the 75th percentile of measured exposure. In line with the findings for inhalation exposure, the calculated delta$_{TRA}$s indicate a tendency of the TRA to underestimate exposure at higher exposure levels. The Mean Absolute Error (MAE) is 1.44, indicating that on average the modelled exposure differs approximately a factor 28 from the 75th percentile of measured dermal exposure.

Figure 13 illustrates the effect of the PROC on underestimation by the TRA (delta$_{TRA}$). Of the PROCs covering at least 5 % of the exposure scenarios, PROC8a (transfer of chemicals, not-dedicated) shows more underestimation than the other PROCs.

To investigate the effect of modifying variables as concentration of the substance, type of setting (industrial/ professional), duration of the activity, presence of LEV and use of dermal protective equipment on underestimation, delta$_{TRA}$ was plotted for each of these variables. Figure 14 shows that higher tendencies for underestimations were found for industrial versus professional type of settings, and for scenarios where the initial base estimate was not reduced by modifying variables (e.g., concentration of the substance, presence of LEV and use of (chemical protective)

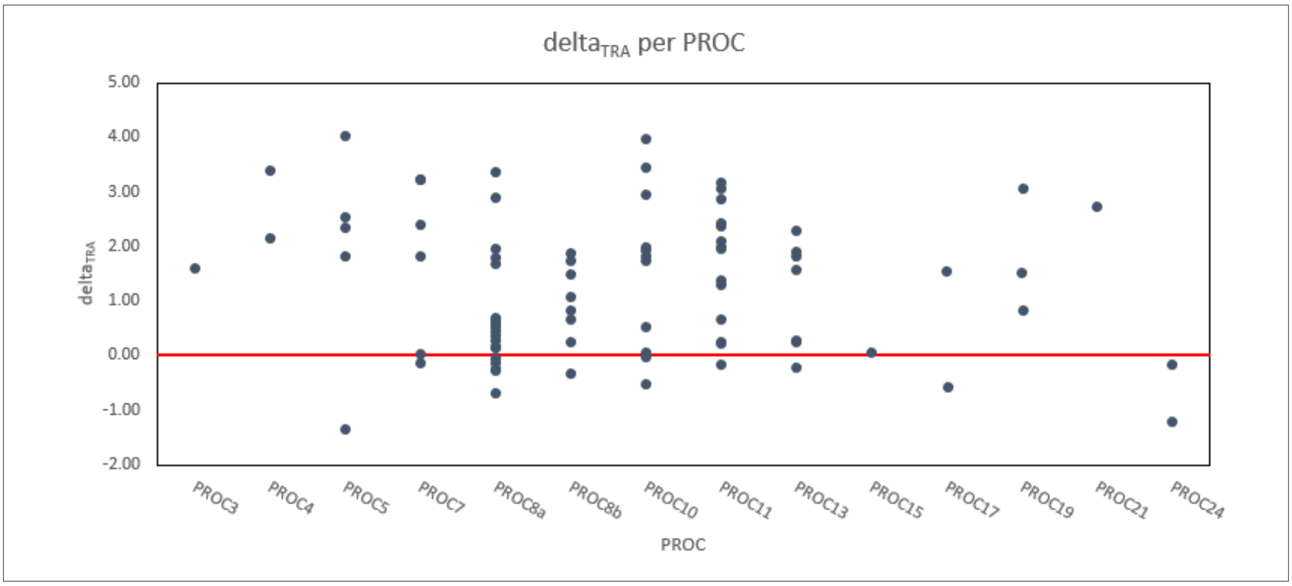

Figure 13. Delta$_{TRA}$ per PROC for long-term dermal exposure

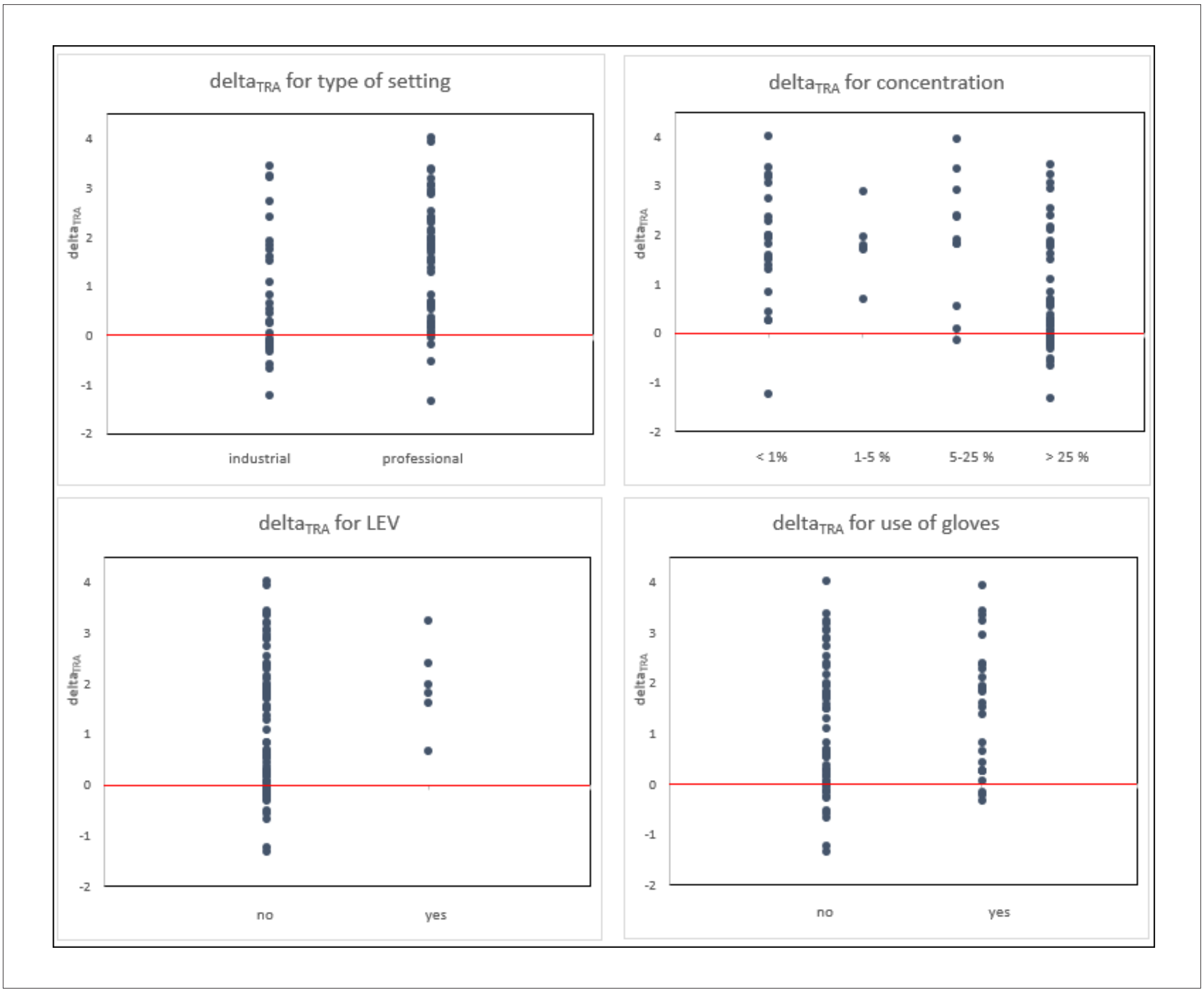

Figure 14. Delta$_{TRA}$ for type of setting (industrial/professional), concentration of the substance, presence of LEV and use of (chemical protective) gloves for long-term dermal exposure

gloves). No clear trend was found for duration of the activity (data not shown). As most of the underestimations occurred for PROC8a, the effect of modifying variables was also investigated for PROC8a scenarios solely. However, for this subset of scenarios similar tendencies to underestimate measured exposure were found as for the full dataset.
Overall, for long-term dermal exposure the percentage of underestimated situations by the TRA Worker amounts to 18 % (table 4).

Agreed changes to the TRA Worker tool

The results of the analysis on the three databases indicate that for some exposure scenarios the TRA Worker underestimates measured exposure. For long-term inhalation exposure this concerns in particular the estimates for PROC7 scenarios in an industrial setting with presence of LEV as well as PROC10 scenarios in an industrial setting for medium volatility liquids. For long-term dermal exposure this applies to the base estimate for PROC8a scenarios in an industrial setting.

In order to address these shortcomings and simultaneously improve the internal tool consistency the Task Force has decided to implement changes to the TRA Worker tool. For inhalation exposure, the LEV (efficiency) aspect is addressed by aligning LEV efficiency across the tool for industrial predictions at a standard of 90 % (instead of 95 % for PROC7 and PROC8b in the current version 3.1) and for professional predictions at 80 % (instead of 90 % for PROC7 and PROC8b in the current version 3.1). The aspect of underestimation for PROC10 scenarios in an industrial setting for medium volatility liquids is addressed by doubling the base estimate from 50 to 100 ppm. For internal tool consistency the base estimate for PROC10 in a professional setting for medium volatility liquids was doubled from 100 to 200 ppm to keep the logic of professional exposures at twice the level of industrial exposures. With respect to dermal exposure, the base estimate for PROC8a is doubled in order to generate suitably conservative exposure estimates and to distinguish the PROC8a base estimate from the PROC8b estimate.

Other scenarios associated with underestimates had insufficient numbers of data sets to make meaningful changes. Furthermore, for all three databases the majority of scenarios were overestimated by the TRA Worker, in some cases by several orders of magnitude. However, with the tool intended to be conservative, rather than accurate, no changes were proposed to reduce the degree of overestimation. The effects of the proposed changes were quantified in terms of percentage of underestimated scenarios (before and after changes; table 4). For all three databases the implementation of changes result in lower percentages of underestimates by the TRA Worker.

Calculation of 'false negatives'

After implementation of the changes, the TRA Worker still underestimates long-term inhalation exposure by 13 % on average, short-term exposure by 8 % on average, and long-term dermal exposure by 13 % (table 4). While the TRA Worker as a Tier-1 screening tool for REACH risk assessment has to be conservative, there are no agreed standards for the interpretation of what might constitute low, medium or high conservatism. Therefore, a different approach has been taken to evaluate the performance of the TRA Worker as screening tool for risk assessment of regulated chemicals under the EU REACH regulation.

In REACH risk assessment (ECHA, 2016) the outcome of the exposure assessment is compared with the Derived No Effect Level (DNEL) by calculation of the Risk Characterization Ratio (RCR):

RCR = exposure / DNEL

When the RCR is less than unity (RCR<1), the risk is considered to be acceptable (safe use).

An attempt has been made to assess the probability of so-called 'false negatives' for the updated TRA Worker (i.e., after the implementation of the changes). A 'false negative' is defined as the situation where the outcome of the risk assessment based on exposure prediction using the TRA Worker leads to the conclusion that the use is safe ($RCR_{TRA\ estimate}$ <1; TRA/DNEL <1), while in reality, based on real measurements, the conclusion should be that the use is NOT safe ($RCR_{P75\ measured}$ ≥ 1; P75/DNEL ≥ 1).

In all three databases a selection has been made of the datasets where a DNEL for the substance has been derived. For substances without a DNEL an (internationally accepted) Occupational Exposure Limit (OEL) has been used instead, if available. For all cases with a DNEL or OEL, the $RCR_{TRA\ estimate}$ has been calculated. Where the outcome of the $RCR_{TRA\ estimate}$ was less than unity (TRA/(DNEL or OEL)<1; safe use), also the $RCR_{P75\ measured}$ has been calculated (P75/(DNEL or OEL)). The cases where the RCR_{P75} measured ≥ 1 are 'false negatives'. The results of this exercise have been summarized in table 5 and demonstrate that the probability of an incorrect decision on safe use when using the TRA Worker in REACH risk assessment is in the order of 2-3 %.

Discussion

In this study the ECETOC TRA Task Force has attempted to review and use all the published studies on the performance of the TRA Worker tool since 2010. The conducted review shows that a performance assessment for the full scope of the TRA Worker tool cannot be achieved. Only a limited number of PROCs were evaluated in the published studies and secondly, only a small number of the combination of PROCs, setting, fugacity and modifying variables, e.g. LEV or general ventilation, have been studied. In many of these situations 6 or more measurement results were not available, and in some cases even a single measurement result was used in these studies. To allow a meaningful analysis, such datasets with less than 6 individual measurements were not regarded as valid for a detailed analysis and hence were excluded by the Task Force.

The rationale for the exclusion of datasets with less than 6 measurements is twofold.

Firstly, the review of the validation studies showed that most of them followed the approach of matching individual measurement results with a TRA Worker estimate, despite the fact that the TRA Worker is providing the 75th percentile of an exposure distribution. One of the implications of the approach used by the studies is that specific workplaces with many measurement results have more weight in the overall picture than comparable ones with fewer results and may lead to skewed results. Occupational exposure levels vary from day to day and between individual workers, but can be characterized using descriptive statistical parameters such as the geometric mean and geometric standard deviation. The TRA Worker was never intended to predict the actual exposure level on a single day or for a single individual worker but rather to provide the typical high-end of the exposure distribution under a particular set of circumstances (i.e., the 75th percentile of the exposure distribution, being the high-end of the inter-quartile band predictions by EASE, the basis for the TRA Worker).

Secondly, the standard EN 689 (CEN, 2018) now has formalized that, in order to define the shape of the exposure distribution for a given set of circumstances, six or more

Table 5. Calculation of percentage of 'false negatives' for the three databases (after implementation of changes)

	Long-term inhalation	Short-term inhalation	Long-term dermal
# datasets	129	38	82
# datasets with DNEL or OEL	129	29	32
# datasets with RCR_{TRA} < 1 AND RCR_{P75} ≥1	5	0	1
Percentage 'false negatives'	5/129 = 2.3 %	0/29 = 0 %	1/32 = 3.1 %

measurement results are typically needed. Based on this standard, the Task Force has focussed its review effort on data sets of six or more measurements as being the most informative to assess tool performance.

Although the Task Force therefore set aside a considerable number of the exposure scenarios included in the original published research, the part that has been taken forward for detailed review and reanalysis is considered more reliable since it included only datasets reflecting the existing workplace exposure with sufficient confidence. However, it should be noted that any conclusions related to the performance of the tool are limited to those combinations of PROCs, setting, fugacity and modifying variables for which sufficient datasets were available. Further research covering a wider scope of the PROC activities is recommended.

A main question is which organizations should initiate or coordinate further research. Recently, the International Society of Exposure Science (ISES) Europe has developed a strategy in which exposure modelling is one of the priority areas (Schlüter et al., 2022). One of their strategic objectives is the improvement of existing models and tools by model evaluation and generation of measurement data. ISES Europe intends to play a role in this, not so much in financing research projects, but more by serving as an independent platform that brings scientists and practitioners together to develop research projects and supports organizations in acquire funding for this research. In our opinion it is a logical step to undertake further research on a wider scope of PROC activities as part of the activities by this platform.

Based on information on the use of PROCs in registration dossiers (personal communication, ECHA, 2020), priority should be given to validation of the TRA Worker tool for the PROCs 1, 2, 3, 8a and 8b (all used more than 1.000.000 times in registration dossiers) and secondly to PROCs 4, 5, 9, 10, 13 and 15 (used between 500.000 and 1.000.000 times in registration dossiers). In our opinion the research should focus more on the base estimates of the TRA Worker tool rather than on the modifying factors.

In the process of creating the three curated databases, a verification was conducted of the input parameters coded by the authors of the published validation studies. For a significant number of the exposure scenarios the Task Force disagreed with the input parameter selection by these authors and decided to make changes to the input parameters. In particular for inhalation exposure this resulted in a high percentage of corrections for the selected PROC and ventilation status (general ventilation, LEV). More detailed information on the justification of these input parameter changes is provided in ECETOC Technical Report 140 (2022) and Urbanus et al. (2020). Some of the issues in coding input parameters appear to be related to lacking clarity on the definition and description of PROCs or insufficient experience with the assignment of PROCs. Furthermore, in the coding of operational conditions and risk management measures (e.g., ventilation status), assessors tend to overestimate the quality of the workplace instead of coding in a more conservative way in situations where only limited information on workplace conditions is available.

This indicates that further clarification is needed on how to assign PROCs to work activities and how to select the correct value for modifying variables, taking into account the required conservativeness of the tool. ECETOC intends to address this in updated user guidance and on-line training sessions.
The regression analysis shows that a considerable portion of the variance in measured exposures could be explained by the TRA Worker estimates. In particular for long-term inhalation exposures this amounts to 64 %. Furthermore, both for inhalation and dermal exposure the TRA Worker in general is highly conservative. The MAE varied between 0.65 (long-term inhalation exposure) and 1.44 (long-term dermal exposure), indicating that on average the estimated exposures differ a factor 5 to respectively 28 from the measured exposures. As ECETOC has intended the TRA Worker as a conservative screening tool and is not aiming for a high accuracy of the tool, ECETOC will not consider the implementation of changes to improve the accuracy of the tool.

Although the TRA Worker tool is intended as a conservative tool, the results from the three databases demonstrate that underestimation by the tool may occur. In particular for the higher exposure levels the TRA Worker tends to underestimate exposure. However, this only appears for exposure scenarios in industrial settings. No underestimation was identified for the long-term inhalation scenarios in professional setting and only one respectively three for the short-term inhalation and long-term dermal scenarios. A stratified analysis indicated that for certain PROCs in industrial setting modifying variables are related to the underestimation by the tool, e.g., fugacity and presence of LEV for inhalation exposure. For dermal exposure the underestimation does not seem to have a relation with modifying variables, but occurs in particular for one of the investigated PROCs for which relatively many datasets are available (PROC8a). These findings provide an opportunity for the ECETOC Task Force to implement changes to the tool. LEV efficiency will be aligned for all PROCs (90 % for industrial setting, 80 % for professional setting), inhalation exposure base estimates for PROC10 (medium volatility) will be doubled, and the dermal exposure base estimate for PROC8a will be doubled. Table 4 shows that these changes have a considerable impact and lead to a significant reduction of underestimations.

As shown in table 4, after the implementation of the proposed changes, there are still exposure situations where the TRA Worker underestimates exposure. Whether the degree of underestimation by the TRA Worker is acceptable for a conservative tool is difficult to evaluate, as there are no agreed standards for the degree of conservatism of a tool. The Task Force has attempted to evaluate the performance of the TRA Worker by calculating the percentage of 'false negatives', i.e., the situations where the outcome of the risk assessment based on exposure estimation by the TRA Worker leads to the conclusion that the use is safe, while based on measurement data the conclusion should be that the use is not safe. The results of this exercise demonstrate that the probability of an incorrect decision on safe use when using the TRA Worker in REACH risk assessment is approximately 2-3 %. This is a low probability, taking into account that in testing compliance with occupational exposure limit values, according to the EN 689 standard the statistical test measures whether less than 5% of exposures exceed the occupational exposure limit value with at least 70% confidence (CEN, 2018).

Conclusions

In this study a detailed review has been conducted of the peer-reviewed scientific literature on the validation of the TRA Worker. Based on exposure data for a significant number of frequently occurring activities (PROCs), it is shown that in general the TRA worker tool is conservative and tends to overestimate exposure to chemicals in the workplace. But there are some scenarios in which the tool may underestimate exposure. Possibilities for improvement of the performance of the tool have been identified and will be implemented in an update of the TRA Worker tool (version 3.2). With these limited number of changes implemented, the TRA Worker appears to be sufficiently conservative for the majority of the scenarios investigated and hence suitable as a screening tool in the preparation of REACH dossiers for chemical substances as well as for evaluation of exposure in existing workplaces. This conclusion is supported by the analysis of 'false negatives' when assessing safe use of chemicals in the work environment. The probability of an incorrect decision on safe use when using the TRA Worker is very low (i.e., in the order of 2-3 %).

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Supplementary data

A pdf file with supplementary data can be downloaded from

https://www.arbeidshygiene.nl/-uploads/files/TtA_202303_544-SUPPLEMENTARY_DATA.pdf

Conflict of interest

All listed authors are members of the ECETOC TRA Worker Task Force and contributed in the course of their regular employment or without funding. Joost van Rooij is employed by Chemrade Software B.V., that has incorporated the TRA Worker in their software.

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