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Evaluation of exposure assessment tools under REACH: Part I—Tier 1 models

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ABSTRACT

Tier 1 exposure assessment models recommended by the ECHA R14 guidance (2016) were evaluated using measurement data. These models are the ECETOC TRAv2, TRAv3, MEASEv1.02.01, and EMKG-EXPO-TOOL. Fifty-three Exposure Situations (ESs) based on tasks/chemicals were developed from NIOSH field surveys. For each ES, applicable models were then simulated to generate exposure estimates using the input parameters agreed upon at an in-present meeting where six organizations (from the United States and Europe) participated. The exposure data and model estimates were compared in six categories: Aqueous solutions (n=4 with 2 ES; for MEASE only), Liquids with a vapor pressure (VP) ≤ 10 Pa (n=5 with 2 ES; for TRAv2 and TRAv3), Liquids with a VP > 10 Pa (n=251 with 42 ES; for all but MEASE), Metal processing (n=15 with 2 ES; for MEASE only), Powders (n=20 with 2 ES; for all models), and Solid objects (n=20 with 3 ES; for all models).

The models were evaluated by determining (1) level of conservatism of the model estimates, (2) GM of the ratios of the measurements to the model estimates, (3) Pearson correlation coefficients between the exposure measurements and the model estimates, and (4) estimation of bias, precision, and accuracy. The level of conservatism of the model estimates was then defined as high if the %M/T ≤ 10%, medium if 10% > %M/T ≤ 25%, low if %M/T > 25% and presented by exposure category, task operating condition based on PROC code, and model input parameters (VP, domain, and LEV presence). In conclusion, all of the models tested in this study were developed to be conservative, but the findings clearly suggest a need to review their exposure estimation mechanisms; that is, not one single model would work for all exposure situations. Probably, re-evaluation of initial exposure estimates of models related to task operation and/or input parameters may be necessary. Although this study contains a broad range of exposure situations, further validation is required for those exposure categories with limited exposure data.

INTRODUCTION

The REACH (Registration, Evaluation, Authorization, and restriction of CHemicals), a regulation enforced from June 1, 2007, by the European Union (EU), requires registration of chemicals (≥ 1 ton per year by May 31, 2018) to the European Chemicals Agency (ECHA) by manufacturers or importers. Registration will require submission of a Chemical Safety Report (CSR) if the application of chemical is classified as having health or environmental effects. The CSR includes a risk characterization, which is used to describe and manage risks. The CSR is drawn from a hazard and exposure assessment; the exposure assessment is based on the development of exposure situations that describe the conditions of use needed in place for a safe use of the substance. According to a database produced by Chemical Abstracts Services (CAS), more than 119 million organic and inorganic chemicals are currently registered (www.cas.org visit in August 2016). CAS Statistical Summary (1907–2006) reported an exponential growth of new chemicals, and approximately 4,000 new chemicals were added daily (Binetti et al., 2008). Due to a high number of new chemicals produced each day, it is almost impossible to perform quantitative exposure assessments for all possible exposure situations of any one chemical (Money et al., 2011). This EU regulation would not be limited to the EU countries. It would considerably affect the United States and other countries because hundreds of companies that produce and export chemicals to the European Union have to conform to this regulation.[N1]

The EU ECHA R14 guidance (2016) defined two types of tiered approaches—Tier 1 and higher tier models—to compensate this issue. Tier 1 includes "Targeted Risk Assessment (TRA)" developed by the European Centre for Ecotoxicology and Toxicology of Chemicals [N2](ECETOC), "Metal Estimation and Assessment of Substance Exposure (MEASE)" developed by EBRC Inc. on behalf of European Association of Metals, and "EMKG-~~Expo-Tool~~EXPO-TOOL (Easy-to-use workplace control scheme for hazardous substances)" developed by Bundesanstalt für Arbeitsschutz und Arbeitsmedizin (BAuA= Federal Institute for Occupational Safety and Health). Tier 1 models are designed to be simple and inexpensive and intended to provide conservative estimates of exposure[N3]. The "higher" tier models are developed to be used if the Tier 1 assessment suggests that the exposure may be inadequately too high. Higher tier models are Stoffenmanager®[N4] developed by TNO (Netherlands Organization for Applied Scientific Research) and Arbo Unie (Work safety union) in The Netherlands and Advanced REACH Tool (ART) developed by six institutions in four countries. Higher tier models are designed to accurately estimate the exposure distribution and are more comprehensive and sophisticated; thus, it is recommended that higher tier models be used by experienced assessors. The background information about the scope, concept, and applicability of each model is well described in the ECHA R14 guidance (2016). Recently, Hesse et al. (2015) performed a conceptual evaluation of the ECETOC TRA (version 2 and 3), MEASE (version 1.02.01), EMKG-EXPO-TOOL, and Stoffenmanager® (version 4.5). They introduced strengths and weaknesses of each model so that model users could possibly compare different tools for the users' specific exposure situations. The detailed information about the ART development are also introduced elsewhere (Tielemans et al., 2011; Fransman et al., 2011; van Tongeren et al., 2011; Schinkel et al., 2011; Cherrie et al., 2011). In addition, the State Secretariat for Economic Affairs (SECO) in Switzerland introduced a tool called TREXMO (Translation of Exposure Models) capable of translating a set of input parameters of one model into another model for all inhalation tier models introduced (https://www.seco.admin.ch/trexmo). This TREXMO ~~tool project~~ has been initiated to ~~reduce the uncertainty of input parameters and thus~~ improve between-user reliability (Savic et al., 2016) and promote the multiple model use (ECHA, 2016). While the testing version is already available online, the team is preparing its first end-user version. Currently, the team is performing internal and external evaluation studies.

Presently, comprehensive validation studies for the models under REACH have not been thoroughly carried out yet. Table 1 shows a summary of external validation studies for the models under REACH and relevant models. These previous studies presented validation results based on relatively small-scale data sets or limited operating conditions (e.g., limited PROC codes for TRA models). In addition, the models in Tier 1 and higher models were calibrated using either their own country's database or a combined database comprising data from several European countries. A comprehensive validation study with independent data sets (e.g., from different continents like the United States or Asia) that were not used in the calibration of the models is necessary.

In 2015, the Institute of Occupational Medicine (IOM) and Fraunhofer Institute for Toxicology and Experimental Medicine completed a project, entitled "The Evaluation of Tier 1 Exposure Assessment Models used under REACH (ETEAM)," sponsored by the BAuA in Germany to compare and evaluate the different REACH models including the ECETOC TRA (version 2 and 3), MEASE (version 1.02.01), EMKG-EXPO-TOOL, and Stoffenmanager® (version 4.5). The findings of this comprehensive study are published as a series of reports (http://www.baua.de/en/Publications/Expert-Papers-/F2303-D26-D28.html): (1) Background Information and Conceptual Evaluation (Hesse et al., 2015), (2) User-friendliness of Tier 1 Tools (Crawford et al., 2015), (3) Between-user Reliability Exercise and Workshop (Lamb et al., 2015a), (4) Uncertainty of Tier 1 Models (Hesse et al., 2015), (5) External Validation Exercise (Lamb et al., 2015b), and (6) Final Overall Project Summary Report (Lamb et al., 2015c). The external evaluation study was based on existing data from a range of workplaces in the European Union and the United States. The quality of contextual information required to run the models would vary because the existing data were collected for different purposes, such as compliance purposes or health hazardous evaluation projects. That is, for missing information on input parameters, assumptions (typically adopting the worst situation) were implemented. In the ETEAM project, a total of 2,098 individual measurements were used for the external evaluation; most data were available for high volatile liquids (> 10 Pa at room temperature, n=1356), followed by nonvolatile liquids (≤ 10 Pa at room temperature, n=316), powder handling (n=254), metal abrasion (n=87), metal processing (n=71), and wood processing (n=14). Each model's conservatism was reported as high if the percentage (%M/T) of measurements (M) exceeding the model estimates (T) ≤ 10%, medium if 10% > ≤ 25%, and low if %M/T > 25%. [SN5]Overall, the models showed to be conservative but not sufficiently conservative in all exposure situations (Lamb et al., 2015). Medium or low levels of conservatism were reported for the ECETOC TRAv2 and TRAv3 across all of the data. The ECETOC TRAv3 resulted in less conservative than the TRAv2, probably due to refining some input parameters. The MEASE showed similar conservatism as the ECETOC TRAv2 and v3; the percentage of measurements exceeding the model estimates was only 11% for powder handling category, which can be considered to be sufficiently conservative. For the EMKG-EXPO-TOOL, high conservatism was reported for the high volatile liquids and medium conservatism for the powder handling task. The %M>T of the Stoffenmanager 90th percentile was 12% and showed less conservative than the EMKG-EXPO-TOOL but more conservative than other models for high volatile liquids. For the powder handling category, the Stoffenmanager overestimated exposures (%M>T=3%). They concluded that the validation results for other categories (metal abrasion, metal processing, and wood processing) were inconclusive because of fewer existing data.

The external validation study done by IOM (Lamb et al., 2015b) was comprehensive and provided valuable information. However, existing data were used for the exposure measurements in this study. That is, no new exposure measurements, specifically to evaluate these models[VD6], were carried out. Assumptions of many input parameters in the models were inevitable due to missing detailed contextual information. The present study was conducted to evaluate the REACH models by using exposure measurements and contextual information gathered specifically for this validation exercise. The same inhalation models tested in the ETEAM project plus ART were used in this study. As shown in Figure 1, the collection of exposure measurements and development of exposure situation (ES) scenarios[SN7] were done by the National Institute for Occupational Safety and Health (NIOSH). The developed ESs were then translated into Microsoft Access Database by IOM and distributed to six organizations—NIOSH, IOM, BAuA, SECO, the Korean Institute of Science and Technology (KIST)-Europe, and the Swiss Institute for Work and Health (IST)—for answering all input parameters of each model. Agreements of each model's input parameters were obtained at a meeting held in July 2015, and all ESs were simulated for each model by NIOSH (for ART) and IOM (all except for ART) using consensus inputs. The findings of this study were presented in three parts: Part I—Tier 1 models, Part II—Higher tier models, and Part III—Assessors' variation. This paper covers the findings of Part I—Tier 1 models.

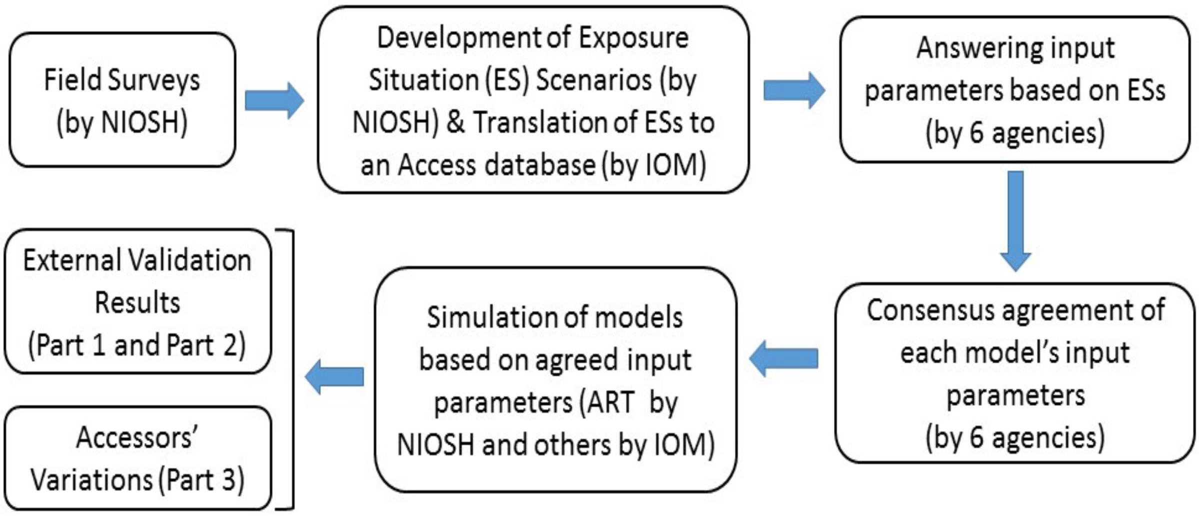

Figure 1. Overall Study Design and Outputs

Table 1. Summary of validation studies of models introduced by REACH

REACH Model	Reference	Task or Data sources	Chemical	Validation results
COSHH Essentials Toolkit*	Tischer et al., 2003	BAuA field studies	Solids (n=226), Liquids (n=732)	Good agreements for solid substances and organic solvent of liter quantities/Poor agreements for small scale of solvent
COSHH Essentials Toolkit*	Jones and Nicas, 2006	34 vapor degreasing industries and 22 bag filling industries	Various chemicals including solids and liquids; n=179 from vapor degreasing and n=159 from bag filling industries	Negative results and suggested systematic evaluation of the model
COSHH Essentials Toolkit*	Hashimoto et al., 2007	12 workplaces of a petroleum company in Japan	12 liquids (naphtha, benzene, toluene, and etc., n=58)	Good agreements by providing safe-sided judgment[VD8]
COSHH Essentials Toolkit*	Lee et al., 2009	Printing tasks	Methylene chloride (n=7), Isopropanol (n=188), and Acetone (n=187)	Good agreements for both short-term task-based and full-shift exposure measurements, but for some situations the probability of underestimation of exposure was > 10%
EMKG-EXPO-TOOL	Kindler and Winteler, 2010	42 situations	Isocyanate (n=390), Solvents (n=378), and Flour dust (n=36)	Underestimation of model estimates for handling of powder and volatile liquids with the existence of local exhaust ventilation; overestimation of exposure for chemicals with low vapor pressure
Stoffenmanager	Schinkel et al., 2010	STEAMbase**	Solids (n=142), Liquids (n=112)	Underestimation of the model for handling bulk materials and overestimation for handling small amounts of products; refined the Stoffenmanager algorithms based on the findings
ECETOC TRAv2 and Stoffenmanager 4.0	Vink et al., 2010	Professional spraying paint indoors	1-methoxypropan-2-ol (PGME) (n=745)	Overestimation of the TRA v2 estimates for the PROCs 8, 11, and 13, but greater variability of the exposure estimates; less conservative of Stoffenmanager estimates
COSHH Essentials Toolkit*	Lee et al., 2011	Batch making task and Bucket washing task in a paint manufacturing industry	Mixture of organic chemicals including acetone, ethylbenzene, MEK, toluene, and xylene (n=120 for Batch making task and n=90 for Bucket washing task)	Good agreements for full-shift exposure measurements, but for bucket washing task, some chemicals showed the underestimation of exposure
ECETOC TRAv2	Kupczewska-Dobecka et al., 2011	shoe manufactures, refinery tasks, and paint/ lacquer production	Toluene (n=73), Ethyl acetate (n=48), Acetone (n=50), O-Xylene (n=11)	Either underestimation of the model exposure estimates or good agreements compared to the exposure measurements; suggested an alternative PROC code (PROC 7 instead of PROC 10)
Stoffenmanager	Koppisch et al., 2011	German MEGA exposure database***	Powders/granules (n=390); machining of wood, stone, and asphalt (n=1133)	Good agreements showing that the proportion of the exposure measurements exceeding the 90th percentile of the tool was 11%

				of powder/granule handling tasks and 7% of machining activity tasks
ART	McDonnell et al., 2011	Pharmaceutical industry	Active pharmaceutical ingredients (n=130) and total inhalable dust (n=62)	Underestimation of the ART estimates; refined the inhalable dust algorithm of the ART
ECETOC TRAv2 and ART	Hofstetter et al., 2012	laboratory-based spray painting tasks	Toluene (n=11 for long-term and n=22 for short-term personal exposure measurements)	Overestimation of exposure estimates by both TRAv2 (3.6 times) and ART (2.9 times) when compared to the personal measurements
ECETOC TRAv2	Ko and Lee, 2013	Glass product and metal oxide manufacturing industry, Cast iron foundry, Chemical product manufacturing industry, and general hospital	Crystalline quarts (n=17), toluene (n=10), xylene (n=10), isopropyl alcohol (n=8), and formaldehyde (n=8)	Overestimation of exposure estimates by the TRAv2 when compared to the personal exposure measurements
Stoffenmanager 5.1	Landberg et al., 2015	Wood, Printing, Foundry, and Spray painting industries	Various chemicals including solids (n=11) and liquids (n=26)	Overestimation of the model estimates for solids; some underestimation of the model estimates (~27%) for liquids

*The previous validation of the UK Health and Safety Executive (HSE) COSHH Essentials toolkit is relevant to the EMKG-EXPO-TOOL because the EMKG-EXPO-TOOL is almost identical and supported by Control Guidance Sheets for various processes; **STOffenmanager Exposure And Modelling database (STEAMbase); ***German MEGA (“Measurement data relating to workplace exposure to hazardous substances”; in German, “Messdaten zur Exposition gegenüber Gefahrstoffen am Arbeitsplatz”) data (from 2000 to 2009) http://www.dguv.de/ifa/GESTIS/Expositionsdatenbank-MEGA/index-2.jsp.

METHODS

Field surveys

From 2012 to 2015, the NIOSH conducted exposure surveys to collect personal exposure measurements at numerous workplaces in the United States. Table 2 lists the types of workplaces and number of exposure measurements categorized into six exposure categories. Six exposure categories based on the physical form and emission generation process are (1) Aqueous solutions, (2) Liquids with a vapor pressure (VP) ≤ 10 Pa at room temperature, (3) Liquids with a VP > 10 Pa at room temperature, (4) Metal processing (e.g., hot metal processes such as casting or smelting), (5) Powders, and (6) Solid objects. Tasks include primer, stripper, and hardener spraying application in aircraft industries; prebatch/batch making, bucket filling/washing tasks in paint manufacturing industries; dry cleaning of fabrics and spot removing tasks in dry-cleaning shops; casting, smelting, and metal powder packing tasks in a solder manufacturing industry; denture making and repair tasks in a denture lab; sample slides preparation in hospital labs; fiberglass material gluing and resin infusion tasks in a wind mill company; and roller cleaning and printing tasks in printing shops[SN9]. A total of 483 personal exposure measurements were collected using either NIOSH or the Occupational Safety and Health Administration (OSHA) sampling and analytical methods. At some workplaces, we collected exposure measurements of multiple chemicals in a mixture using one sampling medium. In this case, only one chemical component having the highest proportion in the mixture was included. Consequently, a total of 293 personal exposure measurements were included. The sampling time ranged from 32 to 712 minutes[SN10], and about 88% of the measurements were sampling times longer than 240 minutes and 63% were longer than 360 minutes. Those measurements collected shorter than 240 minutes still represent the exposure of tasks (i.e., no handling of the interest chemical for the rest of the shift). The detailed information about tasks and number of samples for each task are listed in Supplement Table S1. During the field surveys, contextual information required for each model's input parameters were obtained. In addition, pictures and/or video clips were taken for some tasks, at the companies' permission, to compare if additional information besides written ESs would help the assessors' understanding.

Development of exposure situation (ES) scenarios

After the field surveys, NIOSH developed 53 ESs based on the job tasks and chemicals written in a table format to be used for the validation exercise. Along with the task descriptive information, product information including an analyte concentration, molecular weight, and vapor pressure were also provided. The exposed and non-exposed times for workers at each place were similar in each workplace because of the same work schedule. In a few situations where workers performed the same task but had various exposed/non-exposed times, we developed separate ESs. These ESs are Glue application-Inside tasks (ESs 46 and 47), Glue application-Outside tasks (ES IDs 48–51), and Roller cleaning tasks (ESs 54–56).

One notable observation was that workers performed several subtasks under various control strategies. For example, a batch maker in a paint manufacturing company worked on a batch making task by conducting four subtasks (ES 19): (1) manual addition of solid materials from the top opening of the batch (partial opening of the batch; 10% of 8-hr full shift), (2) transfer of chemical products to other containers (automatic transferring system with partial opening ([< 10 cm opening diameter] of the containers; 20% of full shift), (3) manual cleaning of emptied batches with no presence of any local exhaust ventilation (10% of full shift), and (4) the rest including filling, mixing, rinsing, and shipping done in fully enclosed systems (60% of full-shift). In this example, because Tier 1 models were not able to consider multiple tasks at the same time, we treated several subtasks as one task with the lowest control method.

All ESs were transferred to the Microsoft Access database developed by the IOM (see Figure S1 for a screen shot). The collected individual exposure measurements were not included in the Access database. These exposure measurements were separately stored and not released to the assessors until all simulation works were completed.

Translation of contextual information into models' input parameters

~~Fifty-three~~53 ESs were divided into four batches. Each batch was sent to six ~~accessors~~ assessors from different organizations (NIOSH, IOM, BAuA, SECO, KIST-Europe, and IST). All ~~accessors~~ assessors were familiar with Tier 1 models, but the familiarity of individual ESs varied depending on their experiences.

Individual ~~accessors~~ assessors then translated the descriptive information of each ES independently into the tier model inputs by selecting each model's tab (Figure S1), directing to a screen showing the required model input parameters of a model (for an example, see Figure S2). The tools evaluated in this Part I were the ECETOC TRAv2, ECETOC TRAv3, MEASE v1.02.01 (referred to as "MEASE"), and EMKG-EXPO-TOOL. Table 2 shows a summary of each model's applicability based on the job tasks. The models' applicability for each ES is listed in Table S1. During this task, assessors were allowed to communicate only by emails within the group to be transparent. For those ESs where photographs and/or video clips of the relevant tasks were available, we sent the ESs along with visual task information on the following next batch and asked assessors to enter the model inputs. This was to determine if visual task information would help ~~accessors~~ assessors for obtaining better model estimates (see Part III for the findings).

Once all batches were complete, IOM collated all input parameters of each model into an Excel file. In July 2015, an in-person meeting was held in Switzerland to obtain consensus for inputs of each model after discussing the discrepancies among assessors.

Generation of model estimates

The IOM generated exposure estimates of each tier model following agreement on the final set of inputs. The actual ECETOC TRAv2, ECETOC TRAv3, and MEASE models were used to obtain exposure estimates. The tool decision tree for the EMKG-EXPO-TOOL was incorporated into the database. The logic built into the database was checked by comparing estimates from the actual model and in-database model for 10% of ESs and confirmed no differences.

Data analyses

The EMKG-EXPO-TOOL is known as a task-based tool, whereas the ECETOC TRAv2, TRAv3, and MEASE represent full-shift exposures by applying a conversion factor for the duration of a task (0.1 for < 15 minutes, 0.2 for 15–60 minutes, 0.6 for 1–4 hours, and 1 for > 4 hours[SN11]). Since the collected exposure measurements did not always represent full-shift or task-based exposures, it is necessary to adjust the exposure data accordingly. For example, ES 29 (Denture making task) had 190 minutes of chemical exposed time and 290 minutes of non-exposed time while our sampling time covered a full-shift. In this situation, an exposure measurement based on a full-shift cannot be directly compared to the corresponding exposure estimates obtained from the EMKG-EXPO-TOOL. Another example is that an exposure measurement with 37 minutes sampling time (i.e., task-based exposure) cannot be directly compared to the exposure estimates of the ECETOC TRAv2 and TRAv3. We thus adjusted the exposure measurements using the following steps: (1) convert all exposure data to the task-based exposure data, (2) for the EMKG-EXPO-TOOL, compare the task-based exposure data with corresponding model estimates, and (3) for the ECETOC TRAv2, TRAv3, and MEASE, apply a factor to convert a full-shift model estimate to the corresponding task-based estimate (i.e., divided by a factor of 0.1 for < 15 minutes, 0.2 for 15–60 minutes, 0.6 for 1–4 hours, and 1 for > 4 hours).

For the ECETOC TRAv2, TRAv3, and MEASE, the point estimates were used. For the EMKG-EXPO-TOOL, which predicts an exposure range rather than a single estimation, we selected the upper range value for the comparison in accordance with the REACH guidance. In the ETEAM project (Lamb et al., 2015b), if the EMKG-EXPO-TOOL generated an exposure estimate of > 10 mg/m^3 (for solids) or > 500 ppm (for liquids), a value of 20 mg/m^3 or 1,000 ppm was assigned. However, in this study, we adopted a value of 10 mg/m^3 or 500 ppm by considering that many exposure limit values are within these values.

The comparison between the exposure measurement data and the model estimates were conducted by calculating the ratio of the exposure measurement (M) over the tool estimate (T) for each pair of values. The level of conservatism of the model estimates were then defined as high if the proportion of exposure measurements exceeding the model estimates (%M/T) ≤ 10%, medium if 10% > %M/T ≤ 25%, and low if %M/T > 25%. The results of %M/T were presented by exposure category, PROC code, and model input parameter. Although the EMKG-EXPO-TOOL does not have the PROC code as an input parameter, the PROC codes used in the ECETOC TRAv2 and TRAv3 were applied to this model for the comparison purpose. Input parameters that have a major impact on the model estimation were examined, and those are the allocation of dustiness (high, medium, and low), vapor pressure (high, medium, and low), domain (industrial and professional), and local controls (yes and no). The ECHA R14 guidance (2016) recommends the P90 value estimated from an exposure distribution as a “reasonable worst case” exposure and P75 as a “worst case” situation (such as noncompliant data), rather than using individual exposure data. [SN12]Thus, we also calculated a 90th percentile (P90) value from exposure distribution for each ES having a sample size ≥ 3 and compared it with a model estimate to determine a level of conservatism in the same manner.[SN13] This comparison was limited to the ECETOC TRAv2 and TRAv3.

When examining the ratios of the measurements exceeding the model estimates (M/T), if a GM of the ratios of the measured data and estimates is < 1, we determined the model as conservative to some degree for the situation. [VD14]In this study, a GM of the ratios was used in preference to an AM to reduce the impact of high values of the measured and/or estimated values. Pearson correlation coefficients between the log-transformed exposure measurements and tool estimates were also calculated.

In addition, bias and precision were calculated by using the following equations (Hornung, 1991):

$$Bias = \sum_{i=1}^{n_0} \frac{(\hat{y}_i - y_i)}{n_0} , \qquad Precision = \sqrt{\sum_{i=1}^{n_0} \frac{[(\hat{y}_i - y_i) - bias]^2}{n_0 - 1}}$$

Relative bias was then calculated as follows (Schinkel et al., 2010):

$$Relative\ bias = \left(e^{-\text{[SN15]}bias} - 1\right) * 100\%$$

where $\hat{y}_i$ =predicted exposure level for the i[th] set of exposure factors in the validation set (log scale), y_i = measured exposure for the i[th] set of exposure factors (log scale), and n_0 = number of measurements in the validation set. The bias indicates a distance of the model estimate from the true value, whereas the precision estimates variability. A positive bias implies overestimation by a model compared to an exposure measurement; a negative bias implies underestimation. The smaller value of the relative bias indicates the more accurate results for the exposure estimation. All data analyses were performed using Statistical Analysis Software (SAS) v. 9.4 statistical software package.

RESULTS

Description of workplace measurement data

Table 2 shows a summary of the exposure measurement data (task-based) collected by exposure category. Note that among a total of 293 inhalation exposure data, liquids with VP > 10 Pa category has the most exposure measurements (~86%) compared to other exposure categories because of the companies' willingness to participate in the surveys and type of activity/substance used. Aqueous solution category has the least number of measurements (n=4 with 2 ESs). In the category of liquids with VP > 10 Pa, formaldehyde exposure from the sample preparation task in a pathology lab (ES 35) showed the lowest exposure (0.02 mg/m^3), while styrene exposure from the glue application task inside a wind blade (ES 47) showed the highest exposure (6653.3 mg/m^3). Compared to the high VP category, other exposure categories showed lower ranges of exposure measurements, ranging from 0.002 mg/m^3 to 1.82 mg/m^3. Overall, the geometric mean (GM) value was lower than the arithmetic mean (AM) value. Especially, the GM (24.45 mg/m^3) was considerably lower than the AM (214.44 mg/m^3) for the liquids with VP > 10 Pa category, indicating a skewness of the data distribution. The detailed exposure measurements per ES are listed in Supplement Table S1.

Table 2. Summary of the task-based exposure measurements (by exposure category)

Exposure Category	Workplaces	ES No	n	Applicability of Tier 1 models [(1)]	Personal Exposure Measurements (Task-based)				
					AM (mg/m^3)	GM (mg/m^3)	GSD	Min (mg/m^3)	Max (mg/m^3)
Aqueous solutions	Aircraft industry	2	4	MEASE only	0.92	0.73	2.31	0.24	1.82
Liquids with VP ≤ 10 Pa	Aircraft industry	2	5	All but MEASE and EMKG-EXPO-Tool	0.07	0.05	2.83	0.02	0.16
Liquids with VP > 10 Pa	Paint, aircraft and wind mill industries, dry-cleaning shops, hospital labs, denture lab, and print shop	42	251	All but MEASE	214.44	24.45	9.84	0.07	6653.28
Metal Processing	Casting and smelting industries	2	11	MEASE only	0.15	0.04	6.20	0.003	0.62
Powders	Metal powder generation and packing industry	2	11	All models	0.44	0.24	3.73	0.03	1.44
Solid Objects	Solid object packing/shipping	3	11	All models [VD16]	0.09	0.03	5.64	0.002	0.33
Overall		53	293		183.74	10.76	20.08	0.002	6653.28

Abbreviations: ES No=number of exposure situations (ESs) developed by NIOSH; n=number of workplace measurements; AM=arithmetic mean exposure; GM=geometric mean exposure; GSD=geometric standard deviation; min=minimum; max=maximum. [(1)]Applicability of models were based on job tasks.

Comparison of workplace measurement data (task-based) with model estimates

1. By exposure Category

ECETOC TRAv2: Among 278 exposure measurements from 49 ESs, approximately 90% of measurements were available for liquids with VP > 10 Pa (n=251 from 42 ESs), followed by powders (n=11 from 2 ESs), solid objects (n=11 from 3 ESs), and liquids with VP ≤ 10 Pa (n=5 from 2 ESs). The results of TRAv2 estimates are presented in Supplement Table S2. When the P90 values from exposure distributions were selected, the comparable sample sizes were reduced especially for the liquids with VP > 10 Pa category by excluding number of exposure measurements < 3. For exposure measurements with individual data and P90 values, the GMs of the ratios of the measurements over the model's estimates were less than 1 for all exposure categories, indicating overestimation of the model (Table 3). When the level of conservatism was tested with individual measurement data, the liquids with VP > 10 Pa category showed a medium level of conservatism (%M/T=22%) while other exposure categories presented high levels of conservatism (%M/T=0). Figure 2 shows the exposure measurements versus the model's estimates (both log-transformed) for the liquids with VP > 10 Pa. The level of conservatism using the P90 values became one level down for liquids with VP > 10 Pa (from medium to low level). Pearson correlation coefficients (ρ) between the TRAv2 estimates and measurements (both log-transformed) showed a moderate correlation for liquids with VP > 10 Pa (Table 4). For the powder handling, a weak negative correlation (r=-0.113) was observed when calculated with individual data. For the other two categories, only one model estimate was obtained and thus no correlation coefficient could be calculated. The bias calculation with individual measurements demonstrated overestimation of the model estimates for all exposure categories (i.e., all positive biases) with precision ranging from 1.04 to 1.95, although exposure categories having sample size ≤ 11 showed high values. The relative bias calculations indicated that the ECETOC TRAv2 is more accurate for estimating liquids with VP > 10 Pa category than other categories, but it should be noted that the results for the other categories were based on a small sample size (≤ 11). When the same calculation was carry out with P90 values, the bias/relative biases show the same pattern across the exposure categories.

ECETOC TRAv3: The same number of ESs and exposure measurements tested in the ECETOC TRAv2 were available for this model, and the estimation results are presented in Supplement Table S3. None of the model estimates exceeded the corresponding exposure measurements (both individual and P90 data) for the categories of liquids with VP ≤ 10 Pa and powders. For the solid objects category, the model showed a medium level of conservatism (%M/T=18%) with individual data and a low level (%M/T=33%) with P90 data. For the liquids with VP > 10 Pa, the model's conservatism was low when compared with individual and P90 measurement data (Table 3). For exposure measurements with individual data, the GMs of the ratios (M/T) were < 1 for all exposure categories, indicating overestimation of the model. However, for exposure measurements with P90 values, the GM of the ratios was 1.39 for the liquids with VP > 10 Pa, indicating underestimation of the model, whereas the GMs of the ratios were < 1 for other exposure categories. The correlation coefficients between the measurements (both individual and P90 values) and the TRAv3 estimates were moderate for the liquids with VP > 10 Pa and poor for the solid objects (Table 4). A weak negative correlation was observed for the powders with individual data. The estimations of bias, precision, and relative bias were similar to those observed from the ECETOC TRAv2.

<u>MEASE</u>: Only 37 exposure measurements were available for the comparison because of the elimination of exposure data related to liquids. The model's estimates are presented in Supplement Table S4. None of MEASE estimates exceeded the exposure measurements for the metal processing and powders categories, whereas almost half of the model estimates were higher than the measurements for the aqueous solutions and solid objects categories, indicating poor levels of conservatism (Table 3). The MEASE estimates were weakly correlated with the measurements for the metal processing task (r=0.254), while negative correlations were observed for the aqueous solutions and powders categories (Table 4). The GM values of ratios (M/T) < 1 and positive biases with precision ranging from 1.3 to 2.4 of all exposure categories implicate the model's overestimation of exposures. Note that this result was based on limited data sets.

<u>EMKG-EXPO-TOOL</u>: Tasks involving an open spray process were not applicable for this model, and thus the number of ESs was smaller compared to the ECETOC TRA models. The estimation results are presented in Supplement Table S5. Overall, the estimates for the EMKG-EXPO-TOOL were higher than those for other models. As shown in Figure 2 and Table 3, only 6% of exposure measurements exceeded the corresponding model estimates for the exposure category of liquids with VP > 10 Pa. None of the model estimates exceeded the corresponding measurements for the categories of powders and solid objects. The model's estimates were moderately correlated with the exposure measurements for the liquids with VP > 10 Pa (r=0.694, p < 0.05) and for all data. For the powders and the solid objects categories, correlation coefficients could not be calculated because only one estimate was obtained for these (i.e., no variability). Like other Tier 1 models, this model also overestimated exposure levels with bias ranging from 2.3 to 3.7 and all GM values of ratios (M/T) < 1. Among exposure categories, the estimations of bias, precision, and relative bias for the liquids with VP > 10 Pa were slightly better than other categories.

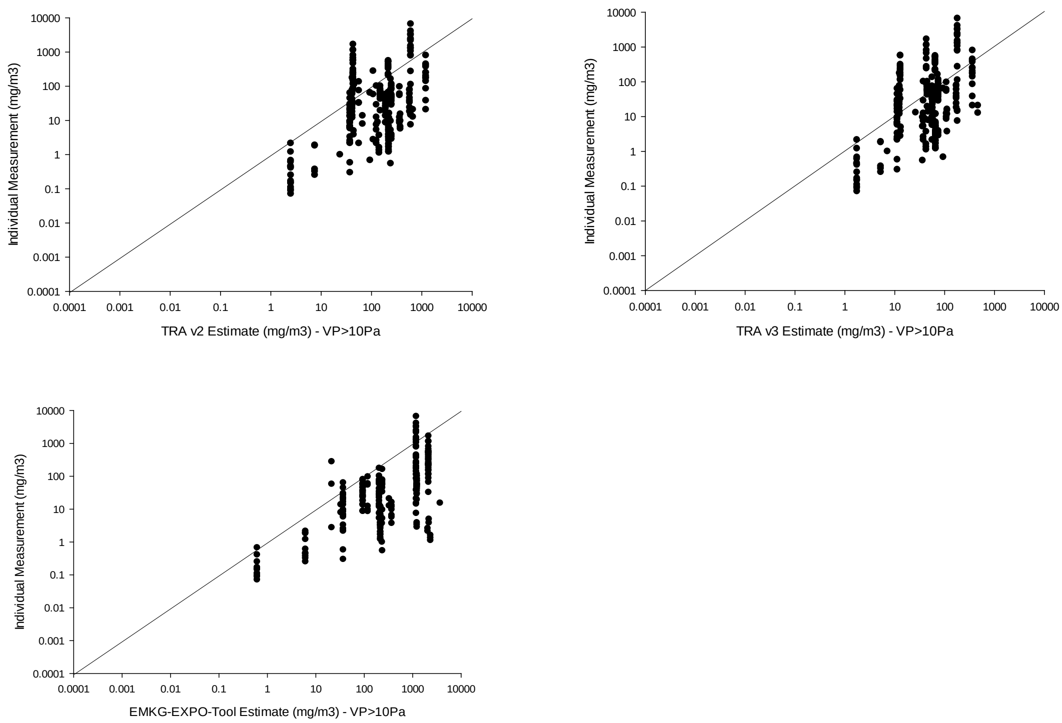

Figure 2. Exposure measurements vs. Model estimates of the ECETOC TRA v2, TRA v3, and EMKG-EXPO-Tool (Exposure category: Liquids with VP > 10 Pa, both log-transformed)

Table 3. Summary of the ratios of the task-based measurements over the models' exposure estimates (M > T) (by exposure category)

Model	Exposure Category	ES No	n	Ratio (Exposure Measurements/Model Estimates)					
				GM	GSD	Min	Max	nM>T	%M>T
ECETOC TRAv2-Individual data	Liquids with VP ≤ 10 Pa	2	5	< 0.01	2.83	< 0.01	< 0.01	0	0
	Liquids with VP > 10Pa	42	251	0.21	7.05	< 0.01	38.73	54	22
	Powders	2	11	0.01	3.80	< 0.01	0.06	0	0
	Solid Objects	3	11	0.03	5.64	< 0.01	0.33	0	0
ECETOC TRAv2 – P90 values(1)	Liquids with VP ≤ 10 Pa	1	1	< 0.01	-	-	-	0	0
	Liquids with VP > 10Pa	31	31	0.50	7.05	-	-	9	29
	Powders	2	2	0.06	1.01	-	-	0	0
	Solid Objects	3	3	0.15	2.05	-	-	0	0
ECETOC TRAv3-Individual data	Liquids with VP ≤ 10 Pa	2	5	< 0.01	2.83	< 0.01	< 0.01	0	0
	Liquids with VP > 10Pa	42	251	0.59	6.78	< 0.01	44.19	96	38
	Powders	2	11	0.04	3.80	< 0.01	0.19	0	0
	Solid Objects	3	11	0.05	7.59	< 0.01	1.11	2	18
ECETOC TRAv3 – P90 values(1)	Liquids with VP ≤ 10 Pa	1	1	0.01	-	-	-	0	0
	Liquids with VP > 10Pa	31	31	1.39	6.16	-	-	17	55
	Powders	2	2	0.19	1.01	-	-	0	0
	Solid Objects	3	3	0.28	3.31	-	-	1	33
MEASE	Aqueous solutions	2	4	0.60	3.17	0.15	2.07	2	50
	Metal processing	2	11	0.01	5.89	< 0.01	0.37	0	0
	Powders	2	11	0.03	3.77	< 0.01	0.15	0	0
	Solid objects	3	11	0.73	5.64	0.04	8.34	5	46
EMKG-EXPO-TOOL	Liquids with VP > 10Pa	40	243	0.10	5.50	< 0.01	13.14	15	6
	Powders	2	11	0.02	3.73	< 0.01	0.14	0	0
	Solid objects	3	11	0.03	5.64	< 0.01	0.33	0	0

ES No=number of exposure situations (ESs) for which data were available; n=number of exposure measurements; GM=geometric mean of the ratios of the measurements over the exposure estimates; GSD=geometric standard deviation of the ratios; min=lowest measurement/ exposure estimate ratio; max=highest measurement/exposure estimate ratio; nM/T=Number of exposure measurements exceeding the model estimates; %M > T=Percent of exposure measurements exceeding the model estimates; (1)90th percentile value from exposure distribution

Table 4. Correlation coefficients, bias, precision, and relative bias between exposure measurements and model estimates by exposure category

Model		n	ρ	Bias	Precision	Relative bias
ECETOC TRAv2-Individual data	Liquids with VP ≤ 10 Pa	5	**	7.29	1.04	146763
	Liquids with VP > 10Pa	251	0.531*	1.58	1.95	387
	Powders	11	-0.113	4.55	1.33	9352
	Solid Objects	11	**	3.53	1.73	3327
ECETOC TRAv2 – P90 values	Liquids with VP ≤ 10 Pa	1	n/a	6.08	n/a	n/a
	Liquids with VP > 10Pa	31	0.492*	0.70	1.95	101
	Powders	2	***	2.85	0.01	1626
	Solid Objects	3	**	1.90	0.72	570
ECETOC TRAv3-Individual data	Liquids with VP ≤ 10 Pa	5	**	6.09	1.04	43965
	Liquids with VP > 10Pa	251	0.548*	0.52	1.91	69
	Powders	11	-0.113	3.34	1.33	2735
	Solid Objects	11	-0.699*	2.95	2.03	1804
ECETOC TRAv3 – P90 values	Liquids with VP ≤ 10 Pa	1	n/a	6.08	-	-
	Liquids with VP > 10Pa	31	0.551*	0.70	2.10	-28
	Powders	2	****	2.85	1.70	418
	Solid Objects	3	-0.974	1.90	1.43	254
MEASE	Aqueous solutions	4	-0.797	0.51	1.27	66
	Metal processing	11	0.254	4.31	1.77	7327
	Powders	11	-0.113	3.62	1.33	3633
	Solid objects	11	**	0.32	1.73	37
EMKG-EXPO-TOOL	Liquids with VP > 10Pa	243	0.694*	2.33	1.71	926
	Powders	11	**	3.71	1.32	4000
	Solid objects	11	**	3.53	1.73	3327

*p-value < 0.05; **Only one estimate was obtained and therefore no correlation coefficient could be calculated; ***Not calculated because only 2 values were available; ρ = Pearson correlation coefficient

2. By PROC code

Table 5 shows the percentage of the individual exposure measurements (task-based) exceeding the model estimates by PROC code, and the gray box indicates a sample size < 10. The description of PROC codes is listed elsewhere (Supplement Table S6).

<u>ECETOC TRAv2</u>: For this model, the highest number of measurements was assigned to PROC 10 (Roller or brushing application, n=114) in the liquids with VP > 10 Pa category. Fewer measurements were assigned to PROC 5 (Batch process for formulation of articles, n=47), PROC 13 (Treatment of articles by dipping and pouring, n=45), PROC 15 (Use as laboratory reagent, n=15), and PROC 21 (Handling of massive metal, n=11) with other PROCs having between 2 and 9 measurements each. The model appeared to underestimate for this exposure category for PROC 3 (Use in closed batch process), PROC 7 (Industrial spraying), PROC 10, and PROC 15, showing moderate or low levels of conservatism. All other PROCs in other exposure categories generated high levels of conservatism (note that the number of measurements were not sufficiently large). The same analysis was performed with P90 values. Only PROC 10 showing the same conservatism (%M/T=46%, n=11) is reportable, and other PROCs were not reported because of a small sample size (< 3) (results not included).

ECETOC TRAv3: Compared to the ECETOC TRAv2, this model was less conservative for the same PROCs. In addition, a moderate level of conservatism (%M > T=18%) was observed for PROC 21 in the solid objects category. The same analysis using P90 values for PROC 10 resulted in very high percentage of exposure measurements exceeding the model estimates (%M/T=91%, n=11). [SN17]

MEASE: Insufficient conservatism was observed for PROC 7 in the aqueous solutions (although based on only 4 measurements) and PROC 21 in the solid objects category. Overall, the number of measurements was limited to ≤ 11 for all PROC codes.

EMKG-EXPO-TOOL: Although this tool does not require an input of PROC codes, the TRA PROC codes were used as a proxy for task description. PROC 3 showed the highest percentage of measurements exceeding the model estimates (67%) but with a small number of measurements (n=3), it would be difficult to confirm any conclusion. PROC 10 shows a moderate level of conservatism but it is very close to the high level. All other PROC codes showed high levels of conservatism.

3. By model input parameter

The comparison of %M/T per input parameter was summarized in Table 6. Note that exposure categories other than the liquids with VP > 10 Pa were not included because only one allocation was selected per input parameter. For the aqueous solutions category of the MEASE, although the LEV input (Yes or No) was comparable, we excluded this as well because of only 2 individual measurements per each choice.

For the liquids with VP > 10 Pa, the majority of measurements was allocated into the medium VP and the absence of LEV for the ECETOC TRAv2, TRAv3, and EMKG-EXPO-TOOL. The ECETOC TRAv2 and TRAv3 showed high levels of conservatism when allocated to the low VP except for the TRAv3 with P90 values, whereas other high and medium VP allocations showed medium or high levels of conservatism. The ECETOC TRAv2 showed less percentage of exposure measurements exceeding the model estimates for the professional domain compared to the industrial domain and for the LEV presence compared to the LEV absence. A similar pattern was observed for the ECETOC TRAv3 (except for the domain input comparison with P90 values), but the percentage of measurements exceeding the model estimates were considerably higher than the TRAv2. The EMKG-EXPO-TOOL resulted in a higher proportion of measurements exceeding the model estimates when it was allocated to the high VP compared to the other VP allocations. The EMKG-EXPO-TOOL did not appear to be impacted by domain and LEV status (although the industrial domain showed very close to a medium level of conservatism).

Table 6. Percentage of exposure measurements above the model estimates (%M > T) by model input parameter (Exposure category: Liquids with VP > 10 Pa)

Model		Input Parameter - %M > T (number of sample size)						
		Vapor Pressure(1)			Domain		LEV	
		High	Medium	Low	Professional	Industrial	Yes	No
ECETOC TRAv2	Individual	35 (37)	22 (190)	0(24)	7(105)	32 (146)	8 (50)	25 (201)
	P90	17 (6)	36 (22)	0 (3)	17(12)	37 (19)	17 (6)	32 (25)
ECETOC TRAv3	Individual	49 (37)	41 (100)	4 (24)	32 (105)	43 (146)	22 (50)	42 (201)
	P90	50 (6)	59 (22)	33 (3)	58 (12)	53 (19)	50 (6)	56 (25)
EMKG-EXPO-TOOL		27 (37)	2 (182)	4 (24)	1 (105)	10 (138)	7 (42)	6 (210)

(1)Low vapor pressure: < 500Pa at a room temperature; Medium vapor pressure: 500 ≤ VP ≤ 10000 Pa; High vapor pressure: VP > 10000 Pa

Table 5. Percentage of the individual exposure measurements (task-based) exceeding the model estimates (%M/T) (by PROC code)

Exposure Category	PROC Code											
	3	5	7	8b	9	10	11	13	15	21	22[1]	23[1]	26[1]
ECETOC TRAv2: %M/T (number of exposure measurements)													
Liquid vapor pressure ≤ 10Pa			0 (5)										
Liquid vapor pressure > 10Pa	33 (3)	0 (47)	25 (8)	0 (9)	0 (8)	39 [2] (114)	0 (2)	0 (45)	47 (15)				
Powder Handling				0 (7)	0 (4)								
Solid Object										0 (11)			
ECETOC TRAv3: %M/T (number of exposure measurements)													
Liquid vapor pressure ≤ 10Pa			0 (5)										
Liquid vapor pressure > 10Pa	67 (3)	9 (47)	25 (8)	0 (9)	0 (8)	64 [3] (114)	0 (2)	4 (45)	87 (15)				
Powder Handling				0 (7)	0 (4)								
Solid Object										18 (11)			
MEASE: %M/T (number of exposure measurements)													
Aqueous solution			50 (4)										
Metal Processing											0 (5)	0 (6)	
Powder Handling													0 (11)
Solid Object										46 (11)			
EMKG-EXPO-TOOL: %M/T (number of exposure measurements)- According to TRA PROC code													
Liquid vapor pressure > 10Pa	67 (3)	0 (47)		0 (9)	0 (8)	11 (114)	0 (2)	2 (45)	0 (15)				
Powder Handling				0 (7)	0 (4)								
Solid Object										0 (11)			

Note that the gray box indicates a sample size < 10; [1]Only for MEASE; [2]%M/T (number of measurements exceeding the model estimates/total numbers) with P90 values=46% (11); [3]%M/T (number of measurements exceeding the model estimates/total numbers) with P90 values=91% (11).

DISCUSSION

Description of workplace measurement data

Although this study attempted to collect sufficient exposure measurements from all exposure categories, most measurements were available for exposures to the liquids with VP > 10 Pa (n=251 out of 293 measurements). Among 53 ESs, ~79% ESs were assigned to this exposure category. This was as expected because volatile organic compounds are widely used across many industries. Compared to this category, the other categories included fewer exposure measurements (n = from 4 to 11) with fewer ES scenarios.

For exposures to the liquids with VP > 10 Pa, the majority of the ESs was limited to situations where LEV was absent or where chemicals had medium VP applications (Table 6). Additionally, the range of operating conditions was limited. For example, PROC 10 showed the highest number of exposure measurements (n=114), whereas several PROCs (PROCs 3, 11, 21, 22, and 23) included fewer measurements (n < 10). This might generate the validation study with a degree of imbalance, especially the MEASE, which included a small number of measurements for each PROC and thus the validation result would not be conclusive.

Comparison of workplace measurement data with model estimates

The current study was initiated as an extended study of the validation study (Lamb et al., 2015b), part of the ETEAM project. The evaluation of the models was performed in four ways by determining (1) the level of conservatism of the model estimates, (2) the GM of the ratios of the measurements to the model estimates (M/T), (3) Pearson correlation coefficient between the exposure measurements and the model estimates, and (4) estimation of bias, precision, and relative bias. The level of conservatism of the model estimates was defined as high if %M/T ≤ 10%, medium if 10% > %M/T ≤ 25%, and low if %M/T > 25%, and presented by exposure category, task operating condition based on PROC code, and model input parameters (VP, domain, and LEV presence).

<u>ECETOC TRAv2</u>: The liquids with VP > 10 Pa category showed a medium level of conservatism (%M/T = 22%), whereas the external validation from the ETEAM project (Lamb et al., 2015b) generated a low level of conservatism (%M/T=26%) but the %M/Ts were close to each other. For this category, PROCs 15 (%M/T=47%), 10 (%M/T=39%), 3 (%M/T=33%), and 7 (%M/T=25%) showed high frequency of measurements exceeding the model estimates (Table 5). Both current and ETEAM studies showed the same high levels of conservatism for PROCs 8b (Transfer of substance from/to large containers at dedicated facilities), 9 (Transfer of substance from/to small containers), 11 (Non-industrial spraying), 13, and 15 for exposures to the liquids with VP > 10 Pa. In contrast, the levels of conservatism for PROCs 3, 5, 7, and 10 for the liquids with VP > 10 Pa were inconsistent by one level between the two studies. For example, the level of conservatism for PROC 10 was medium for the ETEM project and low in this study. Vink et al. (2010) validated the TRAv2 with 745 exposure measurements and reported overestimation of the model estimates for the PROCs 8, 11, and 13. The same results were observed in the present study (even for the same PROCs for the TRAv3). Hofstetter et al. (2012) reported that the TRAv2 estimate in assessing exposure to toluene from spray paint task was 3.6 times higher than the mean exposure concentration measured in a controlled room. Ko and Lee (2013) also evaluated this model with personal exposure measurements of various volatile organic chemicals (n=36) and crystalline quarts (n=17) and reported overestimation of the model estimates to the mean exposure measurements. For exposures to liquids with VP > 10 Pa, the present study showed similar patterns as those two previous studies when considering the GM values of M/T ratios. The conservatism by the input parameter was inconsistent depending on the choice of input. Both current and ETEAM projects observed high levels of conservatism when the model was allocated to the low VP and professional domain (except for P90 values), while other choices in these inputs generated medium or low levels of conservatism. An impact of LEV presence was different between two studies; the conservatism was high for the presence of LEV and low for the absence of LEV in the current study, whereas the results were opposite in the ETEAM project. These findings indicate that the model developer needs to review those inputs showing inconsistent results between the two studies and resulting high or medium level of conservatism. Moderate correlation coefficients (ρ=0.531 with individual data and 0.492 with P90 values) and positive bias (with the highest accuracy among other exposure categories) with similar ranges of precision (1.52–1.81) reported by Shinkel et al. (2010) and Koppisch et al. (2012) promise some level of conservatism for this exposure category.

For the powder handling tasks, none of measurements exceeded the model estimates in this study, while 16% of measurements exceeded the estimates in the ETEAM study. Both current and ETEAM studies showed the same high levels of conservatism for PROCs 8b and 9 for exposures to powders. In contrast, a weak negative correlation for exposures to handling of powders (r = -0.113) indicates a poor conservatism. The model was also highly conservative for exposures to the liquids with VP ≤ 10 Pa and solid objects. Although the findings of this study demonstrated overestimation of the model estimates exhibiting conservatism with some degree (i.e., positive biases and GM ratios < 1), it would be difficult to draw any conclusion because of a small sample size (≤ 11) available for those categories.

ECETOC TRAv3: The revised TRA version—ECETOC TRAv3—was even less conservative than the previous version 2, exhibiting conservatism as medium for the solid objects category and poor for exposures to liquids with VP > 10 Pa, while other categories showed the same high level of conservatism (Table 3). The ETEAM validation study (Lamb et al., 2015b) showed the same low level of conservatism for exposures to liquids with VP > 10 Pa but a lower level of conservatism for exposures to powder handling. For some PROCs, the exceedance percentages of measurements over the tool estimates for the TRAv3 were considerably increased compared to those for the TRAv2 (e.g., from 47% to 87% for PROC 15 and from 39% to 64% for PROC 10). For exposures to liquids with VP > 10 Pa, the TRAv3 showed the same levels of conservatism as the TRAv2 for the VP input (Table 6). Both domain and LEV input parameters showed > 20% of measurements exceeding the model estimates regardless which option the model was allocated. Especially, the TRAv3 showed a conservatism one level down from the TRAv2 regardless of the presence of LEV in this study. When the ECETOC version was updated from v2 to v3, the model developers made a few modifications for the baseline exposure estimates for a number of PROC, domain, and LEV presence. In particular, the ventilation option has been considerably refined by including a wide range of options (seven options including outdoors, indoors, and combinations of indoors, general ventilation, and mechanical ventilation) than the version 2 (LEV presence: Yes or No). The findings of this study and the ETEAM study confirmed that the refinement of ventilation might be one main factor causing underestimation of the model estimates by applying higher control factors than it is supposed to be. All PROCs except for PROCs 5, 10, and 13 for the liquids with VP > 10 Pa showed the same level of conservatism as the ETEAM study; PROCs 5 and 13 showed high levels of conservatism in this study while low levels were observed in the ETEAM study. On the other hand, the conservatism of PROC 10 was low for this study and medium for the ETEAM study. The findings of PROCs 5, 10, and 13 in both studies were based on sample sizes ≥ 45. Thus, it is recommended that the model developers review these PROCs. The results by other PROCs were based on the sample sizes ≤ 11. Like the comparison results between this study and the ETEAM study for the TRAv2 conservatism, similar patterns of conservatism were observed for the TRAv3. The results of moderate correlation coefficients ($\rho = 0.548$ with individual data and 0.551 with P90 values), GM values < 1, and positive bias with a better accuracy compared to that of TRAv2 demonstrated a certain level of conservatism for exposures to liquids with VP > 10 Pa. As with the situations of the ECETOC TRAv2, it is too early to draw any conclusions for other exposure categories due to small sample sizes. To our knowledge, no other studies except for the ETEAM validation study were conducted to evaluate the TRAv3, indicating needs for further studies.

MEASE: Compared to the other models, the MEASE considered only few exposure measurements (total n = 37) because of the model's inapplicability to estimating liquid exposures. With the limited measurements, the MEASE was highly conservative for exposures to metal processing and powders but poorly conservative for exposures to aqueous solutions and solid objects. In contrast, the ETEAM validation results demonstrated less conservative for exposures to metal processing and powder handling (both medium levels of conservatism) compared to the findings in this study. Note that other exposure categories were not considered in the ETEAM study. For the comparison of PROCs between two studies, only PROC 22 and 23 for exposures to metal processing were available; PROC 23 resulted in high level of conservatism for both studies. But the conservatism for PROC 22 was high for the current study and low for the ETEAM study. Overall, the ETEAM study showed considerably higher number of exposure measurements exceeding the MEASE estimates compared to those in this study. Although the results in this study are inconclusive because of small sample sizes, it is still interesting to observe that handling solid objects showed 46% of the measurements exceeding the estimates (5 of 11 measurements) given the information that the MEASE was specifically developed for the metal industry sector. Although the GM values < 1 and positive biases for all exposure categories indicate overestimation of the model estimates, poor correlation coefficients showed inconclusive results. Since the results of this model were based on limited data sets, it is necessary to conduct additional validation studies.

EMKG-EXPO-TOOL: This model resulted in high levels of conservatism for exposures to liquids with VP > 10 Pa (%M/T=6%), powders (%M/T=0%), and solid objects (%M/T=0%). Both ETEAM and current studies revealed the same high levels of conservatism for PROCs 8b, 9, 11, 13, and 15 for exposures to liquids with VP > 10 Pa and PROCs 8b and 9 for exposures to powders. The levels of conservatisms for the current study and the ETEAM study were low (%M/T=67%, n=3) and medium (%M/T=25%, n=4) for PROC 3, high (%M/T=0%, n=47) and medium (%M/T=15%, n=60) for PROC 5, and medium (%M/T=11%, n=114) and high (%M/T=6%, n=245) for PROC 10. The results, especially those based on a small sample size, should be revisited by the model developer. Interestingly, when the model was allocated to the high VP for exposures to liquids with VP > 10 Pa, a low level of conservatism (%M/T=27%) was determined while allocations to the medium and low VP generated high levels of conservatism. On the other hand, the ETEAM project revealed no impact of exposure estimation based on the VP input parameter. Both studies did not appear to be impacted by the input of domain. The presence of LEV generated different results between the current study (%M/T=7%, n=42) and the ETEAM project (%M/T=14%, n=381) suggesting a further study is needed. The correlation coefficients provide a moderate relationship between the exposure measurements and model estimates for exposures to liquids with VP > 10 Pa ($r=0.694$, $p\text{-value} < 0.05$). The GM values < 1 and positive biases for the exposure categories promise some degree of conservatism.

Kindler and Winteler (2010) presented underestimation of the model estimates for handling of powders and volatile liquids with the presence of LEV, whereas the current study did not observe the same results. Among all Tier 1 models in the present study, the EMKG-EXPO-TOOL showed the least percentage of exposure measurements exceeding model estimates. This might happen because this model does not account for the proportion of a substance in a mixture (i.e., assumption of a substance in a mixture as a pure substance), unlike other Tier 1 models. In this study, 40 out of 45 ESs demonstrated a substance in a mixture applied for this model. This assumption can at least partially explain the difference of conservatism compared to the other Tier 1 models. This issue has been discussed in the ETEAM validation study as well (Lamb et al., 2015b). Thus, the findings suggest a need for additional validation using pure chemicals and/or redesign of the model that can account for a mixture of chemicals. As other Tier 1 models, the results for exposures to powders and solid objects are inconclusive because of small sample sizes.

CONCLUSIONS

A comprehensive study was performed to evaluate the Tier 1 models recommended by the ECHA R14 guidance (2016). Only exposures to liquids with VP > 10 Pa have sufficient number of sample sizes for the evaluation study. For this category, the ECETOC TRAv2 and TRAv3 resulted in a medium or high level of conservatism when considering individual and P90 values, whereas the EMKG-EXPO-TOOL demonstrated a high level of conservatism. Moderate correlation coefficients—GM values < 1 and positive biases for the ECETOC TRAv2, TRAv2, and EMKG-EXPO-TOOL models—promise some degree of conservatism. The TRAv3 tends to be less conservative than the TRAv2, which might be related to the refinement of some input parameters (e.g., LEV). For the other exposure categories, it is too early to draw any definite conclusion because of small sample sizes (≤ 11). We could not make any conclusion for the MEASE as well for the same reason. Although no conclusion was made for those aforementioned, we presented the results because they would still be worthwhile for identifying needs for improvement by model developers. For the MEASE and exposure categories having limited data, further evaluation including more exposure measurements for these categories are strongly recommended.

Below is a summary of areas where the performance of the models may need to be improved in future. Note that these recommendations below were made regardless of sample sizes of exposure measurements.

1. ECETOC TRAv2 and TRAv3: For exposures to liquids with VP > 10 Pa, both models showed high percentage of measurements exceeding the model estimates for serval PROC codes and a few input parameters. [VD18]The PROC codes to be considered in the future model upgrade or development are PROC 3 (Closed batch process), PROC 5 (Mixing or blending in batch processes), PROC 7 (Industrial spraying), PROC 10 (Roller application), PROC 13 (Treatment of articles by dipping and pouring), and PROC 15 (Application as laboratory reagent). The model mechanism including input parameters of high and medium vapor pressure, industrial domain, and LEV absence should be reviewed. The ECETOC TRAv3 results also suggest additional input parameters including professional domain and LEV presence for exposures to liquids with VP > 10 Pa for reassessment.

2. MEASE: The model recommends an improvement for exposures to handling solid objects due to a high percentage of measurements exceeding the model estimates for PROC 21 (Low energy

manipulation of substances) and the allocated input parameters. The exposure category of aqueous solutions also needs to be reconsidered; ≥ 50% of measurements exceeded the model estimates for PROC 7 (Industrial spraying) and the associated input parameters.

3. EMKG-EXPO-TOOL: Although this model was conservative across all exposure categories, for exposures to liquids with VP > 10 Pa, the model provided a high percentage of measurements exceeding the model estimates for PROC 3 (Closed batch process) and high VP input parameter, suggesting necessities of the model improvement.

In conclusion, all of the models tested in this study were developed to be conservative, but the findings clearly suggest a need to review their exposure estimation mechanisms. That is, not one single model would work for all exposure situations. Re-evaluation of initial exposure estimates of models related to task operation and/or input parameters may be necessary. Although this study contains a broad range of exposure situations, further validation is required for those exposure categories with limited exposure data.

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DISCLAIMER

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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