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Original Article

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Experimental Assessment of Inhalation and Dermal Exposure to Chemicals During Industrial or Professional Activities in Relation to the Performance of ECETOC TRA

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Abstract

For many work situations only insufficient exposure data are available to perform proper risk assessment. Because measuring worker exposure can be time consuming and resource intense, the availability of reliable exposure models is important when performing risk assessments. However, the development and improvement of exposure models are hampered by scarcity of sound exposure data as well as by lack of information on relevant exposure factors and conditions of exposure. This paper describes a study where inhalation and dermal exposure data were collected under defined conditions. Exposure scenarios examined included tasks that have not been investigated in previous validation studies. The results of these measurements were compared with ECETOC TRA model version 3.1 predictions. In this study, five exposure scenarios were selected, namely 'use in a closed batch process' (PROC 4), 'mixing or blending in a partly open batch process' (PROC 5), 'rolling' (PROC 10), 'immersion' (PROC 13), and 'stirring' (PROC 19). These PROCs stem from the descriptors that Registration, Evaluation and Authorization of Chemicals has established to depict the identified uses of chemical substances. These exposure scenarios were selected mainly because little or no data are available for these situations, or ECETOC TRA is likely to underestimate exposure for these situations. Experiments were performed by volunteers for the selected exposure scenarios, in which tasks were performed aiming to represent real workplace situations. In total 70 experiments were performed, during which 70 dermal exposure measurements (5 volunteers × 2 repeats × 7 scenarios) and 32 inhalation exposure measurements (4 volunteers × 2 repeats × 4 scenarios) were collected. Two formulations

were used, namely pure Tinopal SWN powder (solid product, a fluorescent tracer) and 0.5% Tinopal SWN dissolved in 1,2-dichloroethane (1,2-DCE). DCE is considered a moderate volatile liquid. For exposure scenarios using the liquid formulation, both inhalation and dermal measurements were performed, while for exposure scenarios using the pure powder only dermal exposure measurements were performed. In addition, photographs were taken under ultraviolet light to qualitatively assess exposure patterns on hands and body. Volunteers repeatedly performed a selection of tasks under standardized conditions in a test chamber for each exposure scenario. Results show that ECETOC TRA overestimated dermal hand exposure for all PROCs included in the study, and was considered to be conservative. Additionally, ECETOC TRA overestimated inhalation exposure for closed and partially closed processes, but underestimated inhalation exposure for rolling and handling of immersed objects. Qualitative assessment of the hands and body showed mainly the hands were exposed for tasks involving closed and partially closed processes and when handling of immersed objects. Exposure to other body segments were also observed for rolling and stirring. In conclusion, this study gave insights into dermal and inhalation exposure levels during selected task scenarios, and showed that ECETOC TRA is conservative when dermal exposure is estimated. Inhalation exposure estimates for PROCs 10 and 13 tasks with the moderate volatility liquid were underestimated in this study. It may be therefore necessary to re-evaluate base model predictions for these scenarios when medium fugacity liquids are involved.

Keywords: dermal exposure; ECETOC TRA; exposure modelling; inhalation exposure; model validation

Introduction

Chemicals are continuously being introduced on the market that may pose a broad range of potential health hazards (Herber *et al.*, 2001; Phneah *et al.*, 2017; EFSA Scientific Committee, 2019; Li and Suh, 2019). As a consequence, the Registration, Evaluation and Authorization of Chemicals (REACH) was introduced by the European Commission in 2007 to improve the protection of human health and the environment from risks posed by chemicals (REACH Directive 1907/2006/EC). To comply with REACH regulations, for chemicals that are produced in quantities over 10 tons on an annual basis, producers are obligated to demonstrate that no health risks occur for individuals who work with these chemicals by performing human health risk assessment. In general, use of data from exposure measurements is preferred over the use of occupational exposure models. However, measuring worker exposure is considered to be expensive and time consuming (Schinkel *et al.*, 2010). Therefore, in the absence of exposure measurement data, a tiered approach using exposure models to assess exposure has been advocated. Within this tiered approach, screening tools (also referred to as tier one tools) should provide a conservative system that can differentiate between substances of concern and those considered safe within an occupational setting (Schinkel *et al.*, 2011; Tischer *et al.*, 2017). Several screening tools such as ECETOC TRA (ECETOC, 2004) and Stoffenmanager (Marquart *et al.*, 2008) are available. Additionally, it has been observed that most chemical safety reports have been developed using these screening tools, for which in most cases ECETOC TRA was used (Tischer *et al.*, 2017).

As Tier 1 exposure models are intended to be conservative and are widely used in registration dossiers, it is considered important that these models do not underestimate true exposure values (ECHA, 2016; Tischer *et al.*, 2017). Various evaluation/validation studies of existing exposure models have been performed, covering several domains such as worker inhalation and dermal exposure and consumer exposure (Kupczewska-dobecka *et al.*, 2011; Delmaar *et al.*, 2013; Hesse *et al.*, 2015; Lamb *et al.*, 2015; Riedmann *et al.*, 2015; Jung *et al.*, 2016; Marquart *et al.*, 2017; van Tongeren *et al.*, 2017). One of these is the ETEAM project, in which several lower tier exposure models including ECETOC TRA (version 3.1) were evaluated. They suggested that ECETOC TRA is not conservative for some workplace activities, which included mixing or blending in batch processes [process category (PROC) 5], roller application (PROC 10), immersion/dipping (PROC 13), and stirring (PROC 19). Additionally, they found that not enough data were available to evaluate the performance of ECETOC TRA for use in a closed process (PROC 1), use in a closed continuous process (PROC 2), use in a closed batch process (PROC 3), use as a laboratory reagent (PROC

15), and various processes involving metals or minerals (PROCs 21–27a) (Lamb *et al.*, 2015; Jung *et al.*, 2016). Dermal exposure models were evaluated with regard to between-user variability, but were not validated within the ETEAM study due to a lack of data (Lamb *et al.*, 2015).

Marquart *et al.* (2017) evaluated the dermal exposure module of ECETOC TRA. They found that for the majority of exposure scenarios (80%) the model estimates were higher than the corresponding 75th percentiles of measured exposure values. For PROCs for which data were available, the available exposure data often originated from a limited number of studies, with the exception of activities such as transfer (PROCs 8a, 8b, and 9), and professional and industrial spraying (PROCs 11 and 7).

The main objectives of this study were to (i) generate both inhalation and dermal exposure data for workplace activities for which little meaningful exposure data are available or for which there is a likelihood that ECETOC TRA does not provide a conservative exposure estimate, and (ii) compare the results of these measurements with exposure estimates generated with the ECETOC TRA model for these activities to evaluate the performance of the model.

Methods

Experimental design

Taking into account the scope of the study, existing data gaps as identified in recent (validation) studies, and the feasibility to perform representative experiments, five general activities were included in this study. The activities included use in batch and other process (synthesis) where opportunity for exposure arises (PROC 4), mixing or blending in batch processes for formulation of preparations and articles (PROC 5), roller application or brushing (PROC 10), treatment of articles by dipping and pouring (PROC 13), and hand-mixing with intimate contact and only personal protective equipment (PPE) available (PROC 19). The general experimental design thus includes five different activities (PROCs) in combination with two different products. In experiments with the liquid product both inhalation and dermal exposure measurements were conducted. In experiments with the solid product only dermal exposure measurements were conducted. As both within- and between-person variances of inhalation and dermal exposures can be substantial (Kromhout *et al.*, 1993; Loomis and Kromhout, 2004; Kasiotis *et al.*, 2020), multiple volunteers and repeats per volunteer were considered in the design of the study. Overall, 70 experiments were performed (see Table 1).

In total, seven different exposure scenarios were included in the study. For each exposure scenario an experimental design was developed, including relevant determinants of exposure such as the amount of substance and equipment used to represent realistic workplace conditions (see Table 1). In Supplementary Fig. S1, available at *Annals of Work Exposures and Health* online, photographs are presented as illustration of each of the PROCs studied.

In order to perform the experiments in a standardized and reproducible manner, amongst others to reduce the variability in outcomes due to behaviour and environmental conditions, protocols were developed for each exposure scenario, amongst others based on lessons learned from a previous study (Kasiotis *et al.*, 2020), detailing the experimental set-up as well as protocols for sample collection. These protocols were optimized based on pilot tests and discussions with- and input from industrial experts.

Test substances and test products

To be able to combine a quantitative assessment of hand exposure with a qualitative assessment of body exposure, the fluorescent tracer substance Tinopal SWN (7-diethylamino-4-methylcoumarin, BASF) was selected to reflect dermal exposure during all experiments. Tinopal SWN was suitable for the assessment of the dermal exposure, as it proven to be stable in solution and not prone to light degradation (Franken *et al.*, 2019). Two types of formulations (one solid and one liquid) were used. Untreated pure Tinopal SWN (100%, w/w) was used as solid formulation, of which the dustiness was determined to vary between 10 976 and 16 663 mg kg^{-1} (Franken *et al.*, 2019). In case of the experiments with the liquid formulation, the objective was to measure inhalation exposure to a medium volatile substance and dermal exposure in parallel. Assessment of dermal exposure using volatile substances is considered to be difficult as volatile substances tend to evaporate from the (surrogate) skin or penetrate the skin, often resulting in unreliable dermal exposure values (Behroozy, 2013). Therefore, Tinopal SWN, a low volatile substance, was dissolved in a medium volatile solvent to create a 'solid-in-liquid' formulation. Dissolving 1 g Tinopal SWN in 450 ml 1,2-dichloroethane (1,2-DCE), 50 ml glycerol, and 200 ml methanol (MeOH) by stirring of the solution resulted in a homogenous formulation. The homogeneity of the solution was verified by consecutive

Table 1. Experimental study design.

Exposure scenario	Product	# volunteers	# repeats per volunteer	# experiments	Dermal exposure[b]	Inhalation exposure[c]	Experimental set-up
Closed process (PROC 4)	Solid[a]	5	2	10	✓		Amount used: 5 kg Tinopal SWN powder, reused for all experiments. Equipment used: vibratory sieve shaker with detachable lid (lid closed during experiment). Activities: volunteer starts the shaker, and then sits at desk for 7 min. Volunteer stops the shaker and waits 30 s before opening the lid for inspection for 30 s. This step is repeated once and after the second inspection, the volunteer closes the lid after the second repeat.
	Liquid	5	2	10	✓	✓[d]	Amount used: 20 l of liquid product, reused for all experiments. Equipment used: electrical agitator with detachable lid (lid closed during experiment). Activities: volunteer starts the agitator, and then sits at desk for 7 min. Volunteer stops the agitator and waits 30 s before opening the lid for inspection for 30 s. This step is repeated once and after the second inspection, the volunteer closes the lid after the second repeat.
Partially closed process (PROC 5)	Solid[a]	5	2	10	✓		Amount used (5 kg, reused for all experiments), equipment used: vibratory sieve shaker with detachable lid (lid partially opened during experiment). Activities: volunteer starts the shaker, and moves to desk for 7 min. Volunteer stops the shaker and waits 30 s before opening the lid for inspection for another 30 s. This step is repeated once and after the second inspection, the volunteer closes the lid after the second repeat.
	Liquid	5	2	10	✓	✓[d]	Amount used (20 l, reused for all experiments), equipment used: electrical agitator with detachable lid (lid partially opened during experiment). Activities: volunteer starts the agitator, and moves to desk for 7 min. Volunteer stops the agitator and waits 30 s before opening the lid for inspection for another 30 s. This step is repeated once and after the second inspection, the volunteer closes the lid after the second repeat.
Rolling (PROC 10)	Liquid	5	2	10	✓	✓[d]	Rolling flat surface (both sides of door; 3.5 m^2) up- and downward directions, fixed use rate. Trays are refilled by technical personnel.
Handling immersed objects (PROC 13)	Liquid	5	2	10	✓	✓[d]	Smooth immersed object surface; average number of pieces handled (15×); high surface contamination level; medium sized objects. Volunteers dip 15 objects in a dipping bath, and hangs the objects on a drying rack. Volunteers move the objects from the drying rack to a second rack across the room.
Stirring (PROC 19)	Solid[a]	5	2	10	✓		Amount used: 7.5 kg Tinopal SWN powder. Equipment used: 12 small objects (tennis balls) of varying size in a 50 l plastic bucket to simulate the hardening process of e.g. cement, wooden cylindrical stick with a length of about 1 m and 5 cm thick. Manually stirring of the dry powder and taking rest (3 min stirring; 12 min rest)

[a]Dusty solid product.
[b]Quantitative assessment of hand exposure in combination with a qualitative assessment of body exposure to a fluorescent tracer.
[c]Inhalation exposure to a semi-volatile substance.
[d]Inhalation exposure was measured in four of the five volunteers.

sampling (n = 5) of the formulation, and subsequent chemical analysis, which showed negligible fluctuation amongst the measured and the nominal concentration of Tinopal SWN [relative standard deviation (RSD)% = 1.6]. After preparation of the formulation also a visual inspection after storage of the formulation in ambient temperature as well as in a cold room for 6 h. Neither any kind of precipitation nor separation of layers was observed. The volatility of 1,2-DCE is 8.7 kPa. The viscosity of the formulation was determined at 0.8026 $mm^2\ s^{-1}$ following the Rotating Viscometer Method (European Pharmacopoeia Commission, 2010). The surface tension of the liquid formulation was determined at 29.161 ± 0.071 $mN\ m^{-1}$ (Sigma 70, KSV Instruments Ltd, Helsinki, Finland).

Dermal and inhalation sampling

Dermal hand exposure was measured quantitatively by means of pairs of 100% cotton gloves (Tsismetzoglou Co., Athens, Greece), under which black nitrile protective gloves (SemperGuard®, Austria) were worn (one size for all volunteers). The cotton gloves were light green of colour and free of whitening agents to prevent interference with the qualitative dermal assessment method. Each glove was stored and analysed separately in order to differentiate between exposure on the left and right hand and prevent possible cross-contamination.

To measure personal exposure to 1,2-DCE in the air, charcoal tubes [Anasorb CSC coconut charcoal (440/200 mg sorbent layers, FFW separator) from SKC] were placed within the breathing zone of the volunteer (on shoulder), connected to a pump (Gilian, GilAir Plus, Sensidyne LP®, USA) with a flow rate set on 80 ml min^{-1}. The flow rate was monitored by the pump, and recorded at the start and end of each experiment. The charcoal tubes were packed individually in aluminium foil to prevent any diffusion from the tubes and stored in air-tight ziplock bags before analysis, as well as to prevent possible cross-contamination.

For the qualitative assessment of dermal exposure a fluorescence method as developed in a previous study (Franken *et al.*, 2019) was used. In short, photographs of the volunteers were taken in a ultraviolet (UV)-room before and after the conduction of each experiment. In this UV-room, a set-up with UV rays irradiating double TL armatures was placed for optimal diffuse lighting over the entire body region. Photographs were taken using a Nikon P90 camera set on ISO 3200, F/8. Three consecutive photos of both the front and back of the volunteers were taken with a shutter time of 1/80, 1/20, and 1/5 s, to take into account possible under- or overexposure of the photographs. For the visual evaluation, no under- or overexposure of photographs was observed. Therefore, the photo with shutter time of 1/20 s was selected.

Test location

Two identical containers (2.6 m × 7.1 m) equipped with a shower, mechanical ventilation, and a digital device recording the temperature and humidity were available for the performance of the experiments. The mechanical ventilation was altered in order to control air exchange rates, and ran on the lowest setting during all experiments resulting in an air exchange rate of 23.6 h^{-1}. Of these two containers, one container was dedicated to the conduction of the experiments and one container was equipped as UV-room. The container dedicated to the conduction of the experiments was cleaned thoroughly and visibly inspected (using a portable UV light) after each experiment to avoid cross-contamination.

Recruitment and safety of volunteers

Medical ethical approval for this study was obtained by the Ethical Committee of BPI. Volunteers were recruited amongst trained professional workers that participated in previous (field) studies, taking into account easiness in performing the tasks and training. During recruitment, safety data sheets of the chemicals used in the project were presented to volunteers in their native language, as well as a consent form explaining the scope of the project, the experimental work and the chemicals involved. During the process of recruitment, an occupational physician and the safety officer were present as well as during the pilot tests to guarantee the safe commencement. Suitable PPE was provided to all volunteers to minimize exposure during the performance of the experiments.

PPE used by the volunteers during the trials were safety goggles (3M SF200 series, St. Paul, Minneapolis, USA), rubber boots, filter masks (pro2000 PF10, Scott Safety, UK) for respiratory protection, full-face mask (SR 500, Sundström, Sweden), and short sleeved black nitrile protective gloves (EN 374), as well as UV light protection glasses (Honeywell, North T2400 tactile, Clear Lens Safety Spectacles, Cromwell Co., Leicester, UK) during taking the photographs in the UV-room. Both the safety officer and the occupational physician of BPI endorsed the selection of PPE provided.

Prior to the start of the experiments, the volunteers were trained by the scientific personnel on how to perform the experiments following the protocols. This ensured that experiments were performed in a standardized and reproducible way while taking into account safety requirements and protective measures.

Sample preparation and extraction

After the experiments, the dermal sampling gloves and charcoal sampling tubes were collected in a clean and covered area located close to the test location.

The field scientist removed the gloves and put each of them in a screw cap plastic polyethylene pot with a unique label. The samples were transported to the laboratory and were analysed within 2–3 working days. High-performance liquid chromatography (HPLC) grade methanol (Fisher Scientific) was used as an extraction solvent. The solvent was added in the sample pot, ensuring the glove was almost covered by the solvent (at least at ¾ level). Next, the pots were placed on a platform shaker and were extracted for 30 min at 180–200 rounds per minute (rpm) at ambient temperature. Afterwards, the pots were placed in an ultrasonic bath for 2 min to enhance extraction efficiency. Overall, the extraction efficiency of the gloves was sufficient and recovery rates were >90%. Validation of the extraction is described in more detail elsewhere (Franken *et al.*, 2019; Kasiotis *et al.*, 2020).

Also, the charcoal tube was removed from the volunteer, wrapped in aluminium foil, packaged in an air-tight ziplock bag and labelled after each experiment. For extraction, the front and back sections of the tubes were transferred into separate 4 ml vials. To the vials with the front sections 3 ml carbon disulfide (CS_2) was added, and to the vials with the back sections 2 ml CS_2 was added. The vials were shaken several times over a period of approximately 30 min to extract the 1,2-DCE. Next, the CS_2 extract was transferred to gas chromatography (GC) injection vials for the analysis.

Chemical analysis

For the analysis of Tinopal SWN in the extracted dermal samples, a Shimadzu (Kyoto, Japan) LCMS-2010 EV Liquid Chromatograph was used, consisting of a SIL-20A prominence autosampler equipped with an SPD-M20A diode array detector coupled in line with a fluorescence detector (RF-10AXL). The liquid chromatography (LC) separation was accomplished on a Zorbax Eclipse Plus C18, 3.5 µm, 150 × 2.1 mm i.d. chromatographic column using an isocratic system consisting of acetonitrile (ACN):water (1:1) containing 0.2% formic acid (both ACN and formic acid were of HPLC grade, Fischer Scientific). The flow rate was set at 0.4 ml min^{-1}. The total run time was 9 min, with Tinopal SWN eluting at 4.5 min. LC–mass spectrometry (MS) solution v3.0 software was used for processing of the analytical results. The validation of this analytical method is described elsewhere (Kasiotis *et al.*, 2020), which showed good recovery rates (average 93 ± 0.07%, RSD 7%), stability and linearity ($r^2 > 0.999$). The limit of quantification was determined at 0.00014 µg cm^{-2}.

For the analysis of 1,2-DCE in the inhalation samples, the extracts were analysed according to standard ISO 9486 (ISO, 1991), using a Shimadzu QP2010 Plus GCMS. The GC was equipped with an Agilent VF624ms column (30 m × 0.25 mm × 1.4 µm film). The MS was run in scan-mode with the scanning range set to 33–200 amu. Together with the samples, a calibration curve ranging from 25 to 500 mg l^{-1} was constructed and analysed. The front and back sections of the charcoal tubes were analysed separately to determine whether breakthrough occurred. Breakthrough for all samples was less than 4%.

The analysis of the blank inhalation samples showed that, regardless of the location where the blanks were prepared (laboratory or field), no cross-contamination occurred as they were found free of analyte.

Comparison of measured exposure values with exposure estimates from ECETOC TRA

The ECETOC TRA V3.1 model estimates, both dermal and inhalation exposure of workers, are based on information about the concentration of the substance in the formulation, volatility/dustiness of the substance, PPE used by the worker, ventilation rate during the activity and duration of the activity (ECETOC, 2004, 2009, 2012, 2014, 2018). The characteristics of each of the exposure scenarios in relation to relevant categories of the parameters as applied in the ECETOC TRA model are presented in Table 2. In general, categories for dustiness, vapour pressure, and concentrations differed between the assessment of dermal and inhalation exposure. As the ventilation rate during the experiments was 23.6 h^{-1}, for inhalation exposure the category ‘enhanced ventilation’ was assigned, which according to ECETOC TRA corresponds to an ACH > 10. As protective gloves were only worn underneath the sampling gloves, in case of dermal exposure the category ‘no protective gloves’ was assigned. ECETOC TRA distinguishes between processes performed under ‘industrial’ or ‘professional’ circumstances, based on the assumption that industrial processes are more controlled and workers are better trained in the use of control measures. Therefore, a lower base estimate is applied for each PROC in case of industrial use conditions. As the experimental design mostly resembles what is considered as ‘professional use’ (instead of ‘industrial use’) in ECETOC TRA, these estimates were taken into account for all exposure scenarios.

Table 2. Overview of study characteristics in relation to ECETOCTRA model parameter input categories.

Exposure scenario	Characteristics per exposure situation						Inputs for ECETOC TRA parameters[a]		
	Exposed surface area	Product	Duration (min)	Route of exposure	Dustiness/vapour pressure	Conc.	Duration	Dustiness/vapour pressure	Conc.
Closed process (PROC 4)	480 cm^2, two hands, face only	Solid	17–18	Dermal	10.976–16.663 mg kg^{-1}	100%	>4 h (default)	High	>25%
		Liquid	17–18	Inhalation	8.7 kPa	64%	>4 h (default)	500–10 000 Pa	>25%
				Dermal	Low volatile	0.14%		<0.01 Pa	<1%
Partially closed process (PROC 5)	480 cm^2, two hands, face only	Solid	16–17	Dermal	10.976–16.663 mg kg^{-1}	100%	>4 h (default)	High	>25%
		Liquid	16–17	Inhalation	8.7 kPa	64%	>4 h (default)	500–10 000 Pa	>25%
				Dermal	Low volatile	0.14%		<0.01 Pa	<1%
Rolling (PROC 10)	960 cm^2, two hands	Liquid	25	Inhalation	8.7 kPa	64%	>4 h (default)	500–10 000 Pa	>25%
				Dermal	Low volatile	0.14%		<0.01 Pa	<1%
Handling of immersed objects (PROC 13)	960 cm^2, two hands	Liquid	6–8	Inhalation	8.7 kPa	64%	>4 h (default)	500–10 000 Pa	>25%
				Dermal	Low volatile	0.14%		<0.01 Pa	<1%
Stirring (PROC 19)	1980 cm^2, two hands	Solid	15	Dermal	10.976–16.663 mg kg^{-1}	100%	>4 h (default)	High	>25%

[a]Ventilation, PPE, and professional/industrial were all the same over all experiments: enhanced general ventilation; no PPE; professional use.

Dermal exposure values were converted from µg to mg kg^{-1} day^{-1} in the following way: Tinopal SWN level as measured on both hands (total hands, in µg)/1000 µg/70 kg (average weight of a person as considered by ECETOC TRA) to match the output of ECETOC TRA. For inhalation exposure, the measured values were presented as PPM to match ECETOC TRA output units.

For each exposure scenario, the 75th percentile of the distribution of the measured exposure values was calculated and compared with the corresponding ECETOC TRA exposure estimate (which estimates the 75th percentile) (ECETOC, 2009).

With regard to the measured values which were compared with ECETOC TRA predictions, it was assumed that the measurements with regard to inhalation exposure reflect an 8 h time-weighted average (8-h TWA), which is considered a worst-case approach since it is likely that non-exposure times occur during the working day. With regard to dermal exposure, since workers typically wash their hands and/or remove/lose contamination from their hands (for instance by touching other surfaces) during their shift, the measurements were considered to be task-based exposures, as cleaning/cross-contamination of the hands is hard to simulate in an experimental setting. ECETOC TRA has exposure modifiers for non-exposure times which would be used for dermal exposure to estimate task-based exposures, but the model excludes the use of this option for high dusty solids and non-volatile substances (ECETOC, 2012). Therefore, the estimations from ECETOC TRA are considered task-based predictions, while the estimates are similar for shift exposure predictions.

All (model) calculations were performed by the authors of the current study, and checked with the LRI monitoring team, which included members of the ECETOC TRA taskforce that developed the ECETOC TRA model.

Statistical analysis

All calculations were performed using SAS statistical software (V9.4). Figures were generated using Sigmaplot (V12.5). For comparison purposes (used in descriptive statistics as well), exposure values for exposure scenarios using a solid product were normalized to reflect the concentration of Tinopal SWN used in the liquid formulation (based on an admission of the density of the liquid product to the value of 1 due to its proximity to this value) by dividing them by a factor of 714 to correct for the difference in concentration between the two types of product.

Results

Tinopal SWN exposure values as measured on the hands are presented in Fig. 1 and Table 3. The boxplots as presented in this study show the lower 10% of the distribution (dots), 10th percentile (whisker), 25th percentile, 50th percentile (median), 75th percentile, 90th percentile (whisker) and upper 10% of the distribution (dots). After normalization, it can be observed that exposure scenarios in which the liquid product is handled lead to higher measured exposure values compared with exposure scenarios in which the solid product is handled. This comparison can especially be made for closed (PROC 4) and partially closed (PROC 5) processes, as these experiments were performed with both the solid and the liquid product. For these exposure scenarios measured exposure values were a factor ~4 higher when the liquid product was used [geometric means (GMs, in µg) of 12.5 and 6.8 for closed and partially closed processes using the liquid product, compared with GMs of 4.0 and 2.7 for closed and partially closed processes using the solid product, respectively]. Rolling (PROC 10) and immersion/dipping (PROC 13) resulted in the highest measured exposure values (GM 1079 and 1541, respectively). Stirring (PROC 19) resulted in the highest measured exposure of all exposure scenarios in which the solid product was handled (GM 9.7). During the experiments for the exposure scenarios of closed process, partially closed process, and stirring, the volunteers were required to use both hands when performing the tasks, while for rolling and handling of immersed objects volunteers only used one hand to perform the task during the experiments. The relatively large variance of exposure as observed for rolling and to a lesser extent for handling of immersed objects may be due to the fact that volunteers used their dominant hand when performing these experiments. One of the five volunteers was left handed and in some experiments 100% of the observed exposure was allocated to the dominant hand. The observed difference in exposure values as measured during the experiments for closed process and partially closed process may be explained by the level of direct contact of the hands with the equipment, which was less during the partially closed process experiments.

The measured airborne 1,2-DCE concentrations (in ppm) are presented in Fig. 2 and Table 3. The highest airborne concentrations were measured during rolling (PROC 10) and handling of immersed objects (PROC 13), with GMs of 437 and 324 ppm, and the lowest concentrations were measured during partially closed process (PROC 5) and closed process (PROC 4) with GMs

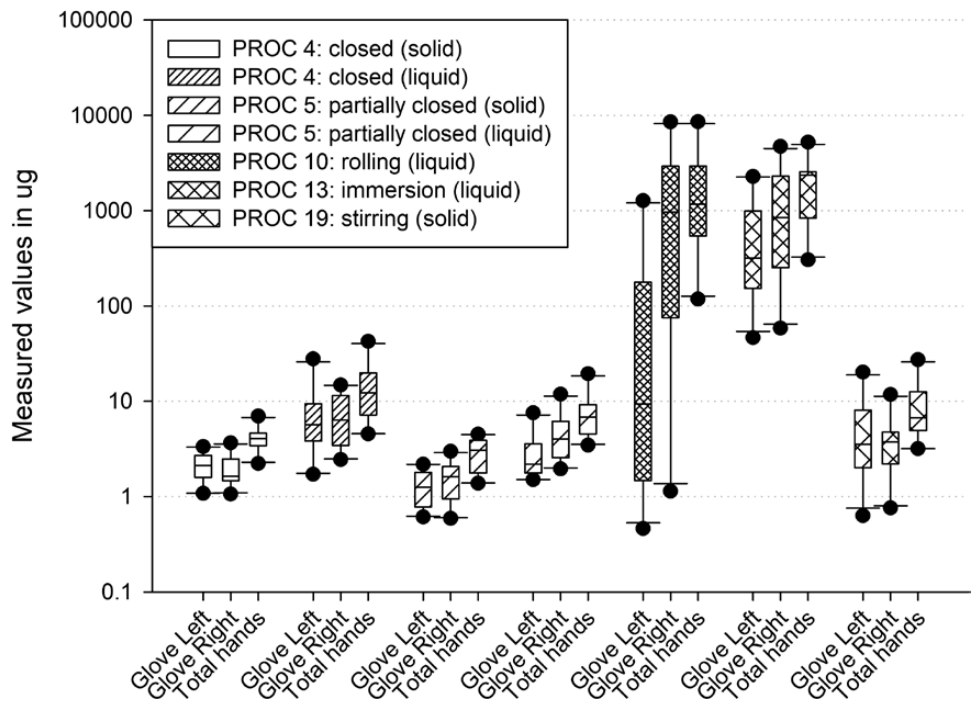

Figure 1. Measured Tinopal SWN levels (in µg) for the left hand, the right hand, and the combined hands per exposure situation, normalized for exposure scenarios with powder towards a concentration of 1.4 g kg^{-1}.

Table 3. Descriptive statistics for measured Tinopal SWN levels on both hands per exposure situation (in µg), normalized for exposure scenarios with powder towards a concentration of 1.4 g kg^{-1}.

PROC	Product	*N*	AM	GM	GSD	Min	P10	P75	P90	Max
Closed process (PROC 4)	Solid	10	4.1	4.0	1.3	2.2	2.6	4.6	5.9	7.0
Closed process (PROC 4)	Liquid	10	15.5	12.5	2.0	4.5	4.6	19.5	31.8	42.6
Partially closed process (PROC 5)	Solid	10	2.9	2.7	1.6	1.4	1.4	3.8	4.4	4.5
Partially closed process (PROC 5)	Liquid	10	7.7	6.8	1.7	3.5	3.9	8.9	14.7	19.4
Rolling (PROC 10)	Liquid	10	2127.3	1078.9	3.7	118.5	161.1	2208.4	6835.4	8550.7
Handling immersed objects (PROC 13)	Liquid	10	2045.6	1540.5	2.4	305.4	406.6	2517.6	3959.5	5230.8
Stirring (PROC 19)	Solid	10	9.7	7.8	2.0	3.2	3.2	12.0	20.8	27.3

AM, arithmetic mean; Max, maximum; Min, minimum; *N*, number of measurements; P10, 10th percentile; P50, median (50th percentile); P75, 75th percentile; P90, 90th percentile.

of 5.3 and 10.2 ppm, respectively. Overall, the variation in measured concentrations is small for all exposure scenarios [geometric standard deviation (GSD) 1.2–1.4], with the exception of partially closed processes (GSD 3.4). The factor 2 difference in measured concentrations between closed processes and partially closed processes may be due to a relatively constant emission and dispersion of 1,2-DCE when the lid of the mixer is partly open compared with a high (peak) emission of 1,2-DCE when the otherwise closed lid is opened.

For the comparison of the measured exposure levels with ECETOC TRA estimates no normalization was applied, since the concentration of the substance in the product is taken into account by ECETOC TRA model (see Table 2). When comparing levels of Tinopal SWN as measured on the hands with the ECETOC TRA model predictions, it can be observed that ECETOC TRA overestimates the measured dermal exposure for all exposure scenarios (see Fig. 3). In case of closed (PROC 4) and partially closed processes (PROC 5, liquid) as well as stirring (PROC 19, solid) ECETOC TRA tends to overestimate respective exposure by several orders of magnitude, while this difference is less pronounced for rolling (PROC 10) and handling of immersed objects (PROC 13). When comparing the measured airborne concentrations of 1,2-DCE with the ECETOC TRA model predictions as can be observed in Fig. 4, it can be observed that ECETOC TRA overestimates the measured inhalation exposure for closed and partially closed processes, but underestimates the measured inhalation exposure for rolling and handling of immersed objects. During closed processes higher concentrations were measured compared with partially closed processes, while ECETOC TRA predicts a factor 2 higher exposure for partially closed processes compared with closed processes. Furthermore, ECETOC TRA predicts similar exposure estimates for partially closed processes, rolling, and handling of immersed objects while the concentrations as measured during rolling and handling of immersed objects were significantly higher compared with the concentrations measured during partially closed processes.

When assessing dermal body exposure qualitatively, it was observed that rolling (PROC 10), stirring (PROC 19), and to a lesser extent handling of immersed objects (PROC 13) generally resulted in dermal exposure on various body parts. After closed (PROC 4) and partially closed (PROC 5) processes some fluorescent tracer was visible on the back of the volunteers, which is attributed to settling of Tinopal SWN particles on the chair during the experiment followed by transfer of settled Tinopal SWN from the chair (where the volunteer sat when the equipment

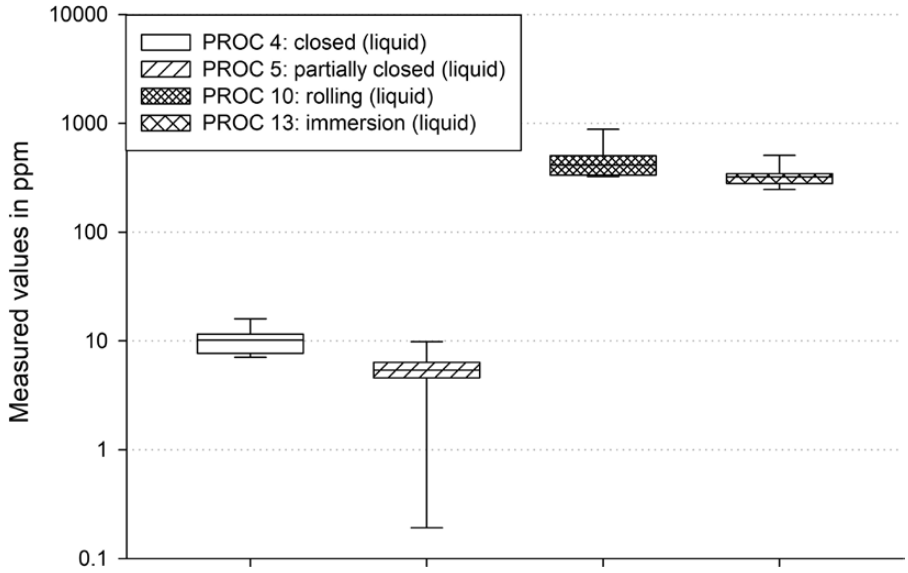

Figure 2. Measured 1,2-DCE concentrations (in ppm) per exposure situation.

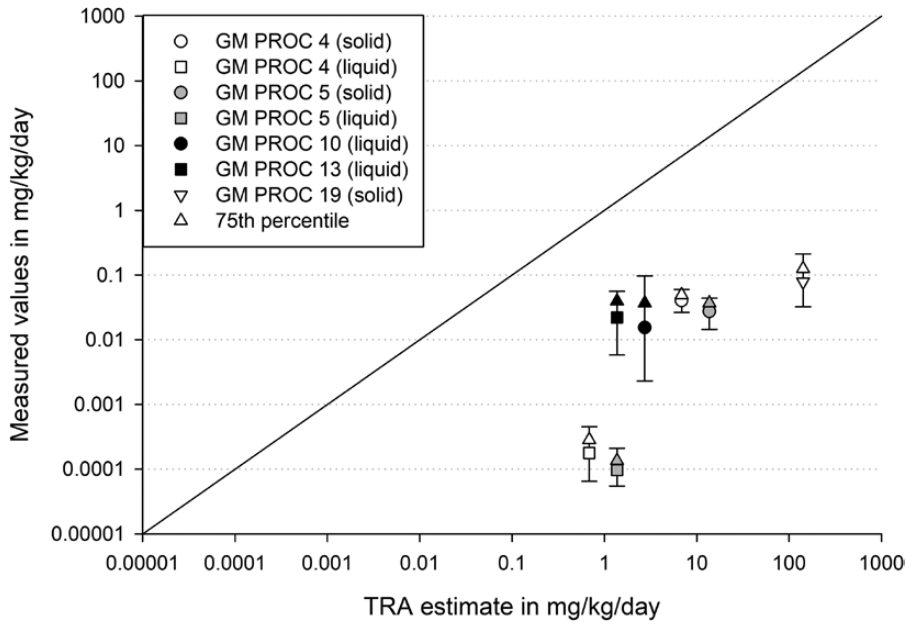

Figure 3. ECETOC TRA dermal exposure estimates compared with measured dermal exposure values in mg kg^{-1} day^{-1} for each exposure situation.

was running). After rolling, Tinopal SWN was mainly observed on the dominant hand and forearm as well as the upper and lower legs. After handling of immersed objects, Tinopal SWN contamination was mainly observed on both hands and to a lesser extent on the lower legs (probably due to dripping). After stirring, Tinopal SWN contamination was observed on both hands, as well as the mid-section of the body, and on the head around the nose and mouth. This was surprising since the volunteers wore a half-piece respirator during the experiments, suggesting that the respirator either did not fit properly (influenced also by the move of the volunteer during the specific trial) or cross-contamination occurred when the mask was

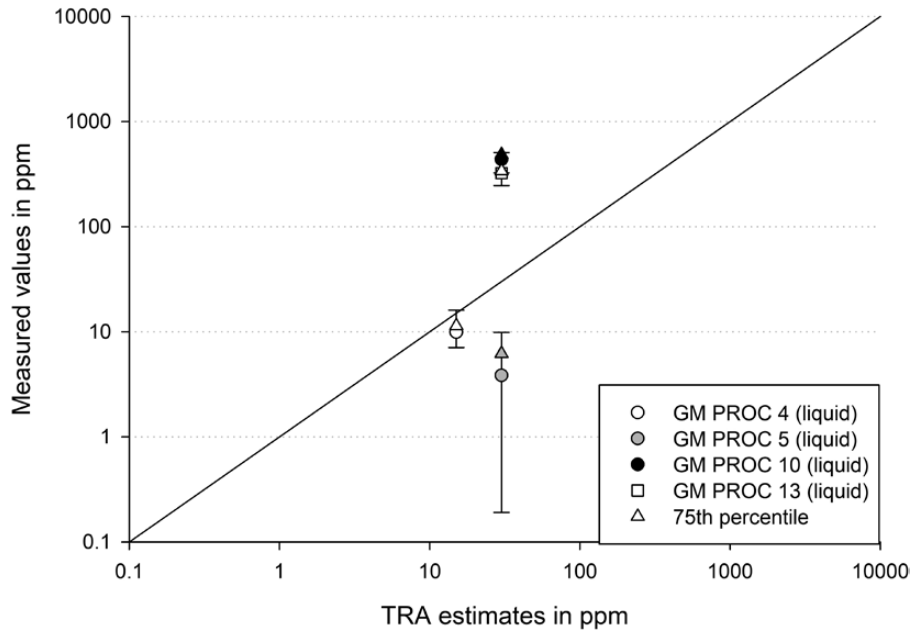

Figure 4. ECETOC TRA inhalation exposure estimates compared with measured inhalation exposure values for 1,2-DCE in ppm for each exposure situation.

removed. Example photographs taken under UV light after an experiment for all exposure scenarios are provided in Supplementary Fig. S2, available at *Annals of Work Exposures and Health* online.

Discussion and conclusion

The objective of the current study was to generate dermal and inhalation exposure data for combinations of exposure scenarios and product types for which no exposure data with sufficient contextual information was available. In total 70 experiments were performed. During all experiments dermal exposure to Tinopal SWN (as a dusty solid product or as a liquid product dissolved in 1,2-DCE) was measured. In 32 of the 70 experiments inhalation exposure to 1,2-DCE (a medium volatile substance) was measured. When ECETOC TRA model predictions were compared with measured exposure values for the seven exposure scenarios in this study, ECETOC TRA predictions exceeded measured exposure values for all dermal exposure scenarios and can therefore be considered conservative. However, in the case of inhalation exposure, ECETOC TRA underestimated exposure for two out of the four exposure scenarios (rolling and handling of immersed objects).

When comparing the inhalation exposure for (medium) volatile substances as estimated by ECETOC TRA taking into account 'enhanced general ventilation' for the exposure scenarios in this study with the results of the ETEAM study the results are partially in agreement with the ETEAM study, as the ETEAM study showed that ECETOC TRA predictions exceeded measured values for 25–50% of the measurements as available for the five exposure scenarios (Jung *et al.*, 2016). However, in the current study underestimation of measured (inhalation) exposure values was only observed for rolling and handling of immersed objects and not for closed and partially closed processes. Lamb *et al.* (2015) and van Tongeren *et al.* (2017) reported that ECETOC TRA was considered less conservative for more volatile substances, and stated that no consistent trends could be observed with regard to concentration, although they suggested that ECETOC TRA would be more conservative for lower concentration categories. In the current study, there was an approximately 225 factor difference in measured exposure values between exposure scenarios with liquid product (containing 0.14%, w/w Tinopal SWN) compared with exposure scenarios with solid product (100%, w/w Tinopal SWN). However, as the concentrations of Tinopal SWN in the two products differ a factor 714, other factors might have an influence on the observed difference in measured exposure levels observed [i.e. characteristics of the product (liquid/solid, dustiness/volatility)], interaction of product with

sampling matrix (as the powder mostly remains at the outside of the gloves and some dust might be removed, while the liquid product is much more absorbed by the gloves).

For dermal exposure, Marquart *et al.* (2017) performed a validation of the ECETOC TRA dermal model. Although a wide range of PROCs were covered in their study, not all exposure scenarios were included due to lack of data [e.g. for exposure scenarios dealing with closed processes (PROCs 1–4) and exposure scenarios in which solid products are handled (PROCs 8–9)]. Although only small datasets were available, Marquart *et al.* (2017) also found that ECETOC TRA conservatively estimates dermal hand exposure for partially closed processes containing liquid product (PROC 5), rolling liquid product (PROC 10), and manually handling immersed objects (PROC 13). They observed that ECETOC TRA exposure estimates were biased towards (severe) overestimation of dermal exposure at low measured exposure values, while there seemed to be a tendency towards underestimation at higher measured exposure values. Therefore, they reasoned that ECETOC TRA is most likely sufficiently conservative for exposure scenarios where low exposures are expected due to the closed processes (PROCs 1–3). However, they advised to gather measurements for PROC 4 as for this exposure scenario more opportunity for exposure arises. Data from the current study suggest that ECETOC TRA is sufficiently conservative for PROCs 4 and 5, which is not in line with expectations of Marquart *et al.* (2017).

Use of an interception technique like gloves to measure dermal hand exposure generally results in a 3–6 times higher measured exposure value compared with use of removal techniques such as washing or wiping (Marquart *et al.*, 2017; Kasiotis *et al.*, 2020). However, due to large variations in these factors between different exposure scenarios, no standard correction factor could be derived (Kasiotis *et al.*, 2020). Marquart *et al.* (2017) found that ECETOC TRA often underestimated exposure compared with results of measurements for which an interception method was used. As in the current study gloves were used, the ECETOC TRA model could be considered to be even more conservative for all dermal exposure scenarios examined in this study.

While in this study modelled exposure estimates were compared with the results of measurements performed during controlled experiments (mimicking realistic workplace situations as much as possible), other studies mainly took into account available historical data from literature or existing exposure databases (Lamb *et al.*, 2015; Jung *et al.*, 2016; Marquart *et al.*, 2017). When using historical data one has to rely on contextual information as provided with the data and professional judgement to assign model parameters, which may result in misinterpretation of the data as well as differences when choosing model inputs. For example, in the study of Marquart *et al.* (2017), 20 occupational hygienists who were considered experts in working with ECETOC TRA were asked to estimate exposure using the ECETOC TRA model. There was a lack of consensus with regard to assignment of PROCs (in 38% of the cases), categories for dustiness or volatility (36%), type of setting (industrial or professional) (14%) as well as the remaining parameter categories (≤12%) (Marquart *et al.*, 2017). Also, ECETOC used the dataset as developed within the ETEAM study to reproduce their results, and identified 118 (out of 184) cases where they disagreed with the ECETOC TRA input parameters as assigned by ETEAM (ECETOC, 2018).

The PROCs as used in REACH (and ECETOC TRA) are generally broadly defined, which can lead to discussion about which activities exactly fall within each PROC. For example, during the experiments for rolling only the actual application of the liquid product was measured, as (re)filling of the tray can also be considered as transfer (PROC 8b or 9). However, in practice filling the tray and perhaps even mixing the product before filling is often considered part of the exposure scenario and included as part of the exposure scenario when exposure measurements are performed. The same is the case for the experiments regarding closed and partially closed processes, where the filling and discharging of the equipment were not part of the experiments, although charging and discharging are mentioned in the descriptions of these PROCs. Therefore, more variability in the results of workplace measurements is expected, compared with the results of measurements collected during standardized experiments in this study. The same holds true when using historic data, as the variance in exposure can be expected to be even larger since different datasets gathered in different measurement studies are pooled. This is confirmed by the comparison of the dataset with measurements of volatile substances as used in the ETEAM study (overall GSD of 24) (Lamb *et al.*, 2015), and the dataset of 32 inhalation measurements as collected in this study (overall GSD of 9.1). It is thus more representative to compare variance of exposure on exposure scenario level, since the GSD of 24 reported by Lamb *et al.* (2015) represents different types of activities inherently resulting in a large GSD when calculated from an entire dataset. Unfortunately, no GSDs per PROC were reported so that a comparison of the variance of exposures between the studies on PROC level was not possible.

Within the dermal model of ECETOC TRA, an exposed skin surface area between 240 and 1980 cm^2 as well as complete skin contact with the substance across the default surface area is assumed, after which the value is combined with the predicted skin loading to calculate the dermal dose. (ECETOC, 2009). For example, ECETOC TRA assumes an exposed skin surface area of 480 cm^2 on the front side of both hands (240 cm^2 per hand) for PROCs 4, 5, and 13. Based on the qualitative assessment of the presence of the fluorescent tracer as visible on the photographs taken under UV light it was observed that for closed and partially closed processes mainly the fingertips seem to be contaminated, both on the front and the backside. The assumed total exposed surface area of 480 cm^2 for these exposure scenarios appears to be in line with these observations. However, the backside of the fingertips also seem to get contaminated, which contradicts the assumption of ECETOC TRA that only the frontside of the hands are exposed in case of these PROCs (ECETOC, 2009). For handling of immersed objects, exposure was observed on the entire front side of the hand, and mainly the fingers on the backside of the hand, which suggests that an assumed surface area of 960 cm^2 might be more accurate. For rolling (PROC 10) and stirring (PROC 19) an exposed surface area of, respectively, 960 cm^2 (front and back of both hands) and 1980 cm^2 (front and back of both hands and forearms) was assumed. However, both the quantitative and the qualitative assessment suggest that during rolling mainly the dominant hand is exposed (84–100% of the total hand exposure was found on the dominant hand). In other studies often only total hand exposure values (both hands together) were reported (Garrod *et al.*, 2000; Gijsbers *et al.*, 2004; Links *et al.*, 2007). Additionally, (re)filling is often measured together with rolling, which might result in contamination on both hands. Therefore, no strong conclusions can be made regarding exposure patterns for this PROC. The qualitative assessment for stirring showed that generally both hands were exposed on both sides, and the forearms are likely to be exposed as well. This type of information can be used to improve the reasoning behind the assumed surface areas as applied in ECETOC TRA.

A limitation of the current study is that for inhalation exposure, the assumption was made that measured exposure values reflect the 8 h TWAs. In reality, workers likely are not performing the same task for an entire work day making this assumption a worst-case scenario, and introducing some uncertainty to the comparison. Additionally, only inhalation exposure to medium volatile substances (in this case 1,2-DCE) was measured, thus excluding inhalation exposure to Tinopal SWN powder. The main reason for this was that for measuring Tinopal SWN on gloves as well as measuring 1,2-DCE in the breathing zone validated measurement and analytical methods already existed. This was not the case for measuring Tinopal SWN in the breathing zone, and performing a validation study for this type of measurements was considered out of scope for the current study.

The results of this study can also be used when formulating future research. First, the results of the experiments performed under controlled conditions showed little variation of exposures. Therefore, experimental studies such as this one are able to provide more insights into reported model bias for several exposure modifiers such as local exhaust ventilation, concentration, ventilation, and volatility/dustiness. Controlled experiments can be performed where one of these parameters is varied while the remainders are kept constant. The influence of these exposure determinants on actual exposure provides useful insights and is helpful in underpinning model scores. It must be taken into account that controlled experiments might explain relationships between exposure determinants and measured exposure values, but these interactions might be different in actual workplace circumstances when also other (unknown) factors come into play. Therefore, such experiments need to be carefully designed.

Next, the fluorescent method as applied in the current study provides valuable information on the distribution of exposure over the entire body without chemically analysing samples. This method allows for assessment of exposure scenarios where body exposure is relevant, provides information about relevant exposure routes, and can aid in the development of measurement strategies. Additional experiments over a multitude of exposure scenarios not captured in the current study would provide general understandings of distribution of dermal exposure on the hands and the rest of the body, and could for instance be used for the improvement of dermal exposure models.

In conclusion, the current study gave good insights into both dermal and inhalation exposure levels for selected PROCs and provided useful information for future improvements of the ECETOC TRA model. ECETOC TRA exposure estimates were conservative for all dermal exposure scanrios, predictions exceed measured values by several orders of magnitude. For inhalation, ECETOC TRA exposure estimates were conservative for closed and partially closed processes, but underestimated exposure values for rolling and handling of immersed objects. The developer of ECETOC TRA should reconsider the base predictions for PROCs 10 and 13 with regard to medium fugacity liquids. Additionally,

ECETOC may wish to reconsider the assumed TRA skin exposed surface areas for hands assumed for PROC 13.

Supplementary Data

Supplementary data are available at *Annals of Work Exposures and Health* online.

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References

Behroozy A. (2013) On dermal exposure assessment. *Int J Occup Environ Med*; **4**: 113–27.

Delmaar JE, Bokkers BG, ter Burg W *et al.* (2013) First tier modeling of consumer dermal exposure to substances in consumer articles under REACH: a quantitative evaluation of the ECETOC TRA for consumers tool. *Regul Toxicol Pharmacol*; **65**: 79–86.

ECETOC. (2004) Targeted risk assessment. Technical Report No. 93. Brussels, Belgium: European Centre for Ecotoxicology and Toxicology of Chemicals. ISSN 0773-8072-93. Available at http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-093.pdf. Accessed 17 October 2019.

ECETOC. (2009) Addendum to ECETOC targeted risk assessment. Report No. 93. Technical Report No. 107. Brussels, Belgium: European Centre for Ecotoxicology and Toxicology of Chemicals. ISSN 0773-8072-107. Available at http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-107-Addendum-to-ECETOC-TRA-report-93.pdf. Accessed 17 October 2019.

ECETOC. (2012) ECETOC TRA version 3: background and rationale for the improvements. Technical Report No. 114. Brussels, Belgium: European Centre for Ecotoxicology and Toxicology of Chemicals. ISSN 0773-8072-114. Available at http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-114-ECETOC-TRA-v3-Background-rationale-for-the-improvements.pdf. Accessed 17 October 2019.

ECETOC. (2014) Addendum to TR114: technical basis for the TRA v3.1. Technical Report No. 124. Brussels, Belgium: European Centre for Ecotoxicology and Toxicology of Chemicals. ISSN 2079-1526-124. Available at http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC_TR_124.pdf. Accessed 17 October 2019.

ECETOC. (2018) Targeted risk assessment: further explanation of the technical basis of the TRA v3.1. Technical Report No. 131. Brussels, Belgium: European Centre for Ecotoxicology and Toxicology of Chemicals. ISSN 2079-1526-131. Available at http://www.ecetoc.org/wp-content/uploads/2018/02/ECETOC-TR-131-Targeted-Risk-Assessment-Further-Explanation-of-the-Technical-Basis-of-the-TRA-v3.1.pdf. Accessed 17 October 2019.

ECHA. (2016) Chapter R.14: Occupational exposure estimation. In *Guidance on information requirements and chemical safety assessment*. Helsinki, Finland: European Chemicals Agency.

EFSA Scientific Committee. (2019) Guidance on harmonised methodologies for human health, animal health and ecological risk assessment of combined exposure to multiple chemicals. *EFSA J*; **17**: 5634.

European Pharmacopoeia Commission. (2010) Chapter 2.2.10: Viscosity—rotating viscometer method. In Jones D, European Directorate for the Quality of Medicines & Healthcare, European Pharmacopoeia Commission, Harvey J, Mateos A, editors. *European Pharmacopoeia*. 7th edn. Strasbourg: Council of Europe, European Directorate for the Quality of Medicines and Healthcare. pp. 28–30. Available at https://www.drugfuture.com/Pharmacopoeia/EP7/DATA/20210E.PDF. Accessed 26 May 2018.

Franken R, Spaan S, Kasiotis K *et al.* (2019) *SysDEA: systematic analysis of dermal exposure to hazardous chemical agents at the workplace*. 1st edn. Dortmund: Bundesanstalt für Arbeitsschutz und Arbeitsmedizin. Project number F 2349. doi:10.21934/baua:bericht20190116

Garrod AN, Guiver R, Rimmer DA. (2000) Potential exposure of amateurs (consumers) through painting wood preservative and antifoulant preparations. *Ann Occup Hyg*; **44**: 421–6.

Gijsbers JH, Tielemans E, Brouwer DH *et al.* (2004) Dermal exposure during filling, loading and brushing with products containing 2-(2-butoxyethoxy)ethanol. *Ann Occup Hyg*; **48**: 219–27.

Herber RFM, Duffus JH, Christensen JM *et al.* (2001) Risk assessment for occupational exposure to chemicals. A review of current methodology. *Pure Appl Chem*; **73**: 993–1031.

Hesse S, Schroeder K, Mangelsdorf I *et al.* (2015) *Evaluation of tier 1 exposure assessment models under REACH (ETEAM) project—substudy report on gathering of background information and conceptual evaluation*. 1st edn. Dortmund: Bundesanstalt für Arbeitsschutz und Arbeitsmedizin. Project number F 2303. ISBN 978-3-88261-155-7.

ISO. (1991) *ISO 9486:1991 EN: workplace air—determination of vaporous chlorinated hydrocarbons—charcoal tube/solvent desorption/gas chromatographic method*. Geneva, Switzerland: International Organization for Standardization.

Jung C, Tischer M, Schlüter U. (2016) *Further stratification of the ETEAM study results*. 1st edn. Dortmund:

Bundesanstalt für Arbeitsschutz und Arbeitsmedizin. Project number F 2303. doi:10.21934/baua:bericht201612192016

Kasiotis KM, Spaan S, Tsakirakis AN *et al.* (2020) Comparison of measurement methods for dermal exposure to hazardous chemicals at the workplace: the SysDEA project. *Ann Work Expo Health*; **64**: 55–70.

Kromhout H, Symanski E, Rappaport SM. (1993) A comprehensive evaluation of within- and between-worker components of occupational exposure to chemical agents. *Ann Occup Hyg*; **37**: 253–70.

Kupczewska-Dobecka M, Czerczak S, Jakubowski M. (2011) Evaluation of the TRA ECETOC model for inhalation workplace exposure to different organic solvents for selected process categories. *Int J Occup Med Environ Health*; **24**: 208–17.

Lamb J, Miller BG, MacCalman L *et al.* (2015) *Evaluation of tier 1 exposure assessment models under REACH (ETEAM) project—substudy report on external validation exercise*. 1st edn. Dortmund: Bundesanstalt für Arbeitsschutz und Arbeitsmedizin. Project number F 2303. ISBN 978-3-88261-157-1.

Li D, Suh S. (2019) Health risks of chemicals in consumer products: a review. *Environ Int*; **123**: 580–7.

Links I, Van Der Jagt KE, Christopher Y *et al.* (2007) Occupational exposure during application and removal of antifouling paints. *Ann Occup Hyg*; **51**: 207–18.

Loomis D, Kromhout H. (2004) Exposure variability: concepts and applications in occupational epidemiology. *Am J Ind Med*; **45**: 113–22.

Marquart H, Franken R, Goede H *et al.* (2017) Validation of the dermal exposure model in ECETOC TRA. *Ann Work Expo Health*; **61**: 854–71.

Marquart H, Heussen H, Le Feber M *et al.* (2008) 'Stoffenmanager', a web-based control banding tool using an exposure process model. *Ann Occup Hyg*; **52**: 429–41.

Phneah SL, Hassim MH, Ng DKS. (2017) Review of chemical hazard based occupational health assessment methods for chemical processes. *Chem Eng Trans*; **56**: 1813–8.

Riedmann RA, Gasic B, Vernez D. (2015) Sensitivity analysis, dominant factors, and robustness of the ECETOC TRA v3, Stoffenmanager 4.5, and ART 1.5 occupational exposure models. *Risk Anal*; **35**: 211–25.

Schinkel J, Fransman W, Heussen H *et al.* (2010) Cross-validation and refinement of the Stoffenmanager as a first tier exposure assessment tool for REACH. *Occup Environ Med*; **67**: 125–32.

Schinkel J, Warren N, Fransman W *et al.* (2011) Advanced REACH Tool (ART): calibration of the mechanistic model. *J Environ Monit*; **13**: 1374–82.

Tischer M, Lamb J, Van Tongeren M. (2017) Evaluation of tier one exposure assessment models (ETEAM): project overview and methods. *Ann Work Exp Health*; **61**: 911–20.

van Tongeren M, Lamb J, Cherrie JW *et al.* (2017) Validation of lower tier exposure tools used for REACH: comparison of tools estimates with available exposure measurements. *Ann Work Expo Health*; **61**: 921–38.