The Use of Exposure Models in Assessing Occupational Exposure to Chemicals

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Hanna Landberg

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Abstract

Humans do often experience occupational exposure to chemicals, which could lead to negative health effects if the risks aren't managed. Proper risk assessments of exposure to chemicals is needed and can be performed in different ways. The exposure assessment part of the risk assessment can be performed by exposure measurements or by using exposure assessment models. The use of exposure assessment models is recommended by the authority of the REACH-legislation ECHA. It is of great importance that these exposure assessment models are studied and continues to develop.

The genral aim of this thesis was to study the use of three exposure assessment models: ECETOC TRA, Stoffenmanager® and the Advanced REACH Tool (ART), when performing exposure and risk assessments. We collected all data (input parameters for the models and exposure measurements) while visiting work places in a total of 7 types of indusries.

The between user reliability was low when 13 users used Stoffenmanager® assessing 11 exposure situations which the users were studying simultaneously visiting the 4 workplaces. The lack of agreements were calculated for Stoffenmanager® and ART (50^{th} percentile) when assessing 29 exposure situations in 11 companies in 7 types of industries. The GM of measured exposures were used for comparison. The lack of agreement was higher for ART. ART underestimated the exposure in general but mostly for exposure situations concerning solids. Stoffenmanager® overestimated exposures with low measured exposure and underestimated exposures with high measured exposures. Stoffenmanager® estimated solids better than liquids. The level of protection was calculated for the same exposure situations as for the lack of agreements but the 90^{th} percentile of the models were used for comparison with the GM of the measurements. ECETOC TRA had lowest level of protection with 31 % of the measured exposure exceeding the modelled exposure, Stoffenmanager® 17 % and ART 3 %. When comparing the outcomes from the models (90^{th} percentile) with limit values, ECETOC TRA had most false safe situations (the risk was considered safe by the model when in fact it was unsafe using measurements) compared to the other models. The risk assessment approach under REACH legislation was studied by the comparison between observed RCRs (calculated with the three models) and registered RCRs (presented in the e-SDS). The data was collected when visiting companies studying situations at the work places. In general, the registered RCRs were much higher than the observed RCRs but still about 12 % of observed RCRs were above 1 using Stoffenmanager®. The observed RCRs above 1 had significant ($p < 0.001$) lower DNEL values and higher vapour pressures compared to observed RCRs below 1. When combing the results of our studies, ECETOC TRA shouldn't be recommended as a protective (Tier 1) model since it has lowest level of protection, highest amount of false safe situations and didn't present the most situations with RCRs > 1. Generic exposure scenarios (under REACH) may not provide safe use of chemicals based on our results.

Key words Exposure assessment model, Occupational hygiene, REACH, validation, between-user reliability, Occupational exposure assessment, risk assessment

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To my Parents

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Populärvetenskaplig sammanfattning

Människor kommer i kontakt med kemiska ämnen i sin vardag - på arbetet, via den yttre miljön eller som konsumenter. Vi kan både andas in dem, få dem på huden eller få i oss dem genom det vi äter. Kontakt med kemiska ämnen kan ge en negativ påverkan på vår hälsa, i olika grad beroende på kemikaliens giftiga egenskaper och hur mycket vi får i oss. Därför är det viktigt att bedöma risken för påverkan på rätt sätt.

En riskbedömning består av en farobedömning och en exponeringsbedömning. Denna avhandling belyser exponerings- och riskbedömningar för arbetares exponering via inandningsluften. Det traditionella sättet att göra en riskbedömning på är att mäta kemikalier i luften och jämföra halterna med ett gränsvärde som är satt för att skydda arbetares hälsa. Olika arbetare får olika höga exponeringar, beroende bl a på hur de jobbar och med vilka arbetsuppgifter. Därför måste man göra upprepade mätningar för att få en så rättvis bild av exponeringen som möjligt men det är kostsamt, tar tid och kräver expertis. Det är inte heller rimligt att mäta alla kemiska ämnen som en arbetare utsätts för, i alla situationer. Som ett alternativ har man därför utvecklat modeller för att möta de krav som finns från myndigheter. Det finns olika modeller, sådana som ger en uppfattning om risk och föreslår hur risken kan sänkas (control banding) och sådana som beräknar en exponering, där utfallet presenteras på samma sätt som vid mätningar genom att ange luftkoncentrationer. Modellerna är kalibrerade mot mätdata och inkluderar de variationer av exponeringen som finns på arbetsplatser.

Den europeiska kemikalielagstiftningen REACH började gälla 2007, och gäller för industriella kemikalier som tillverkas i EU eller importeras dit. Enligt REACH, ligger ansvaret för hur man ska hantera kemikalierna på ett säkert sätt på tillverkaren eller importören. Det innebär att tillverkaren eller importören ska göra exponeringsbedömningar, och ta fram riktvärden för vilka exponeringar som betraktas som ofarliga (Derived No Effect Level, DNEL). Exponeringsbedömningarna ska göras för alla sätt som en farlig kemikalie hanteras på, och för att göra det, rekommenderas att man ska använda exponeringsmodeller. Det är alltså väldigt viktigt att dessa modeller illustrerar de verkliga förhållandena och att de utvecklas för att kunna vara användbara.

Det generella syftet med denna avhandling var att studera och utvärdera de tre exponeringsmodellerna ECETOC TRA, Stoffenmanager® och the Advanced REACH Tool (ART), när de används för att beräkna exponeringsnivåer och senare för riskbedömningar.

Det första vi studerade var hur utfallet från Stoffenmanager® varierade när olika användare modellerade samma situation. 13 användare besökte 4 olika företag i 4 olika branscher och studerade 3 situationer på varje företag. Det visade sig, att de olika användarna kom fram till mycket olika resultat. När det varierade som mest hade den användare som modellerat högst exponering ungefär 160 gånger högre resultat än den som hade modellerat lägst.

Vi studerade också hur Stoffenmanager® och ART kunde förutspå den verkliga exponeringen som vi mätte i luften på arbetsplatserna. Vi besökte 11 företag i 7 branscher och studerade totalt 29 situationer där exponeringen både mättes och modellerades. För att studera modellernas precision, (hur bra modellerna är) användes modellernas bästa gissning (50 percentilen) som utfall. Resultaten visade att ART modellerade för låga koncentrationer generellt och framför allt för ämnen som var i fast form (damm). Stoffenmanager® modellerade för höga nivåer i situationer där den uppmätta exponeringen var låg och för låga koncentrationer där den uppmätta exponeringen var hög. Stoffenmanager® fungerade bättre för damm än för vätskor. Vi studerade också hur modellerna fungerade när de användes enligt REACH-lagstiftningen. För att säkerställa att arbetare skyddas - ger tillämpningen av modellerna då ett högre värde än det som respektive modell tror är den bästa gissningen. I jämförelse mellan modellerna tog vi även med ECETOC TRA. För ECETOC TRA hade 31 % av situationerna ett högre värde när vi mätte exponeringen än när vi modellerade och det som man enligt REACH skulle förvänta sig var 10 %. Detta betyder att ECETOC TRA inte ger det skydd som rekommenderas enligt REACH. För Stoffenmanager®, var motsvarande siffra 17 % och för ART 3 %.

När vi studerade användandet av modellerna i riskbedömningar, jämförde vi de modellerade rekommenderade värdena med svenska gränsvärden och med DNEL-värden. Här blev mönstret detsamma, att ECETOC TRA var den modell som hade högst antal situationer som gav falskt säkra riskbedömning jämfört med de andra modellerna. Med det menas, att ECETOC TRA bedömde situationen som säker när den egentligen inte var säker baserat på traditionell riskbedömning. Detta kan få allvarliga konsekvenser för arbetares hälsa.

I den sista delstudien tittade vi närmare på REACH-lagstiftningens exponeringsscenarier som tillverkaren eller importören ska ta fram för farliga kemikalier och ge till de som använder kemikalierna. Exponeringsscenarierna är instruktioner som bygger på det som har varit underlag när man har modellerat exponeringen. Grundläggande i REACH-lagstiftningens riskbedömning är något som heter risk characterisation ratio (RCR). Det är en kvot mellan en bedömd exponering och DNEL värdet och den måste vara under 1 när ett scenario registreras. Vi studerade RCR-värdena för 222 exponeringsscenarier och modellerade exponeringen efter att vi studerat dem på plats på företag. Vi jämförde de observerade RCR-värdena med de registrerade RCR-värdena. Generellt kan sägas att de observerade RCR-värdera är lägre än de registrerade. Detta är inte konstigt, eftersom de registrerade RCR-värdera ska representera väldigt generella exponeringsscenarion som ska passa många arbetsplatser. Det som däremot var något överraskande var, att 12 % av scenarierna hade observerade RCR-värden över 1 när vi använde Stoffenmanager®, vilket inte får förekomma enligt REACH. De klassificerades således som osäkra arbetsmiljöer. De observerade RCR-värdena varierade stort beroende på vilken modell som användes och gav alltså vid vissa tillfällen för höga värden. Störst risk för osäkra scenarier sågs för kemikalier med låga DNEL-värden och höga ångtryck. Det kan ifrågasättas, om generella exponeringsscenarier baserade på modeller är ett bra sätt att få fram instruktioner om säker hantering av kemikalier. Jag tror att ett tryggare sätt skulle vara om användare av kemikalier själva uppskattade exponeringen på arbetsplatsen med hjälp av modeller och därtill mätningar vid behov.

List of Papers

This thesis is based upon the following four papers and referred to in the text by their Roman numerals (I-IV).

I. Landberg, Hanna E; Berg, Peter; Andersson, Lennart; Bergendorf, Ulf; Karlsson, Jan-Eric; Westberg, Håkan; Tinnerberg, Håkan. Comparison and evaluation of multiple users' usage of the exposure and risk tool: Stoffenmanager 5.1. *Ann Occup Hyg*; 2015; 59: 821-35.

II. Landberg, Hanna E; Axmon, Anna; Westberg, Håkan; Tinnerberg, Håkan. A study of the validity of two exposure assessment tools: Stoffenmanager and the Advanced REACH Tool. *Ann Work Expo Health*; 2017; 61: 575-588.

III. Landberg, Hanna E; Westberg, Håkan; Tinnerberg, Håkan. Evaluation of risk assessment approaches of occupational chemical exposures based on models in comparison with measurements. (*Submitted)*

IV. Landberg, Hanna E; Hedmer, Maria; Westberg, Håkan; Tinnerberg, Håkan. Evaluating the risk assessment approach of the REACH legislation using exposure models and calculated risk characterization ratios: A case study. (*Manuscript*)

Abbreviations

ART	Advanced REACH Tool
CLP	Classification, Labelling and Packaging
DNEL	Derived No Effect Level
ECETOC TRA	European Centre for Ecotoxicology and toxicology of Chemicals Targeted risk assessment
ECHA	European Chemicals Agency
ES	Exposure Scenario
e-SDS	extended Safety Data Sheet
EXP	Exposure
H-phrases	Hazard phrases
HSE	Health and Safety Executive
PROC	Process Category
REACH	Registration, Evaluation and Authorisation of Chemicals
RCR	Risk Characterisation Ratio
RMM	Risk Management Measures
OC	Operational Conditions
OH	Occupational Hygienist
OEL	Occupational Exposure Limit
SDS	Safety Data Sheet
STEL	Short Term Exposure Limits
SWEA	Swedish Work Environment Authority
TWA	Time Weighted Average

Introduction

General background

Humans are exposed to industrial chemicals in their everyday life - as consumers, at work places and via the environment. Occupational exposure to chemicals is important to manage as it may lead to adverse health effects. To protect workers, risk management needs to be in place. Such should be initiated locally at the workplaces in accordance with national and international regulations. The aim of risk management is to prevent and reduce the risks of exposure to harmful chemicals. In order to achieve this, risk assessments must be carried out. Possible adverse health effects depend mainly on two things in combination; the inherent toxicological property of the chemical and the dose. Hence, risk assessments consist of both a hazard assessment and an exposure assessment of the chemical in question.

Risk assessments of occupational exposure to chemicals have been performed since the beginning of the twentieth century (1). The most common and accepted approach for such risk assessment is by performing exposure measurements and relate the exposure level to a limit value. However, today other approaches have been developed to quantitatively or qualitatively estimate the exposure, and, hence, the risk.

Traditional risk assessment of chemicals

Hazard assessment

H-phrases

Industries use chemicals that could be hazardous for humans and the environment. Suppliers of chemicals are obligated to provide users with a safety data sheet (SDS) which contains information about the chemical. In the SDS, information about hazards and how to control the hazards is described. The users are informed about the hazards through Hazard phrases (H-phrases) which are listed together with the components on the SDS according to the Classification, Labelling and

Packaging (CLP) regulation (EC No 1272/2008) (2). The H-phrases are phrases explaining possible hazards (for example H332 – harmful if inhaled) and could be determined in two ways, either by self-classification or by harmonised classification. The self-classification is made by the manufacturer or by the importer of the chemical to EU if there is no harmonised classification available. The steps for self-classification include gathering available information about the chemical, examining and evaluating the information and, finally, deciding on a classification, according to specified criteria. If there isn't enough information, testing for physical, health and environmental hazards may be necessary. The harmonised classification is based on a proposal submitted to the European Chemicals Agency (ECHA) by a member state or a manufacturer, importer or downstream user. The harmonised classifications are mandatory and mainly regard substances which are carcinogenic, mutagenic or toxic to reproduction (CMR) or are respiratory sensitizers (2).

Occupational exposure limit values

Occupational exposure limit (OEL) values are a well-established concept in countries working with occupational hygiene. The establishment of OELs was initiated in the 1940s and since then OELs have been established for about 3000 substances around the world (1, 3). The OELs are numerical concentrations (in mg/m^3 or ppm) which should not be exceeded in order to protect workers from negative health effects. The OELs can diff between countries, because they may be based on one or more aspects, such as health effects and economic and technical factors. OELs can also be indicative or legally binding (3).

In Sweden, the health effects of use of a chemical are evaluated and based on scientific toxicological and epidemiological studies, discussed within an expert group before it is communicated to the Swedish Work Environment Authority (SWEA). SWEA defines the OEL, taking both health and economic and technical aspects into account (3). According to SWEA, there are Swedish OELs for about 500 chemical substances (4, 5). The OELs are legally binding and there are two different OELs that can be compared with the exposure. The 8h time weighted averages (8h TWAs) are OELs set to protect workers from long term effects and regards exposure for 8 hours a day in an entire working life at worst. The short term exposure limits (STELs) are OELs set to protect workers from acute effects and are time weighted for a maximum of 15 minutes or in some cases for 5 minutes (6). In this thesis, only the 8h TWAs have been used.

Exposure and exposure assessment

Variability and uncertainty

The occupational exposure of chemicals varies between worker, occasion (within worker) and site. Hence, to assess the exposure, multiple exposure measurements must be performed. The variability of exposure can be explained by known and unknown factors and the first large evaluation of exposure variability was performed by Kromhout et al. in 1993 (7). Kromhout and co-workers developed a database containing about 20 000 chemical exposures from about 500 groups of workers. They concluded that the day-to-day variability was generally larger than the between-worker variability. Several other papers have also studied the variability of exposures; this has substantially increased our understanding of occupational exposure and contributed to optimized sampling strategies to cope with the variabilities (8-13).

Besides the variabilities addressed above, there is an uncertainty concerning the assessed exposure level that also needs to be addressed. The uncertainty of the exposure assessment is not due to the natural behaviour of exposure; instead it has to do with the method used when estimating the exposure. The uncertainty could be diminished by gathering more data (14). Further, one way to handle an uncertainty (but also the variability) is to use a percentile higher than the 50^{th} percentile (best guess) outcome when comparing the exposure level with a limit value.

Exposure measurements

Air measurements followed by laboratory analysis of the collected samples are often considered as the golden standard of how an exposure assessment should be performed. Airborne exposure of chemicals can be monitored in different ways: either by personal samplers or by stationary samplers. Exposure assessment with personal samplers placed in the breathing zone of the worker gives information on the personal exposure and are needed for comparison with OELs. The first personal air sampler was developed in the 1960s by Sherwood and Greenhalgh and today there are several samplers and techniques available (15). The exposure can also be assessed by detection of biomarkers of exposure in, i.a., blood or urine. Biomarkers are not included in the studies of this thesis (16)

Different methods for personal air sampling are available and in this thesis we have mostly used active sampling techniques but also passive samplers. In active sampling, a pump is connected to a tube containing different adsorbent agents or filters. The pump is pumping air through the adsorbent (vapours and gases) or filter (particle matters) in a constant speed which later on can be used to calculate the exposure in mg/m^3 (16). In passive sampling, the vapours and gases are not pumped through an adsorbent, instead the vapours and gases are following Fick's law by molecular diffusion to the adsorbent area (1, 16).

Different exposure measurement strategies may be applied depending on the aim of the measurements. For compliance, different recommendations have been developed to include the variability and uncertainty of the exposure and the first was published by NIOSH in the 1970s (17). Health and Safety Executive (HSE) in the UK is recommending that at least three measurements should be performed and the median exposure should then be a third of the OEL to make sure the OEL is not exceeded (18). In the 2011 a guidance from the British Occupational Hygiene Society and the Nederlandse Vereniging voor Arbeidshygiene “Testing compliance with occupational exposure limits for airborne substances” was published (19). This guidance recommends at least three measurements to be performed and the exposure should be a tenth of the OEL. Otherwise, more measurements need to be included. In this thesis, the recommendations of HSE were followed due to limitations of resources.

Exposure assessment based on quantitative models

Exposure assessments based on air measurements are costly and time consuming. Many small and medium sized companies do not have the resources for measurements and risk assessments may therefore be lacking altogether. One way to handle these problems is by performing exposure assessments based on models that are free of charge and easily available. Models do have larger uncertainty than measurements but can be useful when measurements are not possible for different reasons or as a complement. Models that assess a distribution of the exposure include the variability of the exposure better than measurements, because the numbers of measurements performed are usually too few.

The development of exposure models began in the 1990s. Cherrie and colleagues 1996 proposed a new method for structured assessment of concentrations (20). Their method was based on the theory that occupational exposure can be explained by three factors in both near- and/or far-field. The three factors were: intrinsic emission of the substance, the method of handling the chemical and the effect of control measures such as local exhaust ventilation. The exposure could then be reduced by the use of personal protection equipment as well. This source-receptor model is still a base for the development of exposure models available today. These models calculate scores that are calibrated against exposure measurements. Today, several models are free of charge (to some extent) and available on the internet for use. The input parameters of these models vary in numbers and details. The outcome could also vary from one single outcome value in mg/m^3 to a distribution of exposure levels, also in mg/m^3. As stated before, exposure models have larger uncertainty than exposure measurements, which can be handled by using a higher percentile as outcome than the 50^{th} percentile corresponding to the median exposure. Instead, the 90^{th} percentile (worst case) is recommended when using exposure assessment models.

Control banding

Besides the quantitative exposure models, there are other models taking the whole risk assessment approach into account. These other models are not only calculating and rank an exposure but they also compare the ranking of the exposure with the ranking of a hazard assessment and recommend control measures to be installed to reduce the exposure if needed. These models are often referred to as control banding tools and were developed in order to help small and medium sized enterprises to meet the requirements of regulations. Control banding tools were first developed in the 1970s by the pharmaceutical industry. HSE in the UK developed a program called Control of Substances Hazardous to Health (COSHH) essentials in the 1990s (21). Another well-established control banding tool is Stoffenmanager®, developed in the Netherlands and, further, the Easy-to-use workplace control scheme for hazardous substances (EMKG) tool, developed in Germany (22).

The ranking of the exposure is often grouped in intervals (bands) and not presented as a single value outcome as for the exposure assessment models. The hazard assessment is based on the H-phrases from the CLP-regulation and is also grouped into intervals. The outcomes could primarily be seen as risk prioritising in the classic colours green, yellow and red. The estimates are quite rough and the tools should be considered as screening tools to use as a first step of the risk assessment process at companies.

Risk assessment of chemicals by REACH

REACH-legislation

The aim of the EU regulation (EC) No 1907/2006 REACH (Registration, Evaluation, Authorisation of Chemicals) is to (23):

> "… improve the protection of human health and the environment from the risks that can be posed by chemicals, while enhancing the competitiveness of the EU chemicals industry. It also promotes alternative methods for the hazard assessment of substances in order to reduce the number of tests on animals."

Humans may be exposed to chemicals trough work, via the environment or as consumers. REACH puts the responsibility to communicate safe use of chemicals on the companies' manufacturing the chemical or importing them into EU (23). The legislation is administered by ECHA and is implemented step wise. The implementation started in 2007 with the registration of chemicals manufactured or imported in larger amounts (>1 000 tonnes) to EU per year. The last step will be in spring 2018 with the registration of the minor amounts (1-100 tonnes) manufactured or imported to EU per year (24).

Risk assessment approach

The risk assessment approach under the REACH legislation for workers exposed to chemicals is based on a hazard assessment and an exposure assessment as shown in Figure 1. A risk characterisation ratio (RCR) is calculated by dividing the exposure value with the Derived No Effect Level (DNEL) value (25). If the RCR is above 1, either the hazard assessment or the exposure assessment should be revised (for example; control measures could be added to the exposure assessment or more data about the hazards could be generated), until the estimated exposure level is below 1 and the use is considered to be safe. If the RCR-value is still above 1, a tier 2 model could be used instead to receive a closer estimate of the exposure level. When the RCR value is below 1 the exposure scenario (ES) is considered to be safe and the input parameters, such as operational conditions (OC) and risk management measures (RMM) defining the ES should be written in the extended safety data sheet (e-SDS) and be provided to the downstream users. The RCRs are not allowed to be above 1 for a chemical registered at ECHA.

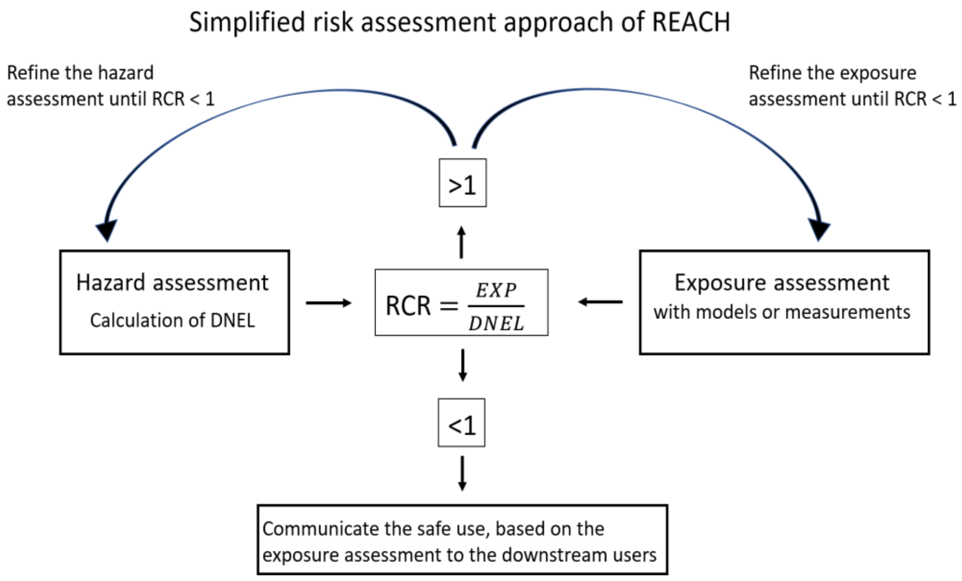

Figure 1
A simplified figure showing the risk assessment approach under the REACH legislation

Hazard assessment

According to ECHA, a hazard assessment should be performed if the chemical is manufactured or imported to EU in 10 tonnes per year or more (26). The hazard assessment should lead to a calculation of a DNEL-value. The DNEL-values should be derived by the manufacturer or the importer of the chemical to EU. Information on hazards should be collected from toxicity tests on humans or animals, from in vitro-evaluations or by (Q)SAR methods and comparisons based on chemical structures and categories (26). DNEL-values should be calculated for all relevant routes of exposure and it may be necessary to calculate for systemic and local effects, chronic and acute effects and by the different routes of exposures (27).

Exposure assessment

If the result from the hazard assessment classified the chemical as dangerous or Very Persistent or Very Bio accumulative (VPVB) or Persistent, Bio accumulative and Toxic (PBT), an exposure assessment should be done (26). The exposure assessment according to ECHA could be done either by measurements or by using quantitative exposure assessment models (27). Since the exposure assessment should be calculated in every way the chemical is handled, there would be a high number of estimations to be performed. This may be hard to accomplish and instead, exposure models are recommended. The models recommended by ECHA are divided into different Tiers. Tier 1 models are the most generic ones that should provide a more protective outcome than tier 2 models for handling the higher uncertainties. Tier 1 models for inhalation exposures recommended by ECHA are: ECETOC TRA; MEASE and, EMKG-Expo-Tool. Tier 2 models are more sophisticated and more detailed information about the exposure situations is required; these models should have a lower uncertainty and therefore also provide a less protective (less overestimating) outcome. Examples of tier 2 models are: Stoffenmanager® and The Advanced REACH Tool (ART) (27). Tier 3 is measurements. The exposure assessment of REACH is recommended to start with tier 1 models and the tier 2 models if necessary. The studies of this thesis include the following exposure assessment models: ECETOC TRA, Stoffenmanager® and ART.

Risk management approach

Extended Safety Data Sheets

When the manufacturer in EU or importer of a chemical has followed the risk assessment approach and calculated RCR-values, some of the input parameters should be written in the e-SDS as Exposure Scenarios (ES) and distributed to the downstream users. The ES contains information about how to handle the chemical in a safe way. Since a chemical could be handled in a variety of tasks, ECHA has categorized the common tasks that chemicals could be used in by different Process Categories (PROCs). There are 28 PROCs defined by ECHA, describing tasks like: laboratory work, industrial spraying, transferring of chemicals and chemicals used in closed process (28). The downstream users are obligated to identify their work by the PROCs and follow the instructions written in the ES (29).

Validation studies of exposure assessment models

Validation studies of exposure assessment models are of high importance and are based on exposure measurements. When a model is developed the outcome of the algorithm is calibrated against exposure measurement data and an exposure level (or interval) is presented as outcome. The outcome of the model is limited to the exposure measurements used when calibrating the model. It is of great concern that the models continue to be validated against exposure measurements and, if possible, be recalibrated to improve the accuracy of the model. For a model to perform well, both accuracy and reliability have to be addressed. Accuracy of exposure assessment models explains how close the model estimates are to the true exposure level (estimated by measurements in our case). Reliability of exposure assessment models explains how often the same result (repeatability) can be estimated by different users.

Reliability of exposure assessment models

Only a few studies have examined the reliability between users applying exposure assessment models. Lamb et al. published a study in 2017 that aimed to evaluate between-user reliability of tier 1 exposure assessment models and Stoffenmanager® (ECETOC TRA, MEASE, EMKG-EXPO-TOOL and Stoffenmanager®). The study concluded that the outcomes between the users varied by several orders of magnitude. Variations between users with higher expertise were as high as between users with lower expertise and the input parameters that varied the most were type of activity and level of dustiness (30). One study has evaluated the reliability of the ART model, which also concluded that the variation between users were high and seemed to improve after training (31).

Accuracy of exposure assessment models

Several studies focusing on the accuracy of the three models ECETOC TRA, Stoffenmanager® and ART have been conducted the last decade and are summarized in Table1. When performing these kind of studies, different approaches need to be used as the outcome from the models is fundamental different. For ECETOC TRA, the outcome is a single value in mg/m^3, but for Stoffenmanager® and ART a distribution of the exposure is presented. Hence, for ECETOC TRA, when comparing exposure measurements with the outcome from the model, the modelled outcome should be higher than the measurements. Some studies concluded that ECETOC TRA in general is protective, but not always (32-36). For Stoffenmanager®, different outcomes of the model have been studied both the 50^{th} percentile (to study the accuracy) and the 90^{th} percentile (to study the level of protection). The studies concluded relatively high accuracy and sometimes high enough level of protection, when evaluating different algorithms within Stoffenmanager® (32, 33, 36-38). As for ART, both the 50^{th} percentile (to study accuracy) and the 90^{th} percentile (to study the level of protection) have been studied. In general, ART may underestimate the exposure, especially for higher exposures (32, 34, 39, 40).

Table 1.
The main aims, materials and part of results of studies validating exposure assessment models

Model	**Study**	**Aim**	**Material**	**Results**
ECETOC TRA	Spinazze *et* al. 2017(32)	Evaluate the accuracy and robustness	Exposure measurements of organic solvents and pesticides provided from the literature Liquids only Default outcome from the tool	Median overestimation factor of 2.0 for organic solvents and median overestimation facor of 3545 for pesticides No significant relations between measurements and predicted exposure Lower level of robustness compared to the other models
	van Tongeren *et* al. 2017 (33)	Validation of lower tier models and Stoffen-manager®	Exposure measurements (nearly 4000) were collected from Europe and US Volatile liquids, metal abrasion, powder handling Default outcome of the model	Level of protetion: 32 % of measurements exceeding the model estimate for volatile liquids. For metal abraison it was 26 % and for powder handling it was 21%.
	Hofstetter *et* al. 2013 (34)	Evaluate the accuracy of models	Exposure measurements of toluene during spray painting scenario Version 2 of ECETOC TRA Default outcome of the model	The outcome from the model was 30 ppm and mean measured concentration was 8 ppm. The model overestimated the exposure by a factor of 3.6
	Kupczewsk a-Dobecka *et* al. 2011 (35)	Describe ECETOC TRA when used to different organic solvents	Exposure measurements of toluene, ethyl acetate and aceton Version 2 of ECETOC TRA Default outcome of the model	Exposures of aceton had a measured mean exposure of 443 ppm, the model underestimated these situations (25 to 255 ppm). For toluene and ethyl acetate the exposure measurements were within the range of the estimated exposures

				(when estimated with and without active ventilation)
	Vink *et* al. 2010 (36)	Explore the implications of using models and analogous data	Exposure measurements of PGEE, PGPE, PnB and PGME[a] Version 2 of ECETOC TRA	The worst case exposure measurement was 34.5 mg/m^3 and the estimated exposure for the different tasks were 5, 135 and 9 mg/m^3 (full shift: 69 mg/m^3)
Stoffen-manager®	Spinazze *et* al. 2017 (32)	Evaluate the accuracy and robustness	Exposure measurements of organic solvents and pesticides provided from the literature 90th percentiles outcomes of the model were used	Median overestimation factor of 7.5 for organic solvents and median overestimation facor of 1.5 for pesticides No significant relations between measurements and predicted exposure Higher level of robustness
	van Tongeren *et* al. 2017 (33)	Validation of lower tier models and Stoffen-manager®	Exposure measurements (nearly 4000) were collected from Europe and US Non-volatile liquids, volatile liquids and powder handling 75th and 90th percentile outcomes from the model were used	Level of protection: For non-volatile liquids 36 and 24 % (75th and 90th percentile) of measurements exceeded the model estimate. For volatile liquids it was 20 and 12 % and for powder handling it was 7 and 3 %.
	Koppisch *et* al. 2012 (37)	Evaluate two Stoffen-manager® equation algorithms	The two equations were about “handling of powders and granules” and “machining of wood and stone” Measurements were extracted from the MEGA database The 50th and 90th percentiles were used	For “handling of powders and granules” the correlation between measurements and estimates were good and had a negative bias of -0.28 with a precision of 1.56 and percentage of measurements exceeded 90th percentile estimates were 11 % For “machining of wood and stone” the correlation between measurements and estimates was good and had a positive bias of 0.52 and percentage of measurements exceeded 90th percentile estimates were 7 %
	Vink *et* al. 2010 (36)	Explore the implications of using models and analogous data	Exposure measurements of PGEE, PGPE, PnB and PGME[a] Version 4.0 of Stoffenmanager®	The worst case exposure measurement was 34.5 mg/m^3 and the estimated exposure for the different tasks were 25.6, 42.2 and 25.6 mg/m^3 (full shift: 16.9 mg/m^3)
	Schinkel *et* al. 2010 (38)	Validation study	Exposure scenarios of solids and liquids The 50th and 90th percentiles were used	For solids, the correlation between estimates and measurements was moderate. The bias for overall solids was -0.90 and the percentage of measurements exceeded the estimates was 19%. For liquids, the correlation between estimates and measurements was good. The bias for overall liquids was –0.42 and the percentage of measurements exceeded the estimates was 10%.
ART	Spinazze *et* al. 2017 (32)	Evaluate the accuracy and robustness	Exposure measurements of organic solvents and pesticides provided from the literature 90th percentiles were used with 95% CI	Median overestimation factor of 1.3 for organic solvents and median underestimation facor of 0.15 for pesticides Significant relations between measurements and predicted exposure Moderate level of robustness

	Savic *et* al. 2017 (39)	Investigate the performance of ART	Exposure measurements collected in switzerland Exposure scenarios of vapours, powders and solids The 50^{th} and 90^{th} percentiles were used	For vapours ART tended to overestimate low measured exposures and underestimate high ones. The modelled exposure was moderately correlated to the measured exposures. The bias were found to be positive. For powders ART tended to overestimate low measured exposures and underestimate high ones. The correlation between estimates and measurements were weak. The bias were found to be negative. For solids ART tended to overestimate low measured exposures and underestimate high ones. The correlation between estimates and measurements were weak. The bias were found to be negative.
	Hofstetter *et* al. 2013 (34)	Evaluate the accuracy of models	Exposure measurements of toluene during spray painting scenario 50^{th} percentile with 95% confidence itnerval	The etimated exposure was 24.2 ppm and mean measured exposure was 8.3 ppm. The model overestimated the exposure by a factor of 2.9
	McDonnell *e*t al. 2011 (40)	Refinement and validation of ART with data from the pharmaceutica l industry	Exposure measurements from the pharmaceutical industry, only for dusts The 50^{th} and 90^{th} percentiles were used	The model tended to overestimate exposures at lower concentrations and underestimate exposures at higher concentrations. Biases were calculated for every task and ranged from - 7.64 to 5.39. 4 of 16 tasks had positive biases, the rest were negative.

[a] PGEE = Propylene Glycol Ethyl Ether, PGPE = Propylene Glycol Propyl Ether, PnB = Propylene Glycol n-butyl ether, PGME = Propylene Glycol Monomethyl Ether

Aim

General aim

The general aim of this thesis was to examine the performance of three exposure assessment models; ECETOC TRA, Stoffenmanager® and ART. The focus was to study how well the models assessed the exposure in comparison with traditional exposure measurements. And, to study risk assessments based on the models according to both the REACH legislation and the traditional risk assessment approach.

Specific aims

I. To study the reliability of Stoffenmanager® 5.1, and the risk assessment outcomes using the control banding part of Stoffenmanager®.

II. To evaluate the accuracy of the models (Stoffenmanager® 5.1 and ART 1.5) by calculating the lack of agreement between measured median exposures and the 50th percentile outcomes of the models. A comparison of distributions between modelled outcomes and measured exposures were also performed.

III. To evaluate the level of protections of all three models by comparing the recommended worst case outcome of the models (described by ECHA guidance for REACH) with measured exposure.

IV. To evaluate risk assessments based on exposure assessment models relative to both OELs and DNELs in comparison with traditional risk assessments based on exposure measurements and OELs.

V. To perform a case study evaluating the risk assessment approach and risk management under the REACH legislation in 10 departments in the chemical industry with focus on the use of exposure assessment models when calculating RCR-values.

Materials and Methods

Study design

Outline of the thesis

The 4 studies in this thesis are all based on the performance of exposure assessment models. Depending on the objective of the studies different models, outcomes of the models and exposure measurements have been used. For instance, some of the studies include the same exposure measurement data and exposure situations but the outcome of the models is different depending on the objective.

The information collected to perform the studies in this thesis started in 2010 and ended in 2017. The collection of data included repeated exposure measurements and collection of input parameters, describing the exposure situations, needed by the models. The collection was performed in 3 steps. In step 1, data for **study I – III** was collected in 2010-2011. In step 2, in 2012-2014, additional data was collected to be used in **study II** and **III**. In step 3, in 2017, data was collected for **study IV** (no exposure measurements were performed in this step). The collection of data is explained in Figure 2 and information about the aims of the studies, which model was used and the data used is summarized in Table 2.

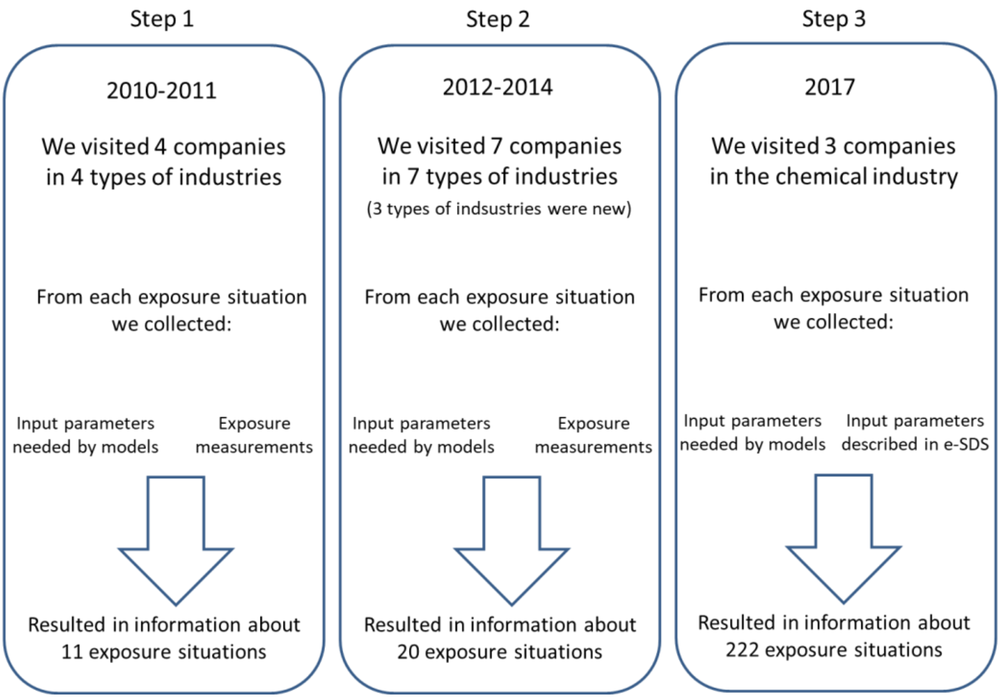

Figure 2
Information about the collection of data included in the 4 studies

Table 2.
Simplified outline of the studies. The steps of information collection are explained in Figure 2

Study	Main aims of the study	Model used	Exposure measurement collected	Input parameters collected	Outcome of model used
Study I	To study the between user reliability and to compare the outcome from the model (consensus) with median exposure measurments to investigate the level of protection	Stoffenmanager®	Step 1	Step 1	The 90th percentile[c]
Study II	To study the agreement between the models ”best case” outcome and median exposure measurements	Stoffenmanager® and ART[a]	9 situations[b] from step 1 and all from step 2	9 situations from step 1 and all from step 2	The 50th percentile
Study III	To study the level of protection of the models by comparing the ”worst case” outcome of the models with median exposure measurements and to compare the modelled outcomes with limit values	ECETOC TRA, Stoffenmanager® and ART	9 situations from step 1 and all from step 2	9 situations from step 1 and all from step 2	The 90th percentile of Stoffenmanager® and ART and the default outcome of ECETOC TRA
Study IV	To study the risk assessment approach of REACH by comparing registered RCRs with observed RCRs calculated with information from worksites	ECETOC TRA, Stoffenmanager® and ART	No measurements were included	Step 3	The 90th percentile of Stoffenmanager® and ART and the default outcome of ECETOC TRA

[a] ECETOC TRA was excluded from this study since it doesn’t provide a “best case” (50th percentile) outcome.
[b] 2 situations were excluded due to few exposure measurements.
[c] Information about the models and their in- and output parameters are explained in the Exposure Assessment Models part of this thesis.

Exposure assessment models

Several exposure assessment models are available for use. In this thesis only three of the models have been studied and only regarding inhalation exposures, i.e. ECETOC TRA, Stoffenmanager® and ART. These models have different developers and require different amount of information about the exposure situation and the outcome is presented differently. However, all three models are based on a source-receptor concept. Information about the three models is presented in Table 3.

Table 3
Information about the three exposure assessment models ECETOC TRA, Stoffenmanager® and ART. Number within brackets is a reference of the information.

Model	**ECETOC TRA**	**Stoffenmanager®**	**ART**
Beyond applicability	Fibres Gases Hot processes Solids in liquids (27)	Fibres Gases Hot techniques and processes Sanding and impact on plastics, glas or metal (41)	Fibres Gases Hot techniques and fumes Solutions of solids in liquids Sanding and impact on plastics, glas or metal (42)
Parts of the source-receptor approach included	Emission, transmission and immission (43)	Near- and far-field emission, background exposure, reduction of transmission and immission. (44)	Near- and far-field emission, activity emission, local controls, segregation, dispersion, separation and surface contamination (45)
Number of input parameters	8 (46)	Around 17 depending on whether liquid or solid and follow-up questions to some answers (41)	At least around 20 but could be many more depending on answers that lead to more questions and if there is far-field exposure (42)
Output	One outcome (default)	50^{th}, 75^{th}, 90^{th} and 95^{th} percentile	50^{th}, 75^{th}, 90^{th} and 95^{th} percentile with confidence intervals of inter-quartile, 80%, 90% and 95%
Level of Tier	1	2	2

ECETOC TRA

ECETOC TRA is a risk and exposure model developed by the European Centre for Ecotoxicology and toxicology of Chemicals (46). The algorithm is based on the EASE model developed by HSE and can be downloaded at ecetoc.org (46-48). In this model, not only the inhalation exposure could be assessed but also exposure to the environment and the consumers. Also, dermal exposure can be assessed. In ECETOC TRA, multiple assessments of the same chemical can be performed simultaneously, which makes the model user-friendly. The model considers emission from the chemical, transmission and immission (43). The model does not distinguish between near and far-field emission and the tasks are described by PROCs as defined by ECHA (28). The outcome of the model is not a distribution; instead, one single protective outcome in mg/m^3 is presented. The input parameters with number of answer alternatives and weighing factors for inhalable exposure are presented in Table 4 (43, 47, 49).

Table 4
Input parameters, number of answer alternatives and weighing factors when avaliable for inhalation exposure using ECETOC TRA

Input parameters	**Number of answer alternatives**	**Weighing factors (range)**
Molecular weight	No alternatives	-
Process Category	34	-
Type of setting	2 (industrial or professional)	-
Substance form	2 (solid or liquid)	-
Vapour pressure or dustiness	No alternatives (vapour pressure), 3 (dustiness)	-
Duration of task	4	0.1-1 (factor of reduction)
Ventilation	6	0-70 (% reduction)
Personal protection	3	0-95 (% reduction)
Substance in mixture	5	0 to 90 (% reduction)

Stoffenmanager®

Stoffenmanager® is a risk and exposure model that was developed by the initiative from the Dutch Ministry of Social Affairs in 2007 (50). The aim was to develop a model that could help small and medium sized enterprises with chemical management. Both inhalation and dermal exposure can be assessed with Stoffenmanager®. Stoffenmanager® consists of two parts. One is a control banding part, presenting a risk and the other is a quantitative exposure assessment part, presenting an exposure level in mg/m^3. The exact input parameters have been explained elsewhere (50, 51) but the input parameters, number of answer alternatives and weighing factors (range) for liquids in the quantitative exposure assessment algorithm is presented as an example in Table 5. The latest version (7) can be found at www.stoffenmanager.nl but in our studies we have used versions 5.1-6.0 (41). Stoffenmanager® also has a REACH module but this is not included in this thesis.

Control banding

The control banding part consists of both a hazard assessment and an exposure assessment. The hazard assessment is based on the H-phrases by the CLP-regulation which is grouped into 5 “bands”, from A (most harmless) to E (most harmful). The grouping of the H-phrases depends on the severity of the H-phrases (52). The exposure assessment is developed from an algorithm by Cherrie et al 1996, updated by Cherrie and Schneider in 1999 (20, 53). The exposure algorithm was recalibrated in 2010 by Schinkel et al (38). The exposure assessment part considers near-field and far-field emissions, background exposure, reduction of transmission and immission (51). The activity is defined in texts and not as PROCs. The outcome of the exposure algorithm (score) is also grouped into “bands” 1 (lowest exposure) to 4 (highest exposure). The bands of the hazard and exposure assessments are then combined and presented as a prioritising number of risks, I (first prioritised) to III (last prioritised).

Quantitative exposure assessment

The exposure assessment part of Stoffenmanager® has the same algorithm as the control banding part but the outcome of the algorithm is not a "band" but a distribution of the exposure (50th, 75th, 90th and 95th percentiles). The recommended outcome to use from developers and from ECHA is the 90th percentile (27, 41). Both variability and uncertainty is incorporated in the outcome presented as mg/m^3.

Table 5
Input parameters, number of answer alternatives and weighing facors of Stoffenmanager® when liquids are estimated with the quantitative exposure assessment part is presented (38, 50).

	Input parameters	Number of answer alternatives	Weighing factors (range)
Component	Name, CAS-number	No alternatives	-
	Solid and/or liquid	2	-
	Vapour pressure	No alternatives	-
Product	Product name	No alternatives	-
	Supplier	No alternatives	-
	Solid or liquid	2	-
	Location	No alternatives	-
	Date of SDS	Dates	-
	Choice of component and its percentage in product	As many as compnents registered	-
Exposure assessment	Name, location and date	No alternatives	-
	Solid or liquid	2	-
	Choice of product	As many as products registered	-
	Dilution	No alternatives	-
	Type of task	8	0-10
	Is the worker in the breathing zone of the emission source	2 (yes or no)	-
	More than one employee carrying out the same task simultaneously	2 (yes or no)	-
	Is the task followed by evaporation, drying or curing?	2 (yes or no)	-
	Personal protection	8	0.05-1
	Volume of working room	4	0.1-10
	Ventilation	4	0.1-10
	Cleaning occurs daily	2 (yes or no)	0-0.03
	Inspection and maintenance of machines and equipment	2 (yes or no)	0-0.03
	Control measures	5	0.03-1
	Is the worker situated in a cabin	3	0.03-1

The Advanced REACH Tool (ART)

ART 1.5 is an exposure assessment model that is a more advanced model as the name reveals. This model has been developed through collaboration between different companies, a university and institutions in order to develop a Tier 2 model according to REACH (42). The model is also based on the algorithms by Cherrie and Schneider 1999 but was further developed by Tielemans et al. 2008 (44). The latest version of the model can be found at advancedreachtool.com. The model considers near- and far field emissions, activity emission, local controls, segregation, dispersion, separation and surface contamination (45). The activity is defined in texts. The outcome is a distribution of the exposure presented by the 50^{th}, 75^{th}, 90^{th} and 95^{th} percentiles. The outcome as a distribution of the exposure takes the variability into account but the uncertainty is handled by adding a confidence interval to the choice of percentile (54). The user can also incorporate measurements and refine the outcome of the model in the Bayesian part of the model (ART B) (55). The exact input parameters are presented elsewhere but in Table 6 some of the input parameters, when estimating exposure of liquids, is presented (45).

Table 6
Some input parameters, number of alternatives and weighing factors used in ART when estimating liquids. Since ART is more complex than Stoffenmanager® and ECETOC TRA, not all input paramteres are shown in the Table (42, 45).

Input parameters	**Number of answer alternatives**	**Weighing factors (range)**
Name, CAS-number	No alternatives	-
Solid; liquid; powders, granules or pelletised material; Powders dissolved in a liquid or incorporated in a liquid matrix; Paste, slurry or clear wet powder	5	-
Temperature	4	-
Vapour pressure	No alternatives	-
Mole fraction	8	-
Activity coefficient	No alternatives	-
Emission source in breathing zone of the worker?	2 (yes or no)	-
Activity class *Activity subclasses*	6 0-2 (depending on activity)	0.001-10
Furthur detailed question about the activity (1-3 questions)	Depending on the activity chosen	0.001-10
General Control Measures *Further detailes (1-2 questions)*	5 2-4	0.0001-1
Secondary Control Measures *Further detailes (1-2 questions)*	5 2-4	0.0001-1
Is the process fully enclosed	2 (yes or no)	0
Do cleaning and preventive maintenance of machineryoccur and is protective clothing used	2 (yes or no)	0-001-0.01

Is general cleaning in place	2 (yes or no)	0.003-0.01
Working area	4	0.003-36
Further detailed questions about the working area (including ventilation)	2-9	0.003-36
Segregation (only far-field exposure)	5	0.1-1
Separation (only far-field exposure)	5	0.1-1
Are secondary sources present	All questions from the beginning	-

Exposure situations

Type of industries and exposure situations

Study I-III

Information about the chosen industries and exposure situations was collected in different steps (Figure 2). For **study I-III,** information was collected in two steps. The industries, exposure situations, agents and sampling methods are described in Table 1 in **Study III**; companies that were visited in step 1 are referred to as A and companies that were visited in step 2 are referred to as B. More detailed information about the companies and the exposure situations can be found in the supplementary file of Landberg et al. 2015 (companies marked as A) and in the supplementary file of Landberg et al. 2017 (companies marked as B). The exposure situations were not chosen randomly but subjectively by occupational hygienists (OH). The OH chose exposure situations, where known potential health risks existed.

For **study I**, 4 types of industries were chosen: printing, foundry, spray painting and wood processing. Within these industries, one company each was visited. For **study II and III**, the industries and companies of **study I** were included and one more company in these 4 industries was added. Additional 3 companies from three other industries were included, resulting in 7 industries and 11 companies.

Study IV

Information included in **study IV** was collected in step 3 (Figure 2). Companies were contacted through the Swedish branch organization for paint and glue. After discussions, 3 companies were recruited. In this study, we did not choose exposure situations but studied all situations, in which the chosen chemicals were handled. It resulted in 222 exposure situations.

Exposure measurements

Exposure measurements were performed and used in **study I-III**. The measurements were taken in the breathing zone of the worker (outside any protection) and at least at three occasions when possible (sometimes only two). To include some of the variability the three occasions were spread out, with at least one week in between and on different workers but always when the same task was performed. The measurements were taken throughout a working day and if the task was not performed during a whole working day, measurements were taken throughout the day and then the time for the task was calculated. Details about sampling and analytical methods are described in the supplementary material of Landberg et al (2017 and 2015)(56, 57).

Collections of data for the models

Collection of data for using the models was collected on the working sites studying the exposure situations. At least 2 occupational hygienists (OH) studied the exposure situations simultaneously (the author of this thesis was one of the OH at most visits). The input parameters needed were written on templates and then inserted into each model by the author **in study II-IV**. In **study I,** another OH was transferring the collected data into the models.

Data evaluation and statistics

Reliability of Stoffenmanager®

The reliability of Stoffenmanager® was studied in **study I** by comparing the outcomes from the quantitative exposure assessment part used by 13 users assessing the same exposure situations. The 13 users consisted of 4 occupational hygienists, 8 safety engineers and 1 representative each from the companies visited. The 13 users visited the companies together to gather information about the exposure. Moreover, exposure assessments were also performed afterwards by 6 OHs who agreed on a consensus assessment for every exposure situation. We calculated quotas between highest and lowest outcomes from the users for each exposure situation and between the 75th and 25th percentiles of the outcomes, as well. A boxplot was made to graphically display the variability between users. The input parameters that had the highest impact on the outcomes were studied by comparing the input parameters of the user's highest and lowest outcomes within an exposure situation. We studied how the outcome changed when changing one input parameter at a time for each situation. We also studied the degree of agreement of a user's input parameters with the consensus assessments.

Model accuracy and level of protection

Comparison of distributions

In **study II,** the accuracy of Stoffenmanager® and ART was studied. One comparison method between the exposure measurements and the outcome of Stoffenmanager® and ART was to compare the distributions of Stoffenmanager® and ART (25^{th}-75^{th} percentiles (with 95% Cl for ART)) with the distributions of the exposure measurements (min-max) for all exposure situations.

Lack of agreement

The lack of agreement is another comparison method that was calculated between the median exposure measurements and the 50^{th} percentile of Stoffenmanager® and ART in **study II**. Lack of agreement was calculated in accordance with Bland and Altman (2010) and in similarity with Schinkel et al. (2010) (38, 58). Lack of agreement is reflected in bias and precision of the method. Bias is the mean differences between the model estimates (50^{th} percentile) and exposure measurements (median) with a standard deviation. If the bias is negative, the model tends to underestimate the exposure and if the bias is positive, the model tends to overestimate the exposures. The equations of bias and precision are presented in **study II**.

Level of protection

The level of protection of the control banding part of Stoffenmanager® was studied in **study I**, where the risk bands of the consensus assessments were compared with a measured risk quota. The measured risk quota was the measured exposure in relation to a Swedish OEL value. If the measured risk quota was below 0.3, the risk was low, and high if the quota was above 1 (18).

In **study III,** the level of protection of ECETOC TRA, Stoffenmanager® and ART was studied by comparing the 90^{th} percentile (worst case) of Stoffenmanager® and ART, and the default outcome of ECETOC TRA with median exposure measurements. The percentage of exposure measurements exceeding the modelled outcome was calculated.

Risk assessment and management

In **study III**, the risk assessments based on models were compared with the risk assessments based on measurements. Outcomes of the exposure assessments based on the exposure models in relation to both OELs and DNELs were compared with the traditional method of performing a risk assessment: exposure measurements in comparison with Swedish OELs. This means that 9 risk quotas were calculated: 4 exposure models (ECETOC TRA, Stoffenmanager®, ART and ART B) divided with Swedish OELs and DNELs and measurements in relation to Swedish OELs. These 9 risk quotas were classified as safe or unsafe for every exposure situation. When quotas based on OELs were above 0.3, and based on DNELs were above 1, they were classified as unsafe. When quotas based on OELs were below 0.3 and based on DNELs were below 1, they were classified as safe.

When comparing the risk quotas based on models with risk quotas based on measurements, each exposure situation was grouped into one of three categories (Table 2 in **Study III**);

1. Same risk assessment outcome:	Modelled risk assessment has the same outcome (safe or unsafe) as the measured risk assessment
2. False safe:	Modelled risk assessment is classified as safe while measured risk assessment is classified as unsafe
3. False unsafe	Modelled risk assessment is classified as unsafe while measured risk assessment is classified as safe

In **study IV,** the data evaluation was done by comparing the RCRs of observed exposure scenarios at the work site with the exposure scenarios registered to ECHA. RCRs are calculated by dividing the assessed exposure level of a chemical with the DNEL of the same chemical.

We collected e-SDS from three companies, visited the companies and studied the exposure situations, where the chemicals from the collected e-SDS were handled. We used ECETOC TRA, Stoffenmanager® and ART to calculate observed RCRs using DNELs from the e-SDS. The observed RCRs were compared with the registered RCRs written in the e-SDS. The Spearman rank correlation between observed and registered RCRs was calculated.

The comparison was done in 2 steps. First, the observed RCRs above the registered RCRs were summarized. Second, the observed RCRs above 1 were summarized and adjusted for when control measures and personal protection was included in the e-SDS but excluded at the worksites. For the adjusted observed scenarios above and below 1, Mann Whitney U tests were applied to compare DNELs and vapour pressure between the groups.

Results and Comments

Reliability of Stoffenmanager®

The quotas between the highest and lowest outcome from the 13 users were highest in the spray painting industry with a factor of 162 in painting locomotive with personal protection. The quota of the painting locomotive without protection situations was also high (factor 97). The highest quotas between the 75th and 25th percentiles were in the core making situation in the foundry industry with a factor of 5.7. The lowest quotas between highest and lowest outcomes were found in the printing industry with factors of 2.0, 12 and 3.3. The lowest quotas between 75th and 25th percentiles were in the spray painting industry and the printing industry with quotas ranging from factor 1.0 to 2.6. In the spray painting industry, both the highest quotas between highest and lowest outcome and the lowest quotas between 75th and 25th percentiles were seen. This means that most users modelled with similar input parameters and only a few modelled the highest and lowest outcomes. This can also be seen in the boxplot (Figure 2) in **study I**. All quotas between the 13 users are presented in Table 5 in **study I**.

The large variations between users can be explained when studying the users' choice of input parameters. Some input parameters varied more than others and some input parameters had a low percentage of agreement with the consensus assessments. Such input parameters were material shaping, type of task, inspection and maintenance of machines, personal protection, breathing zone and control measures. The input parameters that had the highest impact on the outcomes were type of task, breathing zone, ventilation and control measures.

Model accuracy and level of protection

Comparison of distributions

The comparison between the distributions of Stoffenmanager® and measured exposures showed that 12 of 29 exposure situations had separated distributions, which also is illustrated in Figure 2 and 3 in **study II**. Stoffenmanager®

underestimated 7 of the 12 exposure situations and all 12 situations concerned liquids. Hence, all distributions in the wood industry and the flour mill had overlapping distributions. The foundry and plastic moulding industry had no overlapping distributions.

The comparison between the distributions of ART and measured exposures showed that 5 of 29 exposure situations had separated distributions (Figure 2 and 3 in **study II**). ART underestimated 4 of the 5 situations. Most separated distributions were in the wood industry with 3 of 6 situations. One assessment each in the flour mill and foundry had separated distributions and the remaining industries had overlapping distributions.

Lack of agreement

Lack of agreement was examined for Stoffenmanager® and ART and is presented in Table 7. Bias and precision of the exposure situations concerning liquids were 0.22 ± 1.0 using Stoffenmanager® and -0.55 ± 0.88 using ART. For exposure situations concerning dusts, bias and precision for Stoffenmanager® was -0.024 ± 0.66 and for ART, it was -1.4 ± 1.6. In **study II,** modified Bland Altman plots were made and a clear association between outcome from Stoffenmanager® and measured exposure could be seen in Figure 4 in **study II**. Stoffenmanager® tended to overestimate exposures with low measured exposure and underestimate exposures with high measured exposure. No such association could be seen with ART.

Level of protection

Control banding by Stoffenmanager®

The outcome from the control banding part of Stoffenmanager® is presented as risk “bands”, meaning one of the three prioritising categories I, II and III (I = prioritise first, highest risks with red colour and III = prioritise last, lowest risks with green colour). These outcomes were compared to a measured risk quota, where we have divided the measured exposure with a Swedish OEL. For 6 of the 11 exposure situations of **study I,** the measured risk quota and the risk band of Stoffenmanager® was in the same category (low, medium or high risk). For 2 situations, the measured risk quota was higher than risk bands, meaning that 18 % of the measured risk quota exceeded the risk bands.

Quantitative exposure assessments by ECETOC TRA, Stoffenmanager® and ART

The percentage of measured exposures exceeding modelled worst case outcome was calculated and is presented in Table 7. The highest percentage (31%) was observed using ECETOC TRA i.e. it was the model with lowest level of protection. Second highest (17%) was observed when using Stoffenmanager®, which almost has a high enough level of protection, since the worst case outcome is the 90th percentile. The most protective model was ART and ART B with 3 and 0 % of measured exposures exceeding the model outcomes. These results are also illustrated in a scatterplot (Figure 1) in **study III**.

Table 7
Bias and percent of measured exposure exceeding modelled exposure is presented for each model.

Model		**Bias (mean difference and precision)**	**% of measured exposure > modelled exposure**	**Study**
ECETOC TRA		-	31	III
Stoffenmanager®	Liquids	0.22 ± 1.0	17	II & III
	Solids	-0.024 ± 0.66		II & III
ART	Liquids	-0.55 ± 0.88	3	II & III
	Solids	-1.4 ± 1.6		II & III
ART B		-	0	III

Risk assessment and management

Risk assessment based on models in comparison with measurements

The exposure models are in general overestimating the risks when compared to risk assessments based on exposure measurements. The risk assessments in the “false unsafe” group were almost as many as in the “same risk assessment outcome” with the exception of ECETOC TRA; the results are presented in Table 8. ECETOC TRA and ART had the highest amounts of risk assessment in the category “same risk assessment outcome” group when OELs were used. However, ECETOC TRA also had most risk assessments in the “false safe” group compared to the other exposure models. Stoffenmanager® and ART B had no risk assessments in the “false safe” group. The result were the same when DNELs were used but ART B also had risk assessment in the “false safe” group. These results are also displayed in Figure 2a and b in **study III**.

Table 8
Numbers of exposure situations classified in one of the three groups "Same risk assessment outcome", "False safe" and "False unsafe"

Model	**Same risk assessment outcome**		**False safe**		**False unsafe**	
	OEL	DNEL	OEL	DNEL	OEL	DNEL
ECETOC TRA	16	8	3	4	9	4
Stoffenmanager®	15	10	0	0	13	6
ART	14	10	1	1	13	5
ART B	16	12	0	1	12	3

Risk management according to REACH

We compared the RCRs between observed scenarios, studied at the work site, and registered scenarios within the REACH legislation. In general, the observed RCRs are much lower than the registered RCRs. This is not surprising since the registered scenarios are supposed to be generic and include a variety of scenarios; hence worst case is registered to ECHA. However, even though the registered scenarios are worst case, still about 12 % of the observed adjusted scenarios had RCRs above 1 when using Stoffenmanager®. The Mann Whitney U tests showed that both DNEL and vapour pressure were significantly different ($p < 0.001$) between observed adjusted scenarios above and below 1 when using Stoffenmanager®. For the observed adjusted scenarios with RCR above 1, median of the DNEL was 1 and median vapour pressure was 2500 Pa while it was 24.5 and 89 Pa respectively for the observed adjusted scenarios below 1. The correlation between the observed RCRs and the registered RCRs were lower than the correlation between the RCRs based on the different models themselves.

Discussion

General discussion

In the studies of this thesis the usefulness of exposure assessment models estimating exposures at workplaces have been investigated. To be able to work with chemicals without experiencing any adverse health effects, it is crucial to have proper risk assessments and managements in place. The golden standard of risk assessment of occupational exposures is performing exposure measurements and relates the exposure to a limit value. However, this is costly, time consuming and requires experts in the field of occupational hygiene. Even if companies could afford exposure measurements to be carried out, it is not reasonable that all exposures to every chemical should be measured. One way to handle this was to develop control banding tools and then exposure assessment models to help companies coping with demands of risk management of occupational exposures. Today, the REACH legislation is also recommending models to perform exposure scenarios with instructions for safe use for the downstream users to follow. The big question here is what happens when risk assessments are based on models - can the outcome be trusted or are we starting to build our risk assessments on loose grounds?

Studies on exposure assessment models need to be carried out to learn about how and when they work and how to handle any possible problems. At workplaces, it is often not possible to measure all exposure situations; then models can be useful to distinguish between exposure situations that might have a higher risk from those which do not. Studies evaluating the validity of accuracy and precision of the models and the reliability between users are of great importance and that is what this thesis has been focusing on. Before discussing our results in more detail, one should keep in mind that models are models and could never, and are never expected to, give the exact accurate outcome. Models are wrong, but could still be useful as George Box would say (59). The model developers need to continue develop the models and recalibrate them when new representative data is available to increase the accuracy as much as possible. It is not recommended that exposure models should replace exposure measurements; they should work as a complement.

The models may either underestimate the exposure or overestimate it. To handle this uncertainty (but also to handle the variability), the worst-case estimate (90th percentile) could be used. This can be thought of like an easy way to handle the uncertainty, just overestimate the exposure and everything will be fine. However, if the models overestimate the exposure too much, it may have some negative effects. First, it could make companies install unnecessary control measures or personal protections. And second, if companies start to install these control measures that aren't needed it might affect the safety culture at the work places, if workers acknowledge that these measures are unnecessary and start to question other control measures that really are needed. This may lead to "normalisation of deviance" which is a term describing the phenomenon when several small steps increasing a risk are taken from the normal procedure and in the end becoming part of the normal procedure (60). Such normalisation of deviance could have a negative effect on workers' health and should be considered as a serious issue. If the increased risk had been observed at once, it would not become a part of the normal procedure. The normalisation of deviance concept is one reason why finding a balance in how much the models should overestimate the exposure is important.

Reliability

The reliability of Stoffenmanager®, when 13 users modelled the same exposure situations, was studied in **study I**. The results showed that the variability was large between the users, which is in compliance with Lamb *et* al. (2017) and Schinkel *et* al (2014) (30, 31). Low reliability between users when modelling the exposure is an important issue that needs to be dealt with, if models are used as an alternative for estimation of occupational exposures. If the reliability is low, it does not matter how accurate the model estimates the true exposure; the probability that the true exposure will be estimated is still low. However, there are some practical things that could be done to improve the reliability. When using the model, it is recommended that at least two users decide the input parameters through discussion. In this way, misunderstandings and uncertainties may be reduced. Moreover, in Stoffenmanager® and ART, one can print out a report showing all colleagues which input parameters that have been chosen. The model developers can help the users to increase the reliability by giving clear instructions and guidance within the model. To increase the reliability, it is also recommended that proper training should be arranged (31).

In our study, some input parameters chosen by the users had lower agreement with the consensus assessment: personal protection, material shaping, type of task, inspection and maintenance of machines, control measures, and breathing zone. The input parameters that showed the greatest impact on the outcome between our users were type of task, breathing zone, ventilation, and control measures. When combining these results, type of task, breathing zone, control measures and personal protections are input parameters of higher concern when modelling the correct exposure situation.

Lamb *et* al. (2017) also showed that type of task was an input parameter that varied more than others. Type of task is difficult to assess because the nature of a job often consists not of only one assignment at a time but multiple ones. Some users want to model the worst case exposure source while others models the source closest to the worker. We only studied the reliability of Stoffenmanager®, which do not distinguish between types of task of near and far exposures (if there is a far-field exposure, only the same type of situation could be assessed). This may be a problem if the far-field source is from another type of task; then some users will have trouble choosing which emission source to model. This depends of course on how complex the work environment is. If the work environment for example has three workers, all working with the same type of chemicals but with different tasks and with different distance to the source the variation between users may vary even more if the user can choose different tasks of near- and far-field exposures as in ART.

One input parameter was if the worker was in the breathing zone of the emission source or not and is answered by yes or no. This information has a large impact on the outcome of the model. Multiple tasks performed simultaneously during a working day may explain the difficulty in choosing whether a worker is working in the breathing zone of the emission source or not. Especially when working in production lines, a worker may be 50 % of the time in the breathing zone but the other 50 % behind a computer or collecting material for the line. This may be a reason for the high variation of answers. It would be desirable with answers to be more of a gradient than simply yes or no.

For control measures, there are several alternatives available. One issue that might be a reason for answering differently, regarding for example the presence of local exhaust ventilation (LEV), may be that the model users interpret the usefulness of the LEV differently. It is not enough that a LEV is present; it also needs to be effective and close enough to the emission source to reduce the exposure as much as the model is taking into account. This might be one reason why our model users have chosen different answers. However, this issue may be dealt with through training and clear explanations in the model of when to include control measures in the estimations.

For personal protection, there are several alternatives to choose from and the choices have large impact on the outcome. It may be hard to choose between the alternatives, due to lack of information about the protection, some of the alternatives are close to each other. Sometimes, even the workers themselves do not know what type of personal protection they wear. However, the alternatives that are closely related are also close in their reduction factor in the equation and it will not affect the outcome much. Maybe pictures presenting the alternatives of personal protection devices could be helpful to the model users.

Model accuracy and level of protection

Since the results of **study I** showed large variability between users, 2 hygienists were doing all the assessments in the rest of the studies. This was arranged to increase the reliability of between users' assessments.

In **study II,** the accuracy of Stoffenmanager® and ART was studied by comparing the distributions of the models with the distributions of the measured exposures. The lack of agreement between the 50th percentile of the models and median exposure measurements was also examined as to bias and precision.

When comparing the distributions, Stoffenmanager® has a factor of about 10 between the 75th and 25th percentiles, while ART has a factor of about 180. This must be kept in mind when comparing the distributions, since a wider distribution increases the possibility of overlapping distributions. However, for Stoffenmanager® 12 exposure situations of 29 had separated distributions and 7 of these were underestimating the exposure. The bias for liquids of 0.22 indicates a general overestimation of exposures and the bias for solids of -0.024 indicates a small underestimation. Hence, Stoffenmanager® underestimated the exposure in more situations but when overestimations were performed, they were numerically larger than the underestimations. Other investigations (32, 37), studying the accuracy of Stoffenmanager®, also reported overestimations of liquids (factor 7.5 for organic solvents and 1.5 for pesticides when using the 90th percentile of Stoffenmanager®). Another study reported an underestimation of dusts (bias = -0.28 for handling powders and granules). A study by Schinkel *et* al. (2010) (38) presented a bias of -0.42 for overall liquids and -0.9 for overall solids. One reason why our study presented a positive bias may be because we had more exposure situations with low measured exposures; when studying the modified Bland Altman plot (Figure 5) in **study II,** one can see a tendency of Stoffenmanager® to overestimate exposures with low measured exposure and underestimate exposures with high measured exposure. But in general, it seems that Stoffenmanager® estimates solids lower than liquids.

With ART, most of the separated distributions underestimated the exposure, which also was shown in the bias of -0.55 for liquids and -1.4 for solids. Other studies focusing on the accuracy of the ART model concluded that ART overestimated the exposure for liquids with a factor of 1.3 and underestimated with a factor of 0.15 (organic solvents and pesticides respectively) (32). However, that study studied the 75th percentile of ART, and one may suspect that when using the 75th percentile, the result of an overestimation with a factor of 1.3 might be an underestimation, if the 50th percentile would have been used instead. Savic *et* al.

(2017) (39) studied the accuracy of ART and concluded, that ART overestimated exposures with low measured exposure and underestimated exposures with high measured exposure for liquids, solids and powders. This was only shown weakly in our study for exposure situations concerning solids. They also presented a positive bias for liquids but for solids and powders the biases were negative (39). Our study also showed that ART was negatively biased, most because of the exposure situations concerning dusts. McDonnell *et* al. (2011) studied the dust algorithm of ART and also, they found that most biases (depending on type of task, dusts and presence of control measures) were negative (40). According to these studies, it seems that also ART estimates solids lower than liquids.

The tendency of the models to overestimate the exposures with low measured exposure and underestimate the exposure with high measured exposures is obviously a problem. This is especially true when the models underestimate the exposures of high measured exposure, which could lead to false safe exposure estimates at workplaces. However, in **study II** we used the 50th percentiles of the models and not the 90th percentiles as recommended by model developers and ECHA. And one way that might help handling the underestimations is the usage of the 90th percentile, but only if the underestimations aren't too large.

In **study III,** we examined if the 90th percentiles are still underestimating the high exposures**.** In this study we also included ECETOC TRA which couldn't be included in the former study, since it does not provide a 50th percentile outcome. It was surprising to find that ECETOC TRA had a level of protection of 31 %, according to our dataset. This means that 31 % of the measured exposure exceeded the estimate exposures, which would correspond to the 70th percentile. Since ECETOC TRA is recommended as a Tier 1 exposure model by ECHA and therefore should be generic and protective (overestimate the exposure), one may question if ECETOC TRA is protective enough. Our study showed similar result as the previous study by van Tongeren *et* al., who reported a level of protection of 32 % for volatile liquids and 21 % for powders for ECETOC TRA (33). Other studies reported an overestimation of exposure in general, when comparing the median measurements with default outcome of the model (32, 34, 36).

For Stoffenmanager® the level of protection according to our study was 17 %. Since we used the 90th percentile outcome, it would have been ideal that only 10 % of the measurements exceeded the estimations. However, when studying the scatter plot (Figure 1) in **study III,** one can see that the situations underestimating the exposure is close to the 1:1 line and regards exposure situations with high measured exposures, that the model also underestimated in **study II**. These results may affect the risk assessments performed at work places and false safe situations may be accepted. This could affect workers health. However, when using the 90th percentile, one has accepted that 10 % of the measured exposure should be above the modelled exposures. This is considered to be an acceptable risk. Our findings are in concordance with earlier studies such as van Tongeren *et* al. (2017), reported that 24 % of measured exposures exceeded the modelled outcome for non-volatile liquids. For volatile liquids, it was 12 % and 3 % for powders. Koppisch et al. (2012) reported that 11 % of measured exposures exceeded the modelled outcome for exposure situations handling powders and granules. These results indicate, that Stoffenmanager® has a higher level of protection than ECETOC TRA and is therefore better to use as a Tier 1 model.

For ART, only 3 % of the measured exposures exceeded the modelled outcome. This result makes ART the model with highest level of protection, according to our data. In **study II,** ART tended to underestimate the exposure and therefore one may expect ART to be less protective. But in **study II** we used the 50^{th} percentile without taking the uncertainty (95% Cl) into account. In **study III,** we used the 90^{th} percentile and included the 95% Cl, which made the model highly overestimate the exposure. This high overestimation may cause problems of unnecessary instalments of control measures, which may also affect the safety culture on a work place.

Risk assessment and management

In **study III,** we studied different risk assessment approaches, where hazards were based on OEL or DNEL, and the exposures, were either modelled or measured. When comparing modelled exposure in relation to OEL with measured exposure in relation to OEL, we grouped the outcome in one of three groups "same risk assessment", "false unsafe", and "false safe". It is not surprising, that Stoffenmanager® and ART had as much exposure situations in the "false unsafe" group as in the "same risk assessment outcome" group, since the models had higher levels of protection. Moreover, since ECETOC TRA was shown to be less protective, nor is it surprising, that more exposure situations were found in the "false safe" group for this model. Hence, the risk of accepting false safe exposure situations within the REACH legislation might increase when using ECETOC TRA. Stoffenmanager® had no exposure situations in the "false safe" group. When comparing the modelled and measured exposure to OELs we used the breakpoint of 0.3 (cut-off line between safe or unsafe situation) since HSE recommended this for OELs. One way to lower the level of exposure situations in the "false unsafe" group, might be to use the breakpoint of 1 instead. This will decrease the number of situations in this group from 47 to 35. The result that ECETOC TRA had more exposure situations in the "false safe" group is a serious consequence of its low level of protection. According to the results in this thesis, ECETOC TRA should not be recommended as a Tier 1 model within REACH.

In study **IV,** we used the three models ECETOC TRA, Stoffenmanager® and ART to calculate RCR values, when observing how the chosen chemicals were handled at three companies. We compared the observed RCRs with the RCRs registered to

ECHA. One of the key findings was that the observed scenarios do not follow the registered scenarios, meaning that the observed scenarios are specific and have much lower RCRs than the generic registered scenarios. Interestingly, even though the observed adjusted scenarios, in general, had much lower exposures, 12 % of exposure scenarios using Stoffenmanager® had RCRs above 1 (which is not allowed according to REACH). It is also interesting, that the observed adjusted scenarios (taking instructions of control measures and personal protection in the ES into account) with RCRs above 1 are from different scenarios when using Stoffenmanager® or ECETOC TRA. The observed adjusted scenarios with RCRs above 1 had two things in common: higher vapour pressures and lower DNELs. The difference between the groups of RCRs above and below 1 was statistically significant (tested with Mann Whitney U test $p<0.001$). Lower DNEL values (and then often lower OELs) may result in lower exposure, if the companies working with chemicals follow the legislation. If then, in combination with the higher vapour pressure (estimating higher exposures by the models): it is not strange that the RCR value can be above 1. The fact that different exposure models give different conclusions about the exposure scenarios is troublesome and could lead to both different instructions to workers and it could lead to accepting false safe exposure scenarios. These results indicate that the system of generic exposure scenarios has low robustness. The correlations between the observed RCRs themselves are higher than the correlation between the observed RCRs and the registered RCRs which reflects that the registered scenarios are not in concordance with the exposure situations at the work sites. These results question the benefits (very generic, high level of protection and the responsibilities for the manufacturer or importer to EU) of generic exposure scenarios, based on exposure models. One recommendation could be that the exposure scenarios should not be done in a generic way by the supplier but on site by the company itself with the support from the supplier. The supplier knows the chemical but the downstream users have the knowledge about the environment on the floor. Another recommendation could be that the information about the use of chemicals between downstream users and manufacturer or importers needs to be strengthening to improve the work with exposure scenarios and PROCs.

It could also be recommended that Stoffenmanager® should be used as a Tier 1 model, since it identified more false safe situations according to **study IV** and has a higher level of protection according to **study III.** When exposure situations handle chemicals with low DNELs in combination with high vapour pressures, exposure models should be used with caution.

Strengths and limitations

In the 4 studies, we have examined exposure assessment models and we have had the benefit of estimating the exposures while visiting different work places. For **study I, II** and **III** the largest strengths were, that we (including the 13 users) visited all the work places and studied the exposure situations at the same time. In other studied presented, users may have had to interpret the exposure situations from texts or videos. For the same studies, one weakness was the number of measurements. Chemical exposures have a variation and by performing multiple exposure measurements of one exposure situation, this variation can be detected. If too few measurements are performed the measured median exposure could be wrong. In our studies, we performed about three exposure measurements with at least one week between the occasions to include some of the variations. More measurements would be desirable but could not be accomplished.

When studying the reliability of Stoffenmanager® in **study I**, the users did not assess the vapour pressure or level of dustiness by themselves. This information was provided by the authors of the study. The variation would probably be larger, if the users also had to assess these input parameters, since it was experienced from our other studies, that information concerning these parameters was sometimes lacking or different, depending on source.

Another limitation about **study II** and **III** is the number of exposure situations. When doing validation studies of exposure models, it is good to either only evaluate one part (algorithm) of the model at the time or have enough situations to cover all tasks, all control measures or all algorithms within the model. The later alternative is hard to accomplish, which is why different independent studies must be carried out to get a whole picture of the status of the exposure models. Hence, the results of our studies need other study results, before any specific conclusions can be drawn.

For **study IV,** the greatest strength was again the visits at the work places, studying the exposure situations and also that we could get access to the e-SDS from the companies. One limitation was, that no exposure measurements were conducted, which will leave out the “truth” about whether the exposure scenarios with RCR above 1 was a true risk or not.

Future perspectives

To increase reliability between users, it is recommended that the users carry out appropriate training. Perhaps a certificate could be needed before users could start working with the models. The course needed to receive a certificate could be performed as a webinar. The model developers could also increase the understanding by clear instructions and guidance. Studies with aims to investigate how information reaches the users in the best ways could help.

To improve the accuracy of the models, more studies are needed. Studies focusing on chemicals with low measured exposures (maybe chemicals with low vapour pressures) and chemicals with higher measured exposures (maybe chemicals with high vapour pressures or where the tasks generate higher emissions) could help developers handle the problems seen in several studies. The development of the models should also continue; in particular recalibrations based on new exposure measurements, should be performed, since the exposure patterns might differ from older measurements and the techniques at the workplaces develop. Hence, more exposure measurements must be executed.

The exposure scenarios, based on exposure models according to the REACH legislation, needs further evaluations. Our study indicates, that the generic exposure scenarios do not reflect the observed exposure scenarios, studied at the workplace. It would of course be very valuable, if exposure measurements could be performed in a study like ours to give even more information about what really are false safe situations at the workplaces. Studies focusing on the chemicals with low DNELs and/or high vapour pressures should be carried out to find out if exposure models are fit for such substances at all. Maybe users should have a similar mind set like when using control banding tools; exposures of chemical of high concern (CMR-substances, very low OEL/DNEL) should be assessed by experts and not by models.

Generally, chemical exposure should be dealt with in a wider perspective than just making sure an exposure is below a limit value, which should be minimum demands. The models and the REACH legislation do not, for instance, take into account the effect of exposure to mixtures of chemicals. One chemical at a time in defined situations does not correspond to the average work environment. Studies evaluating the risks of mixtures and how to cope with this are needed. The companies should continuously aim at lowering the exposure to chemicals little by little, both for those that are already below a limit value and for those that do not have any limit values. Maybe occupational exposure assurance systems (like quality assurance) should be mandatory for companies working with harmful chemicals.

Conclusions

From the results presented in this thesis the following conclusions can be drawn:

I. The reliability between multiple users using Stoffenmanager® 5.1 was low.

II. Stoffenmanager® 5.1 showed lower agreement when assessing situations with high measured exposures (Stoffenmanager® underestimated the exposure) and low measured exposures (Stoffenmanager® overestimated the exposure).

   ART 1.5 underestimated the exposure in general, which may be systematic as indicated by the calculations of mean difference and precision.

III. The outcomes from the control banding part of Stoffenmanager® presented risk assessments that in general were in the same or higher than the risk assessments based on measurements. Only 2 exposure situations had higher risk based on exposure measurements.

   ECETOC TRA 3.1 had a lower level of protection than Stoffenmanager® 5.1, ART 1.5 and ART B 1.5. This may give a higher risk of accepting false safe situations when using ECETOC TRA.

IV. ECETOC TRA 3.1 had higher number of false safe situations than Stoffenmanager® 5.1, ART 1.5 and ART B 1.5. This might lead to the acceptance of false safe exposure scenarios attached to the safety data sheets. A much higher number of false unsafe situations were presented, this may cause two problems. It could lead to expensive unnecessary investments of control measures, and it may lead to normalisation of deviance which could affect the safety culture at the work place negatively.

V. In general, the observed RCRs had lower calculated exposure than the registered RCRs. However, the number of false safe situations was about 12% when using Stoffenmanager® 6.0. The scenarios with observed RCRs above one when using Stoffenmanager® had significantly higher vapour pressure and significant lower DNEL-values in comparison with scenarios with RCRs below 1.

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