Workshop, 20th October 2020

«Theoretical Background and Application of Occupational Exposure Models»

Background and Scope

ISES Europe identified exposure modelling as one of the major issues for the strategic development of exposure science in Europe for the next years (see e.g. Fantke et al. 2019 and Bruinen de Bruin et. al., 2019).

The aim of this workshop is therefore to discuss the main challenges in developing, validating and using occupational exposure assessment models for regulatory purposes. Various exposure modelling approaches will be introduced and the theoretical background, application and limitations will be presented and discussed. Workshop participants shall engage in the discussion of the applicability of some of the currently available models with the aim to reach a common understanding of the benefits and limitations of the different ways of exposure modelling. In this workshop the ongoing discussion about parts of the theoretical background and applicability of some frequently used tools/models (i.e. ART and STOFFENMANAGER®) as well as the mass-balance based modelling approaches shall be addressed. This discussion highlights the importance of occupational exposure models for regulatory purposes and is extremely relevant to exposure science.

Modelling of occupational exposure

For this reason, the ISES Europe Exposure Models Working Group has taken the initiative to organize this workshop in order to have an open scientific exchange with the aim to discuss the issues mentioned above. For some questions, it shall be attempted to develop a common understanding and draw a roadmap towards future exposure modelling initiatives. To reach this, the workshop shall be characterised by mutual trust and respect for the competence and work of all the scientists, regulators and other participants involved in the workshop and in exposure modelling.

The Editorial 'How Accurate and Reliable Are Exposure Models?' in the Annals of Work Exposures and Health (Fransman, 2017) provided an overview of the current status of regulatory occupational exposure models. In that issue of the Annals, several authors report on the validation of Tier 1 exposure models used in the context of REACH. The papers in this issue of the Annals show that the efforts of the occupational hygiene and exposure science communities to develop useful generic exposure assessment approaches and models have given exposure assessors tools to deal with risk assessments under REACH. However, the results of evaluating these models are worrisome and considered far from perfect. Therefore, modelling results need to be interpreted with caution and more knowledge is needed about different aspects of these models (e.g. model functionalities, applicability domains, uncertainties) to be able to apply these models in a meaningful way.

In addition to the different modelling tools, the workshop shall also discuss other main questions with the aim to introduce both mechanistic and empirical modelling approaches, describe basic features of these approaches, identify their advantages and limitations and classify the reliability of the results.

A number of scientists prepared this workshop collaboratively and will present the highlights: Susan Arnold, John Cherrie, Wouter Fransman, Natalie von Goetz, Henri Heussen, Joonas Koivisto, Dorothea Koppisch, Jessica Meyer, Urs Schlüter.

Natalie von Goetz will chair the workshop; Urs Schlüter will be the co-chair.

It should be clear that a workshop like this can be only one step in this discussion. It is neither the first step as this discussion is on-going for quite some time already, nor can it be the final step as more steps are needed that might be identified during the workshop and need to be initiated as a consequence of this workshop.

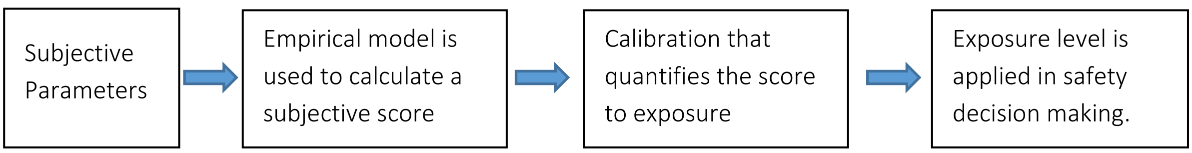
1. Concept of STOFFENMANAGER® and ART

STOFFENMANAGER® and ART are based on a source receptor modelling approach (Cherrie et al., 1997) that has been successfully used in exposure assessment for epidemiological exposure evaluation (Yu et al., 1990; Schneider et al., 1991; Smith et al., 1991; Armstrong et al., 1996; Lewis et al., 1997). This method can be used to predict exposure levels in a similar exposure group (SEG) when relevant exposure modifying factors are quantified individually for each SEG. Quantification is possible by using historical measurement data and contextual information. The modifying factor value is quantified by measuring the change in exposure level over time when a new practice is adopted. The baseline exposure level can be corrected to reflect an exposure level in another exposure scenario by using principal modifying factors. This method can be applied for the SEG with the same principal modifying factors.

STOFFENMANAGER® and ART apply this modelling approach by setting multipliers for the principal modifying factors, calculating a score by using the approach in previously mentioned references and then converting the score to a concentration by using a calibration curve. Modifying factors are based on chemical and physical laws; and in addition, empirical data obtained from literature were used. Where this was not possible, expert “elicitation” was applied for the assessment procedure. Multipliers for all modifying factors were peer reviewed by leading experts from industry, research institutes, and public authorities across the globe. In addition, several workshops with experts were organized to discuss the proposed exposure multipliers. The calibration factor is assigned by comparing the measured exposure levels with the output score that is calculated by using the contextual information registered during the measurement. The calibration factors are assigned for four different exposure groups (Tielemans et al., 2008; Schinkel et al., 2011). In total more than 2,000 good quality measurements were available for the calibration of the mechanistic model. The calibration showed that after calibration the mechanistic model of ART was able to estimate geometric mean (GM) exposure levels with 90% confidence for a given scenario to lie within a factor between two and six of the measured GM depending upon the form of exposure. A random scenario and company component of variance were introduced to reflect the model uncertainty.

According to Koivisto (e.g. Koivisto et al. 2019) this methodology raises the following questions:

- In calibration factor assessment,
  - How does the model parametrization depend on the measurer interpretation of the work environment and interpretation of the registered contextual information by the modeller and the expert review panel?
  - How was missing contextual information estimated (e.g. handling energy factor)?
  - How do different interpretations and decisions effect the calibration factor?
- This empirical modelling approach was shown to work well when applied in SEG where principal exposure determinants are the same. STOFFENMANAGER® and the ART calibration is made for four exposure groups while in reality there are thousands SEGs. How does mixing of different SEGs effect on the use of calibration factors (see e.g. Table 2 in Tielemans et al., 2008)? For example, how do calibration factors using pharmacies, bakeries and woodworking industry reflect to cement handling?
- On what basis are STOFFENMANAGER® and the ART defined as quantitative models (e.g. Cherrie et al., 1996, 2020; Tielemans et al., 2008; Schinkel et al., 2010; Koppisch et al., 2012; Sailabaht, Wang and Cherrie, 2018) when the physical meaning of some equations or parametrization is not entirely clear?
- Empirical exposure model is based on SEG. STOFFENMANAGER® and the ART mixes different SEGs. Is it justified to call them as empirical models when the fundamental logic is different?
- How can a model output be called quantitative when input parameters are subjective decisions? A very simplistic presentation of the logic of this approach is offered in the scheme below.

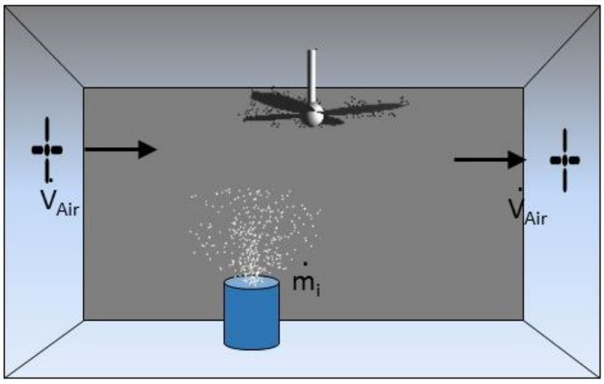


A very simplistic schematic way of describing the development of the ART and STOFFENMANAGER® models that is not meant to present all the scientific knowledge underpinning the models.

- How accurately can a user select a correct modifying factor value, e.g. handling energy factor or emission rate, by interpreting descriptions without physical quantification (e.g. what is emission rate in “cleaning of small objects like knives” with a score of 0.3)?
- Model validation is traditionally considered as comparing the model outputs with theory. How does one evaluate the validation of expert systems models that do not directly follow physical principles?

2. Potential limitations that apply to exposure assessment models (physical/mass balance...)

Since the introduction of the REACH, various risk/exposure assessment tools have been developed and even more tools are currently used for chemical safety assessments. Since the start of the REACH Registration period in 2008, more than 100 000 registrations for more than 23 000 substances had been submitted to ECHA. The European occupational hygiene community will not be able to collect a sufficient number of exposure measurements to obtain exposure estimates for all relevant workplace exposure scenarios. It is also not possible for exposure scientists to develop for each relevant scenario mass balance models. Therefore, a tiered approach was developed for risk assessments in the REACH framework. In order to cover the different aspects of modelling in a tiered approach the workshop should also address limitations that apply to the various exposure assessment (physical / mass balance) models, e.g.:



Example for a “mass balance situation” in a room

- Mechanistic models are often complex, how can users grasp the complexity of such models (e.g. unknown source code, numerical/mathematical simplifications)?
- Not all parameters are well communicated and documented in mechanistic models, how should users deal with parameters that are difficult or impossible to measure? Is it possible to identify “key parameters” for mechanistic modelling for different exposure scenarios?
- All models, including mechanistic models, make simplified assumptions. What effects can such simplifications have? How to estimate systematic error of the simplification? How can we deal with such simplifications?
- Results of mechanistic models also depend on the availability and quality of measured data and input parameters. Is the approach of mechanistic models superior or are the uncertainties similarly high regardless of the type of model?

- How can mechanistic models cover input parameter ranges or exposure ranges occurring in reality?
- Input parameters often depend on each other (e.g. larger treated surfaces results in higher amounts of used chemicals), how can mechanistic models prevent illogical user input when inter-depending parameters are mandatory input for model?

3. Requirements for the validation of models

Different opinions exist about the meaning of the term “validation”. One possible meaning (Tischer et al. 2017) is: Validating a model means checking, if the

a) concept and the theory behind it is sound or generally accepted,
b) output is accurate and precise,
c) tool in which the model is imbedded is user-friendly and
d) between-user reliability is not too high.

In order to check if the concept and theory are sound it has to be examined if information on the model background, the used principles and all methods used to derive the model equations are well documented and publicly available. Only then, it is possible to decide if the model is based on scientifically approved principles. It is also important to look, if the applicability domain is well described by the model developers.

Whether a model output is accurate and precise can be answered by comparing the tool estimates with an independent set of measurement data (Tischer et al., 2003; Tielemans et al., 2011; Landberg et al. 2017) ideally covering a wide range of exposure scenarios and agents. Many validation studies for models examine the correlation coefficient between measured and modelled values or bias and precision (Schinkel et al. 2010; Landberg et al. 2017). The latter quality criteria are taken from Bland and Altman (2010) and are meant for the comparison of two measurement methods applied at the same time to the same subject, thereby expecting the same value. However, considering the variability of exposure as well within one worker between different days as between different workers or even between different companies with different local situations it is questionable if these quality criteria are adequate for the comparison of measured exposure with modelled exposure.

Additionally, Tier 1 model estimates for regulatory occupational exposure assessment are supposed to be conservative. Therefore, some validation studies in this field look for the percentage of measurement values exceeding the modelled exposure (e.g. Schinkel et al. 2010; Koppisch et al 2012). Van Tongeren et al. (2017) defined conservatism of a model as high, when less than 11% of measurements exceeded the tool estimate; medium, when 11 to 25% of measurements exceeded the estimate; and low, when more than 25% of the measurements exceeded the estimate. This approach, which incorporates the between- and within-worker variability in the validation process, has to be considered when compiling standards for model validation.

User-friendliness of a tool is often tested by telephone interviews, questionnaires or workshops. The between-user reliability can be evaluated by asking a group of users to estimate independently different exposure scenarios giving them the same description of work places and then comparing the individual results (Lamb et al. 2017).

- Can we define minimum standards of model validation?
- Which institution is in the position to independently assess the level and quality of validation for models?

4. Special requirements for regulatory exposure modelling

A number of tools (amongst others STOFFENMANAGER® and ART) are widely accepted in regulatory exposure assessment for different regulatory frameworks. ECHA recommends some tools for exposure assessment in the framework of REACH or biocides and EFSA for e.g. plant protection products. In chemical risk assessment, understanding the model and model output is needed to assess the reliability and applicability of the result. Proper knowledge of exposure determinants, i.e. proper model parametrization, is a key to efficient and well-justified predictive chemical safety decision making. Further model development requires international collaboration to meet needs of chemical safety assessment criteria globally.

- What are the criteria for regulatory exposure models?
- What level of over- or under estimation is acceptable to our community, i.e. what precision is needed for well-reasoned chemical safety decision?

5. Final discussion based on the following four key questions

- How can we promote validation exercises for models?
- How can we further develop exposure assessment for regulatory purpose?
- In which regulatory questions can we use exposure assessment models?
- What has to happen so that exposure assessment models are improved in the future?

Terminology and definitions

There are several issues with terminology. It would be worthwhile to develop a common understanding about different expressions and terms, their meaning and use. For example, STOFFENMANAGER® and the ART are called mechanistic models, which is in line with the WHO (2005) definitions for exposure model categorization (Table below). According to WHO (2005) "*Mechanistic exposure models are built on laws of physics and chemistry and data on behaviours and factors influencing exposures*".

Table Model categories according to WHO (2005).

	Mechanistic	**Empirical**
Deterministic	Mathematical constructs of physical/chemical processes that predict fixed outputs for a fixed set of inputs.	Statistical models based on measured input and output values (e.g. regression models that relate air concentrations and blood levels of a chemical or ambient pollutant concentrations with personal exposures).
Stochastic	Mathematical constructs of physical/chemical processes that predict the range and probability density distribution of an exposure model outcome (e.g. predicted distribution of personal exposures within a study population).	Regression-based models, where model variables and coefficients are represented by probability distributions, representing variability and/or uncertainty in the model inputs and parameters.

Another example is the term "tiered approach". A tiered modelling approach could mean that the level of conservativism reduces as the tier level increases. This is for example caused by more precise parametrization and by increasing the number of physical processes in the model. On the other hand, current ECHA recommended models do not have this logic, but higher tier exposure models can overestimate the exposure more than lower tier exposure models (see e.g. Spinazzè et al. 2017).

- Is it worthwhile to agree on a common terminology regarding models and modelling? Possible terms that would profit from such an agreement would be e.g.: "subjective", "(semi-)quantitative", "mechanistic", "source-receptor", "empirical", "validation", …
- Can we agree on a harmonized classification into Tiers of the various exposure assessment models?

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