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Letter to the Editor

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Letter to the Editor

Response Letter to Koivisto *et al*. 'Evaluating the Theoretical Background of STOFFENMANAGER® and the Advanced REACH Tool'

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Abstract

In this article, we have responded to the key statements in the article by Koivisto *et al.* (2022) that were incorrect and considered to be a biased critique on a subset of the exposure models used in Europe (i.e. ART and Stoffenmanager®) used for regulatory exposure assessment. We welcome scientific discussions on exposure modelling (as was done during the ISES Europe workshop) and criticism based on scientific evidence to contribute to the advancement of occupational exposure estimation tools. The tiered approach to risk assessment allows various exposure assessment models from screening tools (control/hazard banding) through to higher-tiered approaches. There is a place for every type of model, but we do need to recognize the cost and data requirements of highly bespoke assessments. That is why model developers have taken pragmatic approaches to develop tools for exposure assessments based on imperfect data. We encourage Koivisto *et al.* to focus on further scientifically robust work to develop mass-balance models and by independent external validations studies, compare these models with alternative model tools such as ART and Stoffenmanager®.

Keywords: exposure assessment; exposure estimation; exposure modelling; regulatory risk assessment; regulation of chemicals; SMEs

Introduction

Recently, Koivisto *et al.* (2022) published a paper questioning the acceptance of the Advanced REACH Tool (ART) and Stoffenmanager® tools for use in REACH and health and safety regulations. This is not the first time that Koivisto has provided incorrect opinions about the development of ART and Stoffenmanager® (Koivisto *et al.*, 2019) on which a response was previously provided (Cherrie *et al.*, 2020). Following these earlier discussions, the ISES Europe Working Group on Exposure Models recommended that continued discussion should take place outside journal publications, to allow for better information sharing, engagement and explanation. A workshop was held on 20 October 2020, to discuss the main challenges in developing, validating and using occupational exposure models for regulatory purposes (Schlüter *et al.*, 2022). During this workshop, the theoretical background, applicability domain, strengths and limitations of different modelling approaches were presented and discussed, focussing on modifying-factor or mass-balance based as two approaches (Schlüter *et al.*, 2022). The workshop concluded that neither modelling approach was superior to the other approach and that uncertainties in the exposure concentration estimates are high regardless of the approach used. This workshop provided useful insights into the different modelling strategies and identified ways forward to improve exposure modelling in Europe and beyond. After the workshop, some of the participants collaborated on drafting the workshop reporting paper (Schlüter *et al.*, 2022). One of the aims of that report was to help and support further discussion that may arise in the future, building this on a common ground of position, but also to highlight that currently there is no consensus on the best approach for exposure model development. Koivisto and (some) co-authors of the Koivisto *et al.* (2018, 2019, 2022) manuscripts were present during the workshop, openly discussed with the other 70 international participants the challenges of occupational exposure modelling. While Koivisto co-authored Schlüter *et al.*, 2022 he (with co-authors) published at the same time their critique on only a subset of the discussed models (i.e. ART and Stoffenmanager®) (Koivisto *et al.*, 2022). In this letter, we would like to respond to the most pertinent statements that we consider to be incorrect.

Incorrect statements in Koivisto *et al.* (2022)

Koivisto *et al.* (2022) spent a lot of effort on explaining the terminology of exposure models as being mechanistic models, empirical models, conceptual models, source-receptor models, mass-balance models, deterministic models, probabilistic models, multiplicative models, statistical models and combinations of these. In a recent ISES Europe paper (Heinemeyer *et al.*, 2021), a proposal for the definition of a model was simply given as 'A conceptual or mathematical representation of one or more exposure processes. WHO/IPCS (2004, part 2)', which shows that this semantic discussion is irrelevant to the situation. Any model is, by definition, a simplification of the real world situation and every model developer tries to do their utmost to predict exposure concentrations with suitable accuracy based on the available information. The ISES Europe workshop (Schlüter *et al.*, 2022) clearly identified that different modelling approaches exist but also points out that regulatory approved exposure models, as well as Control/ Hazard Banding tools, should be able to be used with a reasonable level of information demand and by a wide variety of assessors who may have varying degrees of knowledge and skills (Schlüter *et al.*, 2022). In particular, model tools also need to be accessible to individuals with limited scientific expertise because these methods are intended to be used by health and safety practitioners and others at company level, including those in small and medium-sized enterprises (Cherrie *et al.*, 2020). The exposure assessments must be able to be performed through user-friendly interfaces, which will lower the risk of entry errors and user-variability in the assessment. For this reason, the developers of ART and Stoffenmanager® have always recommended that proper training shall be provided before the tools are used and they have studied and published the inter-user reliability to warn users of the influence of this important source of outcome variability (Schinkel *et al.*, 2014; Landberg *et al.*, 2015; Terwoert *et al.*, 2016; Lamb *et al.*, 2017;). A helpdesk (Stoffenmanager®), a manual (both tools), YouTube instruction movies (Stoffenmanager®), and consultancy advice (both tools) are provided to help users to make exposure assessments. This very important issue of user training was outside the scope in the Koivisto *et al.*'s (2022) paper and was not discussed (as also clearly mentioned by the authors).

Koivisto *et al.* state in the abstract and in the introduction, that their paper is the 'first study evaluating the theoretical backgrounds of each model'. They later cite a work of Hesse *et al.* (2015) with the title 'Evaluation of Tier 1 Exposure Assessment Models under REACH (E-team) Project - substudy report on gathering of background information and conceptual evaluation'. It is clear from the title as well as the contents of Hesse *et al.* (2015) that it contains a conceptual evaluation. In the course of the conceptual evaluation of Hesse *et al.*, the design of each tool was described, in particular their functionalities and structure of use. Model development and background information were summarized as far as publicly available. The model algorithms were analysed and explained including underlying data and principles.

Koivisto *et al.* state that the ART and Stoffenmanager® are two of the most widely used tools for chemical safety assessment. However, another model (ECETOC TRA) is far more widely used for chemical safety assessment under REACH than ART or Stoffenmanager® (Tischer *et al.* 2017). Remarkably, Koivisto *et al.*'s evaluation does not include this most used exposure assessment tool under REACH.

Koivisto *et al.* mention that 'the multipliers in the ART and Stoffenmanager® exposure assessment models are allocated by expert judgements and that scientific reasoning or link to physical quantities are not reported'. This is incorrect. The developers of both ART and Stoffenmanager® have published all their work and scientific reasoning underpinning the models in multiple peer-reviewed papers (Marquart *et al.*, 2008, 2011; Schinkel *et al.*, 2010; Cherrie *et al.*, 2011; Fransman *et al.*, 2011; Tielemans *et al.*, 2011; van Tongeren *et al.*, 2011; Schinkel *et al.*, 2011; McNally *et al.*, 2014). These publications clearly explain that the multipliers for the modifying factors were derived based on data from available scientific literature, and were also based on chemical and physical laws. Only in instances where physical or chemical laws and measurement data were unavailable to underpin the multipliers, expert judgement was used to derive multipliers for the assessment procedure. This process of model development from available evidence has been clearly described in the above-mentioned peer-reviewed manuscripts, as well as discussed and reported during the recent ISES Europe workshop (Schlüter *et al.*, 2022).

Koivisto *et al.* write 'Stoffenmanager® software assumes that worker is always in the Near Field (NF)'. This is incorrect. In fact, one of the questions in the Stoffenmanager® tool with regards to the process is 'Is the task being carried out in the breathing zone of an employee (distance head-product <1m)?'. If this question is answered with 'no' the exposure estimates are calculated for Far Field exposure.

Koivisto *et al.* state that 'Subjective models (like ART and Stoffenmanager®) cannot be quantified by using a calibration factor, regardless of the calibration database quality. Uncertainty or error analysis of subjectively assigned calibration factors is of questionable value, because these factors depend on the measurer's and calibrators' subjective opinions and interpretations'. It is unclear what Koivisto *et al.* mean by 'questionable value' as the linear mixed effect model objectively shows the model uncertainty (and thus the uncertainty of the calibration). The information of the regression model and its interpretation are not subjective opinions and interpretations but a direct result of a rigorous and objective statistical analysis. A vast array of models in numerous fields of application (climate change, atmospheric concentrations of pollutants, models of aircraft crash risks, models of components within nuclear reactors, models of SARS-CoV-2 transmission, etc.) include parameters that are estimated via calibration to observational data. In the 'What's Important About This Paper' section, Koivisto *et al.* state 'Stoffenmanager® and ART are... models that produce qualitative exposure estimates'. However, both models generate exposure estimates in mg/m³, which are clearly quantitative exposure estimates. Koivisto *et al.* state 'The Stoffenmanager® calibration…was later updated by Schinkel *et al.* (2010) and Koppisch *et al.* (2012)'. While the first part of the statement is true, the latter is not. Koppisch *et al.* (2012) is a validation study without a new calibration of Stoffenmanager®.

Furthermore, Koivisto *et al.* report that the calibration database is not available, which is correct. However, the data used for validation and calibration of the Stoffenmanager® and ART have been published in the peer-reviewed literature (Tielemans *et al.*, 2008; Schinkel *et al.*, 2010; Schinkel *et al.*, 2011), which clearly describe the reasoning behind the calibration of the mechanistic model, and the data that have been used for the calibration and the resulting model algorithms. In addition, part of the aggregated data used for the calibration has been made available as the ART exposure database on the ART model website (www.advancedreachtool.com) since the launch of version 1.5 in 2013 to facilitate the users of the model to use these data for upload into the Bayesian update of the model estimate (Schinkel *et al.*, 2013). In addition, Hesse *et al.* (2015) concluded in their evaluation: 'Both the Stoffenmanager® database and the development of the tool are well documented in different publications and project reports, although it requires some effort for non-experts to understand the model basis'.

In comments on the calibration of ART, Koivisto *et al.* (2022) appear to confuse the underlying exposure model of the ART (Tielemans *et al.*, 2011, McNally *et al.*, 2014), with the calibration model of Schinkel *et al.* (2011). The ART calibration model contains random effects for exposure scenarios (which is critical for characterizing error in the mechanistic model estimate) and company. The underlying exposure model of the ART furthermore contains between company, between worker and within worker sources of variability.

Koivisto *et al.* write that 'pooling of data originating from different types of workplaces (e.g., pharmacies, bakeries, construction) for model calibration violates the empirical model basic principles'. They fail to substantiate this claim and do not define or reference any literature that defines such 'empirical model basic principles'. In contrast to this statement, the authors of this response believe that pooling of (calibration) data is a valuable way of increasing the robustness of empirical models and do not see a violation of any scientific principle by doing so. Later in the main body of the Koivisto *et al.* paper they note for Stoffenmanager®, 'The calibration is performed by using different exposure groups (DEGs), which is inappropriate for multiplicative exposure modeling approaches because it blends exposure data from disparate industries, tasks, and agents. This means that e.g. pharmaceutical powder exposure score is translated to an exposure level (mg/m³) by using a calibration factor assigned by using exposure data from e.g. pharmacies, bakeries, construction industry, and woodworking industries'. This is incorrect. Calibrations were undertaken for four substance classes. For each substance class exposure scenarios were developed from a variety of industries and nested as substance within task within industry group, (i.e. a process involving flour dust in bakeries, a process generating wood dust in sawmills, etc). Datasets were split as necessary to develop relatively homogeneous exposure scenarios. ART scores were subsequently calculated for scenarios through the application of the mechanistic model. A comparison of ART scores calculated for these exposure scenarios with measurement data was subsequently made using a (log-normal mixed effect) calibration model. The scenarios compiled over various industry sectors, with variations in product dilution and composition, processes, in setting (indoors/outdoors), room volumes and ventilation and engineering controls, etc. provide a much wider dataset for the calibration of each of the four substance classes. ART and Stoffenmanager® aim to be widely applicable models and so to properly understand the reliability of the models it is imperative to undertake an assessment that covers a wide range of scenarios. Calibration was achieved using a single parameter, which scales the ART score. What Koivisto *et al.* regard as a conceptual weakness is in fact a remarkable endorsement of the underpinning conceptual model: industry is of no relevance when determinants of the scenario are well described by the model. The fit of the calibration model was assessed and reported in Schinkel *et al.* (2011).

Koivisto *et al.* (2022) cite the US EPA Guideline on Air Quality Models (US EPA, 2003) to support their critique of the calibration approaches of Stoffenmanager® and ART. Specifically: 'Calibration of models is not common practice and is subject to much error and misunderstanding. There have been attempts by some to compare model estimates and measurements on an event-by-event basis and then calibrate a model with results of that comparison. This approach is severely limited by uncertainties in both source and meteorological data and therefore it is difficult to precisely estimate the concentration at an exact location for a specific increment of time. Such uncertainties make calibration of models of questionable benefit. Therefore, model calibration is unacceptable'. This quotation by Koivisto *et al.* cannot be traced in the provided reference (the word 'calibration' is not made at all in this EPA document). The statement concerns the correction of quantitative estimates from an erroneous meteorological model using a dataset of non-representative measurement data—in this case model estimates and measurements have the same units. The calibrations of ART and Stoffenmanager® use a correlation between model scores and measurements of worker exposures (mg/m^3) in order to convert dimensionless scores into estimates of exposure. This calibration is not correcting erroneous predictions, it is a change of scales achieved through multiplying by a constant. Furthermore, Koivisto *et al.* (2022) report that 'subjective models cannot be quantified by using a calibration factor', but no reference is given for this statement. We, therefore, conclude that this is a subjective opinion of the authors and not information originating in the EPA guidelines.

Koivisto *et al.* (2022) write that ART and Stoffenmanager® have not been internally or externally validated, but this is incorrect. Many peer-reviewed publications are available on the evaluation and validation of the ART and Stoffenmanager® models (Schinkel *et al.*, 2010; 2014; Koppisch *et al.*, 2012; Jankowska *et al.*, 2015; Hesse *et al.*, 2015; Landberg *et al.*, 2015; 2017; Riedmann *et al.*, 2015; Lamb *et al.*, 2017; Spinazzè *et al.*, 2017, 2019; Tischer *et al.*, 2017; van Tongeren *et al.*, 2017; Lee *et al.*, 2019a; 2019b; Fransman *et al.*, 2020; Schlüter and Tischer, 2020). These peer-reviewed manuscripts clearly show the extensive efforts made to independently evaluate and validate these exposure models by different research groups all over the world. Furthermore, Koivisto *et al.* (2022) report that the validation procedure (as described by Schlüter *et al.*, 2022; Tischer *et al.* 2017) should follow a specific order of validation (1: conceptual evaluation, 2: external validation, and 3: operational analysis) because if prior validation steps fail, the latter ones are of little use. However, this order to follow for validation has not been mentioned in either Schlüter *et al.*, 2022 nor Tischer *et al.* (2017). In fact, Tischer *et al.* (2017) describe these three different aspects of validation are inter-linked in an integrated approach and not to be used as separate validation steps. We, therefore, conclude that this statement by Koivisto *et al.* is an opinion of these authors and not a binding requirement for validating a model.

Koivisto *et al.* (2022) state that ART and Stoffenmanager® are vulnerable to misuse if the subjective selections and interpretations are manipulated to produce a desired outcome. This is true for any exposure assessment model (including mass-balance models) and not specific for ART and Stoffenmanager®. Furthermore, ART and Stoffenmanager® have limited this potential misuse by producing a report, which can be provided at any inspection and/or verification and makes the choices of the users in the exposure assessment transparent and traceable. In addition, within ART and Stoffenmanager®, new versions of components, products and risk assessments can be created and archived to ensure that no information is lost. Information about products, exposure, risks and workplace-related changes can be retained for future use.

In their supplementary material S3, 'External validation of NF/FF model, STOFFENMANAGER® and ART', Koivisto *et al.* say that 'Stoffenmanager® is not conservative enough for a Tier 1.5 tool and underestimates exposure levels'. To prove this, they tried to reproduce the exposure scenarios from a NF/FF model evaluation study from Spencer and Plisko (2007) with Stoffenmanager®. As a result of their calculations, they state in the supplementary material that 'STOFFENMANAGER® underestimated by 15% to 51% when using the 50th percent percentile'. However, Stoffenmanager® gives the 90th percentile of the exposure distribution as conservative output to the users. In the calculation from Koivisto *et al.* the 90th percentile would overestimate the worst-case nearfield measurement from Spencer and Plisko about 4.5 times (445%). In addition to this, in their Stoffenmanager® calculations, Koivisto *et al.* made an incorrect assumption about the working conditions. They assumed that in a one-hour disassembling process of a 5.08 cm, Class 125 Iron Body Gate Valve, where cyclohexane was squirted on the parts, no period of evaporation and drying occurs. A recalculation of the exposure with Stoffenmanager®, assuming a period of drying and evaporation, leads to a 50th percentile of 133 mg/m^3 instead of 116 mg/m^3 calculated by Koivisto *et al.* for the cyclohexane concentration in the nearfield. Furthermore, Koivisto *et al.* use in their supplementary material the 75th percentile of ART because they claim that ART does not report the 50th percentile. This is incorrect. In ART multiple percentiles of the exposure distribution (including 50th percentile) can be chosen by the user (www.advancedreachtool.com).

Koivisto *et al.* (2022) start their conclusion with the statement (without any additional external evidence nor validation data underpinning their opinion) that 'STOFFENMANAGER® and ART have been validated at the 'operational analysis' level. However, their theoretical backgrounds have not been validated and the models' structures and parametrizations are not well understood'. However, their conclusions do not take into account the scientific background (peer-reviewed papers) on model background, structure, parameterization, validation, and evaluation in Europe on which the development of these models is founded. We consider the Koivisto *et al.* (2022) to therefore be an opinion piece rather than a scientific research paper.

Conclusions

The ISES Europe workshop (Schlüter *et al.*, 2022) outlined that 'it is an unanswered question if one modelling approach is superior to other approaches or if the uncertainties are similarly high regardless of the type of approach'. They also report that 'the workshop participants identified a number of necessary actions for modelling approaches (be it mass-balance based or modifying-factor approaches), which could improve the estimation of occupational exposure for regulatory purposes'. Besides the challenge of finding representative contextual input data of work environments, one of the main expected challenges in such model development is translating mass-balance model parameters like 'contaminant mass emission rate' into parameters understandable by non-expert users. The same challenges have already been considered and solved when developing ART and Stoffenmanager® almost two decades ago. In the initial report developing a model for small and medium enterprises, the solution was to translate contaminant mass-balance emission rates to handling categories (LeFeber *et al.*, 2003). During the ISES workshop, it was concluded that 'Another limitation is the lack of direct applicability of simple mass-balance modelling for general scenario exposure assessments if not coupled to e.g. range-values or known statistical variability of the determinant parameters for the specific scenarios assessed'. Koivisto explained during the ISES workshop that 'If measurements of the source strength are not available, a tiered approach needs to be followed, including the estimation of emissions e.g., by assuming that all process losses are emitted to air or read-across to comparable situations' (Schlüter *et al.*, 2022). This seems very similar to the modifying-factor approach that was followed when developing Stoffenmanager® and ART.

In this article, we have responded to the key statements in the article by Koivisto *et al.* (2022) that were incorrect and considered to be a biased critique on a subset of the exposure models used in Europe (i.e. ART and Stoffenmanager®) used for regulatory exposure assessment. We welcome scientific discussions on exposure modelling (as was done during the ISES Europe workshop) and criticism based on scientific evidence to contribute to the advancement of occupational exposure estimation tools. The tiered approach to risk assessment allows various exposure assessment models from screening tools (control/hazard banding) through to higher-tiered approaches. There is a place for every type of model, but we do need to recognize the cost and data requirements of highly bespoke assessments. That is why model developers have taken pragmatic approaches to develop tools for exposure assessments based upon imperfect data. We encourage Koivisto *et al.* to focus on further scientifically robust work to develop mass-balance models and by independent external validations studies and compare these models with alternative model tools such as ART and Stoffenmanager®.

Conflict of Interest

The authors declare no conflict of interest relating to the material presented in this article. Its contents, including any opinions and/or conclusions expressed, are solely those of the authors. Cosanta BV is a private company and the legal owner of STOFFENMANAGER®. H.H. has financially invested in Cosanta BV and is employed by the company.

Data Availability

No data were used in this study.

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