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Advanced REACH Tool (ART): Overview of Version 1.0 and Research Needs

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This paper provides an outline of the Advanced REACH Tool (ART) version 1.0 and a discussion of how it could be further developed. ART is a higher tier exposure assessment tool that combines mechanistically modelled inhalation exposure predictions with available exposure data using a Bayesian approach. ART assesses exposure for scenarios across different plants and sites. Estimates are provided for different percentiles of the exposure distribution and confidence intervals around the estimate. It also produces exposure estimates in the absence of data, but uncertainty of the estimates will decrease when results of exposure measurements are included. The tool has been calibrated using a broad range of exposure data and provides estimates for exposure to vapours, mists, and dusts. ART has a robust and stable conceptual basis but will be refined in the future and should therefore be considered an evolving system. High-priority areas for future research are identified in this paper and include the integration of partially analogous measurement series, inclusion of company and site-specific assessments, user decision strategies linked to ART predictions, evaluation of validity and reliability of ART, exploring the possibilities for incorporating the dermal route and integration of ART predictions with tools for modelling internal dose. ART is initially developed in the scope of REACH but is equally useful for exposure assessment in other areas.

Keywords: Bayesian analysis; exposure modelling; uncertainty

INTRODUCTION

Under the European Union regulation on the Regulation, Evaluation, Authorization and restriction of Chemicals (REACH), many thousands of substances need to be assessed for their safety in use at work over the coming years. It is clear that the availability of reliable and accurate exposure models is critical as the European occupational hygiene community will not be able to collect sufficient number of exposure measurements to obtain exposure estimates for all relevant scenarios. A tiered approach is proposed in which comparatively simple assessments are performed on all substances (Tier 1 assessment), followed by more elaborate evaluations for selected chemicals at higher risk (higher tier assessment). The need for ongoing scientific development of exposure modelling as a discipline is also advocated in a vision document on toxicity testing in the 21st century (NRC, 2007).

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Indeed, it is argued that the exposure community must step up to the challenges to develop a robust and predictive exposure science that can be used to address the complex risk assessment problems that prevail today (Sheldon and Cohen Hubal, 2009).

Only a few generic screening tools for assessing occupational inhalation exposure are available in Europe, such as COSHH essentials (Maidment, 1998), ECETOC TRA (Money *et al.*, 2007; ECETOC, 2009), Stoffenmanager (Marquart *et al.*, 2008), and the 'Easy-to-use workplace control scheme for hazardous substances (EMKG) (http://www.reachhelpdesk.de/en/exposure/exposure.html). Some information on the validity of these models has been published but in general only limited information is available (Schinkel *et al.*, 2010). Another valuable resource of available exposure models is the AIHA book with a description of various methods useful for the exposure assessment community (Keil *et al.*, 2009). In general, however, exposure modelling has been a relatively neglected area in occupational hygiene.

The urgent need for improvements in exposure modelling, particularly incorporating a Bayesian statistical approach, has been expressed repeatedly in the past years (e.g. Creely *et al.*, 2005; Hewett *et al.*, 2006; Ramachandran, 2008). The Advanced Reach Tool (ART) is a higher tier model that follows a Bayesian approach, making full use of mechanically modelled estimates of inhalation exposure and any relevant measurements of exposure (www.advancedreachtool.com). ART has a robust and stable conceptual basis but will be further refined in the future and should therefore be considered an evolving system. Future areas for development are identified in this paper. As with the development of version 1.0, these new initiatives will be carried out in close collaboration with stakeholders such as exposure scientists and practitioners representing industry, governments, and occupational hygiene societies. ART is initially developed in the scope of REACH but is equally useful for exposure assessment in other areas.

This paper briefly reflects the general outline of ART version 1.0, including the mechanistic model, Bayesian update process, type of exposure predictions, and applicability domain. Specific elements of the tool are elaborated on in separate papers.

BAYESIAN MODELLING OF THE EXPOSURE DISTRIBUTION

ART is developed to model inhalation exposure for a defined group of workers sharing operational conditions (e.g. type of handling, product, and work environment) and risk management measures across different plants and locations in Europe. This perspective in the context of REACH can and will be expanded in the future to also include company and site-specific exposure estimates. In statistical terms, it is assumed that every exposure scenario has a distinct exposure distribution that is adequately represented by a lognormal mixed effects model, with mean exposure and random effects representing between-company, between-worker, and within-worker variability. A first estimate of the geometric mean exposure level of a scenario is produced by a mechanistic model as outlined in the next paragraph and discussed in detail by Fransman *et al.* (2011). Information from meta-analyses of the literature provides the initial estimates of exposure variability between-companies, between-workers, and within-workers. Information on between- and within-worker variability was taken from Kromhout *et al.* (1993) and information on between-company variability was derived from Symanski *et al.* (2006) as outlined in a next paragraph.

In Bayesian terminology, these initial estimates of the measure of central tendency and variability are referred to as 'priors', which can then be updated using the likelihood defined by exposure data to yield a more refined posterior exposure estimate. The prior distribution is a representation of knowledge about the parameter a priori before observing any (new) data. This is mathematically combined with the likelihood to obtain the posterior distribution for the parameter. The posterior will ideally provide a narrower probability distribution of the parameter than either the prior knowledge or the exposure data. The posterior and likelihood will converge with an increasing exposure data set. The posterior is critically dependent on the quality of the exposure data and will be more robust when exposure data used for the likelihood are completely analogous and representative for the particular assessment scenario (see also Discussion).

It is important to highlight that ART also produces an exposure estimate in the absence of data, based on the mechanistic model and exposure variability obtained from the meta-analyses. In this respect, the ART model follows a stepwise approach, with an initial mechanistic model estimate and subsequent posterior estimate.

It can be argued that occupational hygienists already intuitively apply Bayesian ideas in daily practice, as they often have to supplement and integrate limited data with subjective judgements. However, a formal Bayesian analysis explicitly takes into account the variability in the available exposure data as well as uncertainty in the prior knowledge. The overall structure of the ART tool with different priors, exposure data, and Bayesian module is depicted in Fig. 1. A detailed description of the Bayesian model in ART, its underlying assumptions, and testing will be given by McNally *et al.* (unpublished data).

MECHANISTIC MODEL

The mechanistic model is based on a conceptual framework following a source receptor approach (Cherrie and Schneider, 1999; Tielemans *et al.*, 2008). This framework describes the stepwise transport of a contaminant from the source to the receptor (i.e. the worker) and defines nine independent principal modifying factors (MF): e.g. substance emission potential, activity emission potential, localized control, segregation, dilution, separation, surface contamination, personal behaviour, and respiratory protective equipment. The latter two MF are not yet incorporated in the mechanistic model and may be included in a later stage. The algorithm consists of a near field (NF) (within 1 m from the worker's head) and far field (FF) component. Others have described a two-zone approach as well and successfully used these algorithms in various applications (e.g. Nicas, 1996).

MFs are structured in a multiplicative manner within these NF and FF components. The principal MFs are structured in a hierarchical manner with multiple underlying determinants on a lower level of abstraction: e.g. for powders, substance emission potential is decomposed into the parameters 'dustiness', 'moisture', and percentage active ingredient (van Tongeren *et al.*, 2011).

Relative weights have been assigned to each underlying determinant category based on analyses from first principles (e.g. the relationship between vapour pressure and substance emission potential), available occupational hygiene literature [e.g. control efficacy values collated by Fransman *et al.* (2008)], numerical simulation results [e.g. for dispersion (Cherrie *et al.*,

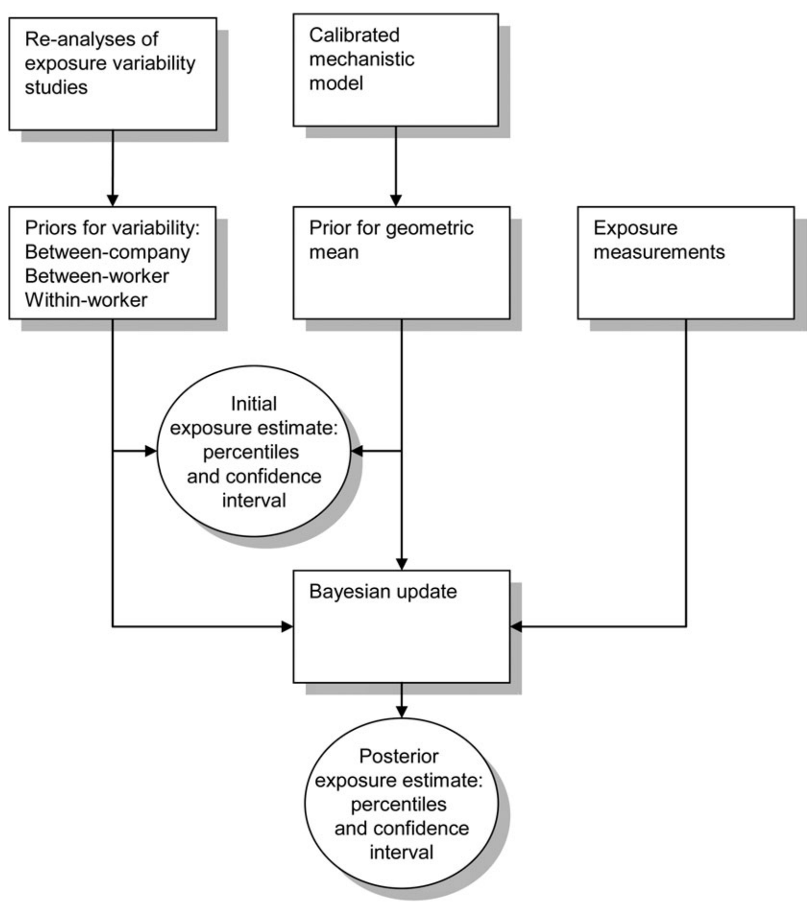

Fig. 1. Schematic outline of ART structure with priors for variability, prior for geometric mean, exposure measurements (likelihood), Bayesian module, and posterior exposure estimates.

2011)], and expert elicitation. A description of the mechanistic model, assignment of multipliers, and its underlying assumptions are presented by Fransman *et al.* (2011). An activity class system for structured assessment of activity emission potential is described by Marquart *et al.* (2011). This is an important element in the ART system as it allows selecting different underlying determinants for different types of activities: e.g. drop height and transfer rate in bagging operations, worker orientation (e.g. overhead work), and spray rate for spraying, etc.

The dimensionless mechanistic model gives a relative score for the geometric mean exposure of a scenario and is fitted to exposure measurements to convert these scores to absolute exposure estimates in milligrams per cubic metre. For this purpose, good quality data covering multiple industries, scenarios, and types of exposure were collated across Europe. The calibration was done using mixed-effects regression models as described by Schinkel *et al.* (2011). These statistical analyses also provided information on the uncertainty of the mechanistic model estimates, which is a prerequisite for the estimates to serve as an informative prior for the geometric mean in a Bayesian analysis.

REVIEW OF LITERATURE ON EXPOSURE VARIABILITY

Exposure concentrations vary substantially in an exposure scenario. This may be due to differences across locations (e.g. ventilation), worker (e.g. behaviour), and time (e.g. time activity patterns). These sources of variability may contribute to between-company, between-worker, and within-worker variability. Separation of variability into its components is a prerequisite for the estimation of both long-term average and shift-based exposure estimates as discussed within the section ‘Exposure predictions: variability versus uncertainty’.

We re-analysed the large database of Kromhout *et al.* (1993) to define priors for within- and between-worker variability. These data suggest differences in the extent to which exposure generally varies within- and between-workers, which may be related to factors such as type of exposure (aerosols versus vapours), environment (outdoor versus indoor), and process (intermittent versus continuous). A more recent systematic review of available literature, also covering occupational groups across locations (Symanski *et al.*, 2006), was used to derive estimates of variability between companies. Details of the derivation of priors for components of variance are described in McNally *et al.* (unpublished data).

APPLICABILITY DOMAIN

Factors affecting emission and dispersion of aerosols and vapours/gases are clearly distinct as aerosols are much larger than air molecules in which they are suspended, and aerosols can be generated in different sizes (Popendorf, 2006). This also affects the way these exposures should be modelled. Separate characterization was therefore necessary resulting in different determinants or weights for the MFs substance emission potential, activity emission potential, and dispersion for aerosols and vapours. In addition, the ART mechanistic model was calibrated separately for vapours, mists, and dusts. Three other exposure forms (gases, fibres, and fumes) are not yet included in the calibration and are therefore outside the applicability domain of the current ART.

EXPOSURE PREDICTIONS: VARIABILITY VERSUS UNCERTAINTY

Variability reflects true differences in exposure situations, whereas uncertainty reflects lack of knowledge about the situation. Basically, variability is a property of nature, whereas uncertainty may be reduced with additional knowledge acquired during the risk assessment process. Variability and uncertainty need to be treated separately in exposure models such as ART. The user of ART can select (i) different percentiles of the exposure distribution (i.e. variability) and (ii) different confidence intervals around that percentile (i.e. uncertainty).

After an initial ART assessment, the user can modify the results by either applying a Bayesian update or revising the scenario. A Bayesian update will result in a reduction of uncertainty of the estimate of a particular percentile, with the extent of reduction depending on the sample size, the variability in the data, the balance in the data set (i.e. number of companies and workers sampled), and the relative difference between model prediction and data. However, the point estimates of a particular percentile of the exposure distribution can either increase or decrease after a Bayesian update, depending on the distribution of the measurement data. Revision of input parameters will obviously result in changes in percentile estimates, whereas the uncertainty around the point estimate will remain unchanged (Table 1).

The extent of exposure variability is related to the averaging time of the exposure assessment, with reduced exposure variability with longer averaging periods. It is clear therefore that this should be taken into account in a sound risk assessment. ART incorporates

Table 1. Influence of Bayesian updating and ART iterations with revised input parameters on predictions of the exposure percentiles and its confidence intervals

Prediction	Influence of Bayesian update with measurements	Influence of iteration with revised input parameters
Percentile (i.e. variability)	Changes in any direction possible, depending on measurement series	Changes in any direction possible, depending on type of scenario revision
Confidence interval. (i.e. uncertainty)	Smaller confidence interval	No influence

both between-worker and within-worker variability and can therefore produce two different exposure predictions (Rappaport *et al.*, 1995):

- Full-shift exposure: ART calculates an overall distribution for full-shift exposures. In this case, the 90th percentile provides the exposure level, which has a 10% probability of being exceeded by the exposure from a randomly selected worker on a randomly selected day. A distinction between both components of variance is not needed for this estimate. This is the type of exposure predictions most often applied by exposure assessors (e.g. in REACH exposure assessments).
- Long-term average exposure: ART calculates the distribution of workers' long-term average exposure (e.g. over a period of months). In this case, the 90th percentile provides the long-term mean exposure level, which has a 10% probability of being exceeded by the long-term exposure from a randomly selected worker. This exposure prediction is preferred when dealing with substances, which can produce chronic health effects (Rappaport *et al.*, 1995).

WORKFLOW OF ART VERSION 1.0

A simplified scheme of the workflow for ART version 1.0 is presented in Fig. 2. The workflow starts with questions on all determinants as included in the mechanistic model to produce an initial exposure estimate. Based on this initial assessment, the user can revise the scenario by changing one or more of the input parameters. Alternatively, the user can upload analogous exposure data to further refine the estimates. The ART version 1.0 tool has a statistical facility to update the initial exposure estimates with exposure measurement data collected from fully analogous exposure scenarios. These data can be uploaded for Bayesian analyses using a simple spreadsheet. However, an in-built exposure database that users can search for analogous existing exposure data is missing and will be implemented in version 1.5. Again, after this updated estimate, the user has the possibility to further revise the scenario and to conduct an alternative assessment. For both the initial assessment and the updated assessment using measurements, the user can select different exposure predictions as is outlined in the previous paragraph.

A WORKED EXAMPLE

This worked example is derived from one of the scenarios of the pharmaceutical industry included in the calibration of ART. A worker is unloading material during a shift. For this example, we assume the worker is only conducting one task; however, ART can cope with multiple tasks and provides a time weighted average of the different tasks, including any unexposed periods.

During this task, the worker is transferring a fine dust (dry product; 100% active ingredient), with a transfer rate of 1–10 kg min^{-1} (routine transfer; drop height >0.5 m) from a blender to a keg. The work is performed indoors (room size equals 300 m^3) with a high ventilation rate of 30 air changes per hour. There are demonstrable and effective housekeeping practices in place. The activity is performed in the near field without any secondary source in the far field. The exposure is estimated for two distinct situations: (i) without any local controls in place and (ii) with a low level of containment, which is not air tight. The relevant ART input parameters are given in Table 2.

Figure 3 shows the geometric mean full-shift exposure predictions for the two situations. The point estimates of the geometric mean are clearly reduced with the revision to low level of containment (obviously, revision to other ART options like moderate or high level of containment would have resulted in a stronger shift). However, the uncertainty as expressed as the inter-quartile confidence interval is in both situations identical.

Alternatively, updating the situation without local controls using 10 exposure measurements (geometric mean = 20 mg m^{-3}; geometric standard deviation = 1.6; covering three sites, repeated measurements of one worker per site) resulted in a shift of the point estimate as well as a reduction of the uncertainty around the estimate. Although the shift of the point

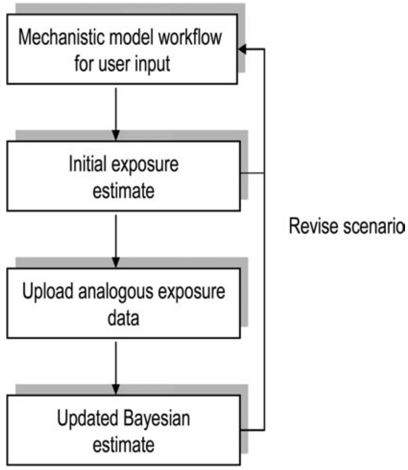

Fig. 2. Workflow of ART version 1.0.

Table 2. Input parameters describing the worked example where a worker in the pharmaceutical industry is unloading a powder

Activity emission potential	Transfer with rate of 1–10 kg min^{-1} Routine transfer Drop height >0.5 m
Substance emission potential	Fine dust Dry product 100% active ingredient
Dilution	Indoor in room of 300 m^3 Ventilation rate of 30 air changes per hour
Local control	Without any control (Situation 1) and low level of containment which is not air tight (Situation 2)
Segregation	No segregation
Separation	No separation
Surface contamination	Demonstrable and effective housekeeping practice in place
Duration of activity	Full shift (100% of the time)
Near field	Yes
Far field	No

estimate was in this particular case upwards (depending on the measurements this might also be downwards), the upper bound of the inter-quartile confidence interval of the updated estimate was still lower as compared to the upper bound of the initial assessment. This reduction in overall uncertainty of the exposure assessment clearly shows the added value of the Bayesian module and provides an incentive to collect additional exposure measurement data while using ART.

CONCLUSIONS AND RESEARCH NEEDS

The ART approach to estimating inhalation exposure for regulatory risk assessment has the advantage of integrating the use of a robust mechanistic model with available exposure data. The tool is able to characterize exposure to dust, mist, and vapours in the absence of exposure data but will provide more reliable estimates with additional measurement data. ART will be useful for risk assessment under REACH and with further development in other situations, such as under the European Chemical Agents Directive. The basis for the tool was, in the course of the development, peer reviewed by independent, leading experts from industry, research institutes, and public authorities. This ensured that consideration of both scientific and practical model issues was given during the course of the development of the ART.

High-priority areas for further development in ART are listed below:

- Currently, ART can only take into account data that are perfectly representative of the assessment scenario. Ideally, the tool should also be able to integrate exposure data across measurement series with varying levels of 'representativeness' or 'analogy'. First attempts have been made to define similarity algorithms to take these factors into account in a Bayesian analyses (McNally *et al.*, unpublished data). However, further methodological work is needed to properly integrate partially analogous measurement series using a weight of evidence approach. The latter would facilitate optimal mining of the ART exposure database that is currently under development and will be implemented in version 1.5.
- ART integrates mechanistic model outcomes and exposure data. This works well when both are reasonably consistent. If both are inconsistent this is an indicator that either the model is not accurate for that situation, incorrect input parameters are used or exposure data are not analogous. The mechanistic model results and posterior estimates are displayed side by side by the tool to allow comparison. However, the ART system has no methodology to cope with these inconsistencies. As also indicated by Hewett *et al.* (2006), further work is required to define guidelines how to make informed decisions in situations of inconsistent priors and likelihood distributions. Currently, there is little in the Bayesian literature on how to deal with these situations.
- Further alignment of ART with the REACH practice and available REACH guidance. This is possible after initial experience with the tool in 2010 and 2011 and might cover various practical issues in the user interface and output.

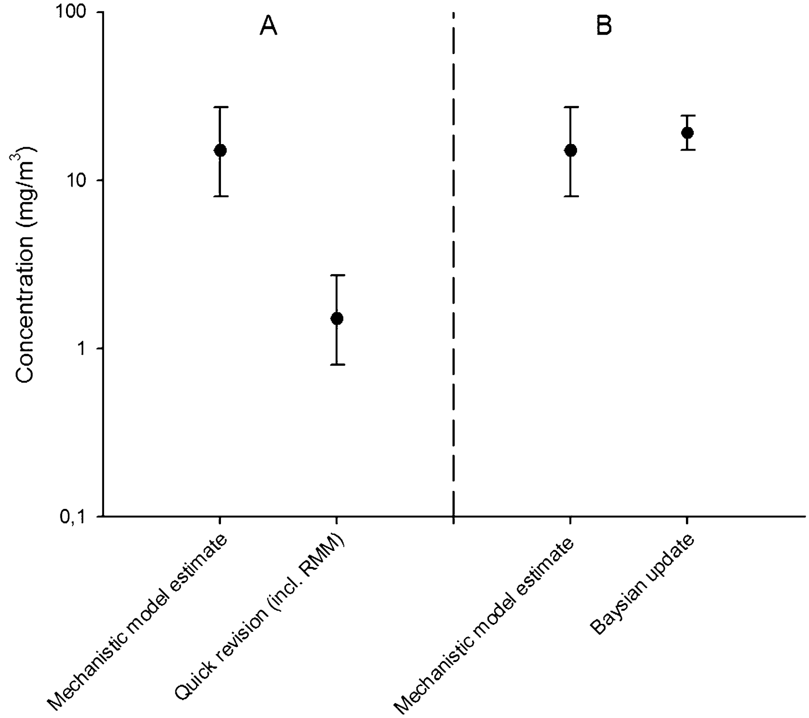

Fig. 3. ART point estimates of the geometric mean exposure and inter-quartile confidence interval for the transfer scenario with and without revision with Risk Management Measures (low level containment) (a) and after Bayesian update (b).

- ART is assessing the exposure distribution of a scenario covering multiple companies or sites. Modifications of ART so that it can also provide company and site-specific estimates are necessary to be useful in, for example, the Chemical Agents Directive. This requires a restructuring of the underlying lognormal mixed effects model.
- User decision strategies, linked to ART predictions, to help identify whether collecting additional measurements (reducing uncertainty) or implementing a control strategy (reducing exposure) would be more appropriate. ART gives formal assessment of uncertainty and thus also provides the opportunity to estimate the value of reducing the uncertainty before proceeding to implementation of controls. Existing approaches in other research areas like 'value of information analyses' (Morgan and Henrion, 1990) are as yet unexplored in occupational hygiene and may be very useful in refining risk management decisions and enhancing its cost-effectiveness. These decision strategies may be very useful in the context of ART but are equally relevant for other exposure models available.
- The validity and reproducibility of ART predictions needs to be evaluated in order to ensure a sound use of the model in the REACH context and beyond. Several hundred exposure measurements from various industrial sectors have been collated after the calibration. These measurement series form the basis for a cross-validation that is currently being conducted. In addition, workshops with experts are planned to explore inter-rater agreement when applying ART. First results are anticipated to become available in the near future and will help identify areas for improvement of the ART mechanistic model. Information gathered in these studies will also help further developing the existing ART training material.
- Expansion of the ART methodology to include dermal exposure is important. Dermal exposure assessment is still in its infancy. Work on the conceptual modelling of dermal exposure (Schneider *et al.*, 1999; van Wendel de Joode *et al.*, 2003) and the RISKOFDERM project (van Hemmen *et al.*, 2003) may provide a starting point for a Dermal ART, although much more work on mechanistic understanding of the exposure process and collection of exposure data is needed. Measurements under experimental as well as under real world workplace conditions using standardized methodologies are required

to built an evidence base for development of a dermal ART.

- Integration of ART predictions of external inhalation and dermal exposure with approaches for modelling internal dose (e.g. PBPK models) would potentially capture the entire source to outcome continuum, which is a prerequisite for a more informative systems approach in toxicology as proposed by NRC (2007).

ART is considered to be an evolving system. The approach has a conceptual basis, which is a good starting point for further development. Continued research activities are needed to move exposure assessment science forward in REACH and beyond.

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