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PAPER

Advanced REACH Tool (ART): Calibration of the mechanistic model

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The mechanistic model of the Advanced Reach Tool (ART) provides a relative ranking of exposure levels from different scenarios. The objectives of the calibration described in this paper are threefold: to study whether the mechanistic model scores are accurately ranked in relation to exposure measurements; to enable the mechanistic model to estimate actual exposure levels rather than relative scores; and to provide a method of quantifying model uncertainty. Stringent data quality guidelines were applied to the collated data. Linear mixed effects models were used to evaluate the association between relative ART model scores and measurements. A random scenario and company component of variance were introduced to reflect the model uncertainty. Stratified analyses were conducted for different forms of exposure (abrasive dust, dust, vapours and mists). In total more than 2000 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.

Introduction

Exposure models are increasingly being used for exposure assessment or guidance of expert judgment in situations where exposure measurements are absent or scarce.[1] Mechanistic exposure models are being developed for workplace exposure assessments under the Chemical Agents Directive 98/24/EC and for regulatory exposure assessments. Recently, the new European regulation for Registration, Evaluation, Authorization and Restriction of Chemical substances (REACH) provides momentum for development and utilization of exposure models. Various screening models are available to serve as an initial Tier 1 approach within REACH, including ECETOC TRA,[2] Stoffenmanager,[3] and the EMKG-Expo-Tool (http://www.reach-helpdesk.de/en/Exposure/Exposure.html). These models are intended to be conservative (*i.e.*, protective) and should discriminate between scenarios of potential concern in terms of exposure and scenarios where exposures are low.[4]

A higher tier, more refined model for inhalation exposure assessments has been developed which is referred to as Advanced REACH Tool (ART) (www.advancedreachtool.com). The ART framework incorporates a mechanistic model and available exposure measurements using a Bayesian methodology in order to produce more precise estimates for specific exposure scenarios.[5] The mechanistic model follows a source–receptor

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Environmental impact

The Advanced REACH Tool (ART) is the first generic higher tier exposure assessment tool incorporating a mechanistic model of inhalation exposure and a database of empirical exposure information. ART is already freely available (www.advancedreachtool.com) for assessing worker exposures in the registration processes in the scope of REACH.
This manuscript presents in a transparent way the shift from a mechanistic exposure model producing relative scores to a mechanistic model estimating geometric exposure levels in units. It will help users to understand and interpret the output of the ART. We believe that publication of studies like this might stimulate further evaluation of exposure assessment models in general.

structure comprising modifying factors (MFs) representing the source, transmission compartments and the receptor.[6,7] The model uses a list of MFs to describe the exposure process in a particular scenario (*e.g.* substance emission potential, activity emission potential, localized controls, dispersion, personal enclosure, segregation, surface contamination and respiratory protective equipment (RPE)). Various sources were used to underpin the multipliers that were allocated to each MF. The output of the mechanistic model is an exposure score that provides a relative ranking of geometric mean (GM) exposure levels for different scenarios. A detailed description of the mechanistic model and its scientific underpinning is given by Fransman and collegues (2010).[8]

In the present study, dimensionless ART mechanistic model scores are compared with exposure measurements collected from various occupational settings, substances, time periods and countries. The objectives of this calibration are threefold: to study whether the mechanistic model scores are accurately ranked in relation to exposure measurements; to enable the mechanistic model to estimate actual exposure levels rather than relative scores; and to provide a method to quantify model uncertainty.

Materials and methods

Collation of exposure data

Occupational exposure data were collected from institutes in the United Kingdom (HSL, HSE, IOM), the Netherlands (TNO), and Germany (BAuA). In addition, exposure data from a large petrochemical company (Shell) and a multinational pharmaceutical company (GlaxoSmithKline (GSK)) were obtained. These company data related mainly to sites in Europe but also included some measurements from sites in Africa and Asia. The data from the Netherlands had previously been used for calibration and validation of the Stoffenmanager[9,10] while the data from HSE were selected from the National Exposure Database (NEDB) and only contains exposure surveys performed within the last five years. The calibration dataset also included data taken from the Bayesian Exposure Assessment Toolkit (BEAT) and the Biocides Technical Notes for Guidance (TNsG). All of the exposure data reflect personal inhalation exposures and relate to either single or multiple activities.

For the measurements reflecting exposure to dust and abrasive dust most of the samples were gravimetrically analyzed, with the exception of the data for grit blasting, where copper was chemically analyzed, and part of the data from GSK which were chemically analyzed for specific Active Product Ingredients (API). Within the vapour and mist scenarios all measurements were chemically analyzed.

Data quality, exclusion criteria, and assignment of ART scores

Guidelines for data quality were defined to rank data into one of the three categories: good, moderate, or poor. In order to obtain a reliable insight into model uncertainty only good quality data were included in the calibration analyses. Poor quality data were excluded whilst moderate quality data may be used in a subsequent cross-validation analysis. Exposure data were labeled to be of good quality if they had the following characteristics:

(1) The required core information (*i.e.*, sampling methods, sample devices and analytical methods) was documented.[11,12]

(2) All of the ART modifying factors could be assessed, or could be reliably assumed for all individual activities during the measurement period; *e.g.*, if a measurement period covered four distinct activities, information on time registration, substance emission potential, activity emission potential, localized controls, dispersion, *etc.* must be available for all four activities.

(3) A unique company/site number was available in order to define a company random effect in the mixed-effects analyses.

The influence of measurement error will increase with decreasing sampling time and will have a substantial impact on exposure levels of measurements with very short sampling times. Therefore exposure measurements with sampling times less than the arbitrary cut-off point of 5 minutes were excluded to warrant representativeness of the exposure measurements. In addition, measurement series with more than 50% of the measurements below the limit of detection (LOD) were excluded.

Based on the contextual information as described above, ART scores were assigned to all MFs by one member of the project team (JS) and subsequently these scores were reviewed by two other members (ET, WF). The ART scores for the data from GSK were assigned by PMD and for Shell by EV. These scores were reviewed by JS and ET. General rules with respect to assignment of number of air changes per hour (ACH) were defined by the project team. In situations where the exact information on ACH was missing, a situation with no ventilation was coded as 0.3 ACH, natural ventilation as 1 ACH and mechanical ventilation as 3 ACH. When multiple activities were conducted during a measurement, ART scores were calculated for each activity and then combined as a time-weighted summation for the activities making up the measurement period. The mechanistic model of ART estimates potential exposure in the breathing zone of the worker (outside any RPE) and the measurement data that were included in the calibration dataset were also measured outside the RPE or in the absence of RPE. Therefore the use of respiratory protective equipment (RPE) was not included in the calibration.

Modeling different exposure forms

Within the ART mechanistic model the substance emission potential MF had to be modeled very differently across the various exposure forms: *e.g.*, for liquids a well defined and intrinsic property like vapour pressure was relevant, whereas for powders a less clearly defined and non-intrinsic feature such as dustiness had to be taken into account.[8]

Given the different innate properties separate calibrations were conducted for each of the following forms of exposure:

Vapours: This is the airborne state of a chemical which, if a sufficiently large amount of liquid were released into a closed room at normal temperature, would not completely evaporate but rather would reach equilibrium with its liquid.

Mists: Any airborne liquid aerosol, *e.g.* water in the form of steam, fog, or a fine spray.

Dust: Solid particles that are formed by aerosolization of already existing powders or by abrasion of solid objects. Both sources of dust were calibrated separately.

The calibration of three other exposure forms, *i.e.* gases, fumes and fibers was outside the applicability domain of ART version 1.0 and therefore outside the scope of this paper.

Statistical methodology

Although a variety of methods for calibrating generic exposure models like the ART model have been used in the past, a natural point of departure for the calibration of any model is to assume the true quantity is proportional to the estimated quantity. That is:

$$\text{Exposure} = \alpha \cdot \text{ARTscore} \tag{1}$$

This deterministic model assumed a perfect relationship between exposure and ART model scores and has the desirable property that the calibrated model predicts zero exposure exactly when the dimensionless non-calibrated mechanistic model does.

However, in practice the mechanistic model of ART does not capture the full heterogeneity of workplace exposures and therefore an 'error' term is introduced (eqn (2)). Although in principle this error term could be additive, this results in highly skewed residuals that do not conform to the assumption of normality required for fitting *via* least squares regression. Instead a multiplicative error is proposed that corresponds to exposure measurements being lognormally distributed:

$$\text{Exposure} = \alpha \cdot \text{ARTscore} \cdot e^{\varepsilon} \tag{2}$$

Transforming this relationship through taking natural logarithms gives:

$$\ln(\text{exposure}) = \ln(\alpha) + \ln(\text{ART score}) + \varepsilon \tag{3}$$

However, as exposure levels vary between scenarios, between premises and between workers, random scenario, company and worker components should also be included resulting in a linear mixed effect model. Unfortunately, unique codes per worker were missing for part of the dataset, therefore no random component for worker could be included in the models.

The linear mixed effects model used for calibration is given in eqn (4), where Y_{ijk} is the exposure level for the kth measurement within the jth company in the ith scenario. X_{ijk} is the ln-transformed exposure level; ln α is the intercept (natural logarithm of the slope on the natural scale); δ_i represents the random effect of the ith scenario, c_{ij} represents the random effect of the jth company in the ith scenario and ε_{ijk} is the residual error term. It is assumed that δ_i, c_{ij} and ε_{ijk} values are normally distributed with mean equal to zero and variances representing the between-scenario, between-company, and within-company components of variance. The companies are nested within scenarios.

$$\ln(Y_{ijk}) = X_{ijk} = \ln(\alpha) + \ln(\text{ARTscore}) + \delta_i + c_{ij} + \varepsilon_{ijk} \tag{4}$$

With this method the relative ART mechanistic model scores are still proportional to actual exposure levels and importantly the effects of individual MFs are preserved. For example, the efficacy of fixed local exhaust ventilation (LEV) at reducing inhalation exposures has been assessed as 90%[8] and with a proportional relationship between model score and actual exposure levels this efficacy is applied over the whole range of model scores. The intercept ($\ln(\alpha)$) represents the estimated exposure if the ART model score is 1.

Effect of scenario definition and data grouping

Including scenario as a random component of variance will give insight into the model uncertainty when the model is used to estimate GM exposure levels at scenario level. Since scenario definitions are to some extent subjective and could have substantial impact on the model uncertainty, two different levels of scenario were defined to investigate its impact.

(1) Broad scenario. A scenario is defined by the main MFs: activity emission potential, substance emission potential, and localized controls. Using this definition large scale bagging operations with and without LEV are two separate scenarios. Similarly, data from bagging operations of granules and fine powders belong to different scenarios.

(2) Refined scenario. As above with the addition that data from different measurement series are assigned to different scenarios. For example, comparable bagging operations of granules from two different studies belong to different scenarios.

For measurement results below the LOD, imputed values based on the maximum likelihood estimation (MLE) procedure were used. Uniform distributions were estimated per measurement series. For measurements below LOD these distributions were used to randomly impute values between zero and the LOD. To fully account for the variance from the imputation, 30 imputations were preformed resulting in 30 datasets. The data were analysed using SAS Statistical Software (version 9.1.3; SAS Institute, Cary, NC, USA). Subsequently PROC MIANALYZE was used to combine the regression results from the multiple datasets. The process of imputation of values for measurements below LOD is described in more detail elsewhere.[13]

Results

The calibration dataset consists of results from 2292 personal inhalation exposure measurements collected by institutes and companies in different countries. Table 1 presents the number of measurements from each country or multinational company per form of exposure. One percent of the measurements ($n = 26$) were excluded because the sampling time was less than five minutes. Furthermore 9% ($n = 210$) of the measurements were excluded because more than 50% of the measurements within a measurement series were below the LOD. After applying these exclusion criteria the dataset had 2056 measurements available, consisting of 159 abrasion, 847 dust, 528 vapour and 523 mist measurements. In the final dataset fewer than 4% ($n = 80$) of the measurements were below the LOD with the highest proportion among the mist dataset ($n = 60$). The median sampling time ranged from 83 (dust) to 238 (abrasive dust) minutes (Table 2).

The calibration datasets consist of very diverse activities with a broad range of products, localized controls and environmental circumstances resulting in large standard deviations. Geometric standard deviations (GSD) between 15 and 22 were found for dust, vapour and mist exposures, while a smaller GSD of 5 was found for exposure measurements during abrasion (Table 2). Within the dataset for abrasion the lowest exposure levels were

Table 1 Overview of the number of measurements per exposure form before and after selections

	UK	Netherlands	Germany	GSK	Shell	Total collected	After excluding measurements <5 min duration	After excluding 50% <LOD	Total in calibration
Dust (abrasive)	35	100	27	0	0	162	162	158	158
Dust	32	409	127	316	0	884	869	847	847
Vapour	19	177	76	0	264	536	536	528	528
Mist	425	245	40	0	0	710	699	523	523
Total	511	931	270	316	264	2292	2266	2056	2056

found for copper exposure during grit blasting where paint containing copper was removed from ships. The highest exposure levels were found during demolishing activities with a jack-hammer. Dispensing a pharmaceutical product in a glovebox resulted in the lowest measured dust exposures, while the highest dust exposures were measured during the unloading of fine powder from a ship. The lowest vapour exposures were found during the collection of quality control samples, with the highest vapour exposures being measured in the shoe repair industry during activities involving solvent-based glues. The lowest mist exposures were measured during pesticide spraying, while the worker was in a tractor cabin, and the highest exposures occurred during antifouling paint spraying.

Table 2 also shows the descriptive statistics for the assigned ART model scores. For abrasive dust and vapour exposure scenarios the range in measured concentration was comparable to the range found in the relative ART model scores. For the dust exposure form the range in measured exposures (4×10^{-7} to 646 mg m^{-3}) was nine orders of magnitude while the range in relative ART scores (3×10^{-5} to 21) was six orders of magnitude. For the mist exposure form the range in measured concentration was two orders of magnitude larger than the range in relative ART model scores.

The ratio of GM measured exposures and the GM from the uncalibrated ART scores varied by a factor of approximately 1.5 for scenarios reflecting exposure to abrasive dust to a factor of 35 000 for scenarios reflecting exposures to vapour.

Using the detailed scenario level definition generally resulted in very limited number of companies per scenario. The broader scenario level definition resulted in a more balanced structure but nonetheless the number of companies per scenario remained fairly small. For the measurements reflecting mist exposure the detailed as well as the broad scenario level definitions resulted in multiple companies per scenario (Table 2).

The results of the statistical analyses are presented per exposure form in Table 3. Model A represents the model without any fixed effects while those with ART model scores included as fixed effects are denoted by Model B. The results of the models are presented for both the detailed and broad scenario definitions. As discussed later, the broad scenario definitions were used for the calibration.

Factually the exponent of the estimated intercept (ln (α)) should be similar to the difference that was found between measured GM and GM of assigned ART scores (Table 2). Overall between-scenario components were the largest variance components, indicating that exposure varies more between than within scenarios. With the exception of the abrasive dust models, the models based on detailed scenario level definitions resulted in higher between-scenario variance compared to models with broader scenario level definitions as a random component.

For the measurement series reflecting exposure to abrasive dust, dust and vapours, including the ART model score in the model (Model B) explained around 60% of the variance that was found in models with only scenario and company as random effects. The lowest proportion of variance explained by the ART model score (30%) was found for exposures to mists. The reduction in the variance was mainly observed for the between scenario variance.

The model uncertainty can be expressed as an uncertainty cfactor (UF) and may be defined as follows: $UF = e^{1.6449\sqrt{\sigma^2_{\text{between-scenario}}}}$. In the ART Bayesian model this factor will be interpreted as providing a 90% probability that the true GM exposure level is within that factor of the model estimate; *e.g.*, an UF of 5 represents a 90% probability that the true GM of a scenario is within a factor 5 of the model exposure estimate. The UFs found for the models with the broad scenario definitions were 2.1, 4.4, 5.0 and 5.8 for the exposure forms abrasive dust, dust, vapour and mist respectively.

The results of model B with the broad scenario descriptions, for each form of exposure, are shown in Fig. 1, illustrating that the variation in GM exposure and GM ART scores was approximately equal for all forms of exposure. The 90% confidence upper limit is derived by multiplying the estimated GM by the respective UF, while the 90% confidence lower limit is derived by dividing the estimated GM by the respective UF.

Fig. 2 shows the residuals of the relation between measured GM exposure minus estimated GM exposure per broad scenario against the ART score. Fig. 2 provides no evidence for a positive or negative correlation between residuals and ART scores, indicating that the relationship between log-transformed ART model scores and log-transformed measured concentrations is proportional.

Discussion

This paper presents the results of the calibration of the mechanistic ART model that is used to estimate GM exposure levels for many exposure scenarios. The calibration of the model with measured exposure data enabled the ART mechanistic model to estimate exposure levels (in mg m^{-3}) rather than relative scores for different exposure forms (abrasive dust, dust, vapour and mist). Furthermore the calibration provided insight into the uncertainty of the estimated GM for specific scenarios. This uncertainty is expressed as an UF ($UF = e^{1.6449\sqrt{\sigma^2_{\text{between-scenario}}}}$) and this

Table 2 Descriptive statistics of the dataset for the exposure forms dust (abrasive), dust, vapour and mist

Exposure form	Number of measurements	Number of companies	Number of broad scenarios	Number of detailed scenarios	N < LOD	Median sampling time/min	AM	GM	GSD	Range
Dust (abrasive)	158	44	21	54	0	238	11.60^a	2.41^a	5.21	4×10^{-2} to 309^a
Art-score dust (abrasive)							9.17^b	1.60^b	5.08	3×10^{-2} to 404^b
Dust	847	114	62	155	16	83	14.86^a	0.94^a	20.02	4×10^{-7} to 646^a
Art-score dust							0.56^b	0.05^b	12.77	3×10^{-5} to 21^b
Vapour	528	118	35	131	4	170	51.52^a	1.70^a	22.00	1×10^{-3} to 1762^a
Art-score vapour							0.002^b	4.8×10^{-5b}	17.80	1×10^{-7} to 0.14^b
Mist	523	245	19	28	60	85	0.55^a	0.03^a	15.72	3×10^{-5} to 30^a
Art-score mist							3.8×10^{-6b}	1.1×10^{-6b}	5.26	3×10^{-9} to 5.0×10^{-5b}

[a] In mg m^{-3}. [b] Dimensionless values.

UF is used to calculate confidence limits around the estimated GM exposure. The analyses indicate that the model could estimate with 90% confidence GM exposure levels within a factor between two and six of the measured GM exposure levels (depending upon the form of exposure).

The influence of different scenario definitions on the calibration results was investigated by running linear mixed effect models separately with two different scenario definitions included as random effect. The broader definition of scenarios resulted in slightly less between-scenario variance and more between company variance. The numbers of measurements from different companies within the detailed scenario level definitions were limited, resulting in unbalanced data. Table 2 shows that the number of companies per scenario is higher within the broader scenario level definitions. For the purpose of REACH, the ART is intended to be used to estimate exposures at this broad level of scenarios. Therefore, the results of the broad scenario definition were used to quantify the relative scores from the mechanistic model of ART. By only fitting the intercept and keeping the regression coefficient at 1, a proportional relation between the measurement data and the model scores is assumed. The residuals presented in Fig. 2 did not provide evidence for any trend between the model residuals and log-transformed ART scores suggesting that the assumption of a proportional relationship between the log-transformed ART score and log-transformed measurement concentrations is justified.

Exposure measurements with values below the LOD can be treated in several ways. Traditionally half the value of the LOD is adopted as the value.[14] At present, more sophisticated methods exist which take into account the variability within these measurements.[13] Especially for linear mixed models that are used to estimate exposure and models that are used to get insight into the uncertainty and variability of exposure estimates, these more sophisticated methods are preferred. Because of the small number of measurements below the LOD, as shown in Table 2, the models based on imputations differed only slightly from models using traditional methods (results not shown).

Several studies found time trends in a range of exposures, with decreasing exposures over time.[15–21] A generic exposure assessment tool like the ART does not take into account these trends in exposure levels over time, although it could be assumed that most of the determinants causing these reduction are described in the MFs of the mechanistic model. This assumption is illustrated by Vermeulen and colleagues (2000) who reported that modeling the effectiveness of local control measures explained almost entirely the observed drop in inhalable exposure levels. However, it is warranted to update the calibration in the future in order to take these time trends into account.

Different exposure levels between countries were reported by de Vocht and colleagues.[22] They reported that a two- to threefold difference in exposure levels was presumably caused by less up-to-date technology and local control measures. The generic mechanistic model of the ART is not able to fully take into account this technology driven variation in exposures and therefore these differences are expressed in the UF. The resulting variability is accounted for in the Bayesian model. However, the dataset used for the calibration contains mainly measurements from western-Europe. Reasonably, technology driven differences in exposure levels could be seen between companies in the same

Table 3 Results of the mixed effect regression models for the calibration of the ART mechanistic model for the different exposure forms

Exposure form	Model	ln α	σ^2_{bs} [c] (95% CI)	σ^2_{bc} [d] (95% CI)	$\sigma^2_{residual}$ [e] (95% CI)	σ^2_{total}
Dust (abrasive)	A[a]-refined	0.91	1.66 (1.07–2.93)	0.07 (0.008 to 4.41 × 10^{10})	0.72 (0.54–1.00)	2.45
	A-broad	1.39	2.56 (1.40–6.09)	0.23 (0.09 to 1.04)	0.70 (0.54–0.96)	3.49
	B[b]-refined	0.43	0.39 (0.19–1.18)	0.30 (0.13 to 1.38)	0.57 (0.43–0.77)	1.26
	B-broad	0.48	0.21 (0.06–4.43)	0.58 (0.34 to 1.18)	0.57 (0.43–0.78)	1.36
Dust	A-refined	−0.05	6.30 (4.73–7.87)	0	2.07 (1.84–2.31)	8.37
	A-broad	−0.55	6.03 (3.37–8.70)	1.35 (0.87 to 1.82)	2.37 (2.10–2.65)	9.75
	B-refined	2.98	1.13 (0.65–1.60)	0.12 (−0.12 to 0.36)	2.17 (1.92–2.41)	3.42
	B-broad	3.01	0.81 (0.25–1.36)	0.38 (0.12 to 0.64)	2.29 (2.03–2.55)	3.48
Vapour	A-refined	0.10	7.65 (5.55–9.75)	0.47 (0.11 to 0.84)	1.18 (1.00–1.36)	9.30
	A-broad	0.95	6.35 (2.97–9.72)	1.34 (0.88 to 1.81)	1.18 (1.00–1.36)	8.87
	B-refined	10.57	0.84 (0.18–1.49)	1.19 (0.59 to 1.79)	1.24 (1.05–1.43)	3.27
	B-broad	10.56	0.95 (0.11–1.78)	1.41 (0.92 to 1.90)	1.23 (1.05–1.42)	3.59
Mist	A-refined	−3.43	4.23 (1.63–6.83)	1.38 (0.67 to 2.09)	2.59 (2.01–3.18)	8.20
	A-broad	−3.67	3.41 (0.92–5.89)	1.47 (0.81 to 2.12)	2.83 (2.26–3.40)	7.71
	B-refined	10.15	1.18 (0.31–2.05)	1.58 (0.84 to 2.32)	2.64 (2.05–3.23)	5.40
	B-broad	10.23	1.14 (0.17–2.10)	1.65 (0.94 to 2.36)	2.62 (2.06–3.18)	5.41

[a] Model A: $\ln(Y_{ijk}) = X_{ijk} = \ln(\alpha) + \delta_i + c_{ij} + \varepsilon_{ijk}$. [b] Model B: $\ln(Y_{ijk}) = X_{ijk} = \ln(\alpha) + \ln(\mathrm{ART}) + \delta_i + c_{ij} + \varepsilon_{ijk}$. [c] σ^2_{bs}: between-scenario component of variance. [d] σ^2_{bc}: between-company component of variance. [e] $\sigma^2_{residual}$: residual error component of variance.

region but are assumed to be larger between different regions of Europe and therefore the influence of this effect is probably underestimated by the current UF.

The calibration was performed on a comprehensive set of exposure measurements. Although the collated exposure data cover a broad range of exposure situations measured at many sites, not all the possible ART MF combinations were included in the dataset. Ideally more exposure data from more companies including more MF combinations would have been available for calibration.

Input parameter uncertainty may impact on the exposure model; *i.e.*, the percentage of a substance in a product may be reported in the material safety data sheet (MSDS) in a range such as 25–50%. Secondly, measurement error such as differences in sample device or laboratory analyses could also be a source of uncertainty. However, measurement error is considered to be relatively unimportant[23] compared to the last and more fundamental type of uncertainty, which is the model uncertainty, as all models are never a perfect representation of reality.[24] The mechanistic model of ART does not consider all possible determinants of exposure and the scaling or scoring of individual determinants (*i.e.* MFs) was based upon scientific evidence and expert judgment. Hence, the scaling may not be a perfect reflection of reality and should be reconsidered if more evidence becomes available. The overall uncertainty found in the calibration incorporates these three types of uncertainty and was used to determine the confidence limits around the estimated GM. The overall uncertainty can be reduced in the future by collecting more exposure data with all the relevant contextual information available or with better underpinning of the scaling of the ART MFs. Therefore more experimental exposure studies providing insight into specific processes (*e.g.* dustiness and efficacy of localized controls) are to be welcomed.

The total percentage of explained variance is 61% for the abrasion exposure form, 64% for dust, 60% for vapours and 30% for mist. ART scores were assigned per measurement and afterwards measurements with, to a large extent, similar exposure determinants were grouped to scenario level. Consequently within a scenario, measurements with more or less similar ART scores were grouped. Differences in model scores were therefore found mainly between scenarios and only to a limited extent within scenarios. Consequently, the ART scores mostly explained between-scenario variability (92% for the abrasion exposure form, 87% for dust, 85% for vapours and 67% for mist). Although a substantial part of the total variance is explained by the mechanistic model, the non-negligible unexplained variance ranged from 1.4 to 5.4 on log transformed scale. This proportion of variance reflects the model uncertainty and the exposure variability found between and within companies.

With this calibration the mechanistic model of ART was able with 90% confidence to estimate GM exposures of a scenario to lie within a factor between two and six of the measured GM (depending upon the form of exposure). When estimating exposures for single companies or for an individual worker not only the model uncertainty found in this calibration (expressed as UF) but also the variability in exposures found between companies, between workers and within workers should be taken into account. The methods used to estimate the variability in exposures between companies, between workers and within workers are described elsewhere.[5]

The relatively low explained variance for mist can possibly be explained by the fact that most of the data were spray application of liquids. During spraying several determinants such as spray equipment, spray pressure, nozzle diameter are likely to influence exposure levels.[25–29] For a generic exposure model such as ART, it is not feasible to include very specific determinants such as these for the spraying scenarios. In addition, these determinants are difficult to quantify and are therefore not included in the mechanistic model. Also a substantial part of the measurements within the exposure form mist were conducted outdoors. Determinants like wind direction and wind speed are known to influence exposure (variability)[30] and are not part of the ART mechanistic model.

Comparing the capability of two different exposure estimation models (*i.e.* Stoffenmanager and ART) to explain variability in exposure concentration can only be done properly when the same dataset is being used. Therefore measurements that were used in the calibration of Stoffenmanager[9,10] were selected from the ART

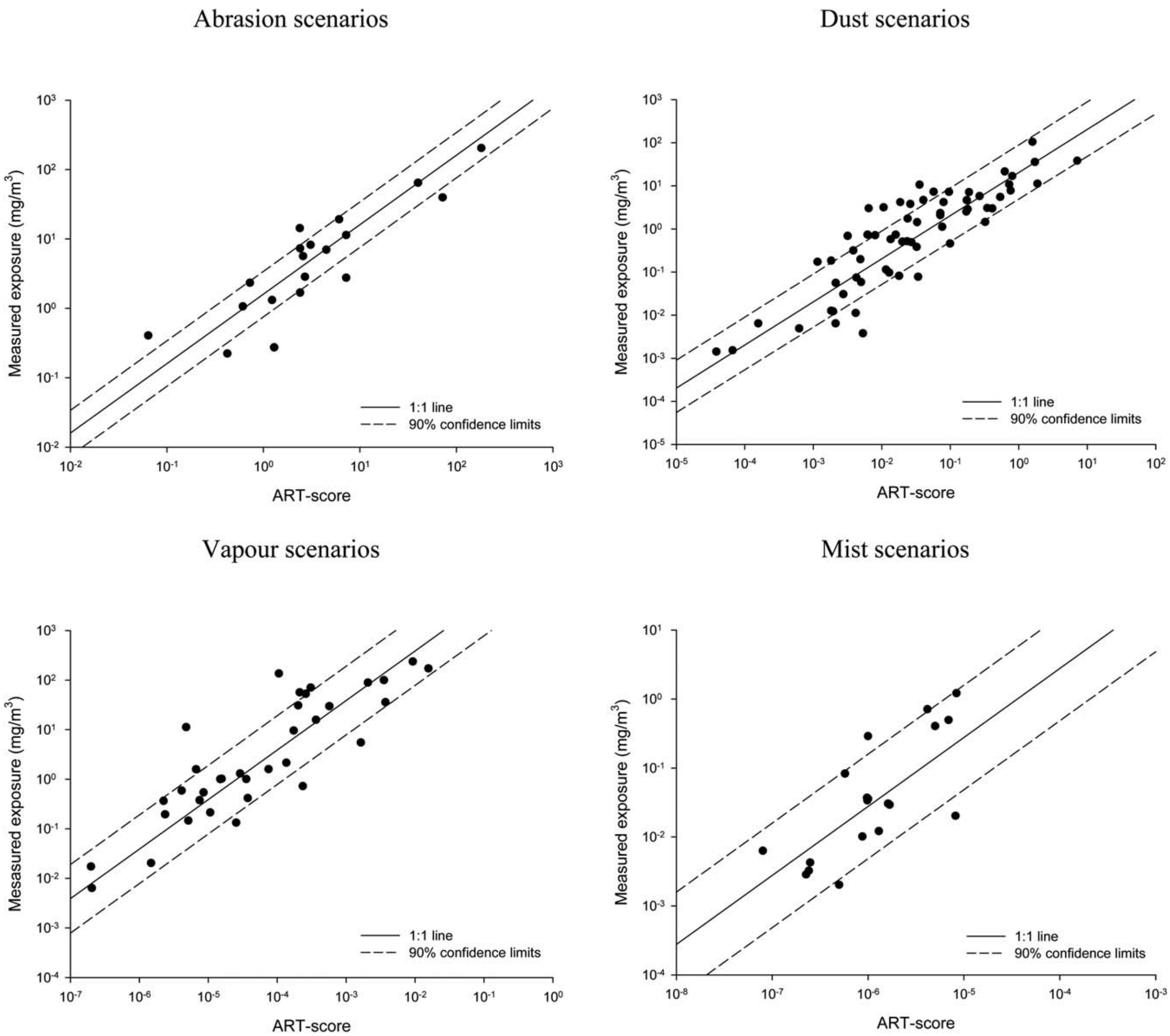

Fig. 1 Visual depiction of the relationship between model scores and actual exposure, per broad scenario definition, for the different forms of exposure.

calibration dataset. For the data reflecting exposure to abrasive dust ($n = 85$) the mechanistic model of ART explained 66% of the total variance while Stoffenmanager explained 47%. Similar results were found for the three other exposure forms. The percentage of variance explained by the ART mechanistic model was 66%, 50% and 50% for respectively dust ($n = 385$), vapour ($n = 164$) and mist ($n = 199$) scenarios. For the same scenarios Stoffenmanager explained 51%, 40% and 43% of the total variance. Overall the ART mechanistic model explained approximately 10% more variance than Stoffenmanager. The improved performance of the ART mechanistic model is most likely due to a more structured characterization of activity emission potential and more precise categories for MFs localised controls and dispersion.

The current modeling framework of lower and higher tier models is useful and necessary to evaluate large amounts of chemicals. However, the exposure models clearly need further development and await the necessary validation research. Surprisingly, only a few validation studies focusing on generic models for inhalation exposure are currently available.[10,31–35] The exposure modeling science will only evolve when more of such comparisons with good quality data become available and thus this field would benefit substantially from the sharing of exposure data.[36]

In conclusion, the mechanistic model of ART was calibrated using broad scenario level definitions and included company as a random component, where the random scenario component was used as an estimate of model uncertainty. Data were used to calibrate the intercept to translate the dimensionless model outcome into an exposure estimate in mg m^{-3}. The proportional relationship between relative model scores and measured exposures was maintained.

This paper showed that the mechanistic model of ART was able to estimate with 90% confidence GM exposures of a scenario to lie within a factor between two and six of the measured GM exposure (depending upon the form of exposure). In the future, evaluation studies investigating the applicability, accuracy and reliability of the mechanistic model estimates are necessary to further test the usability of this exposure assessment tool.

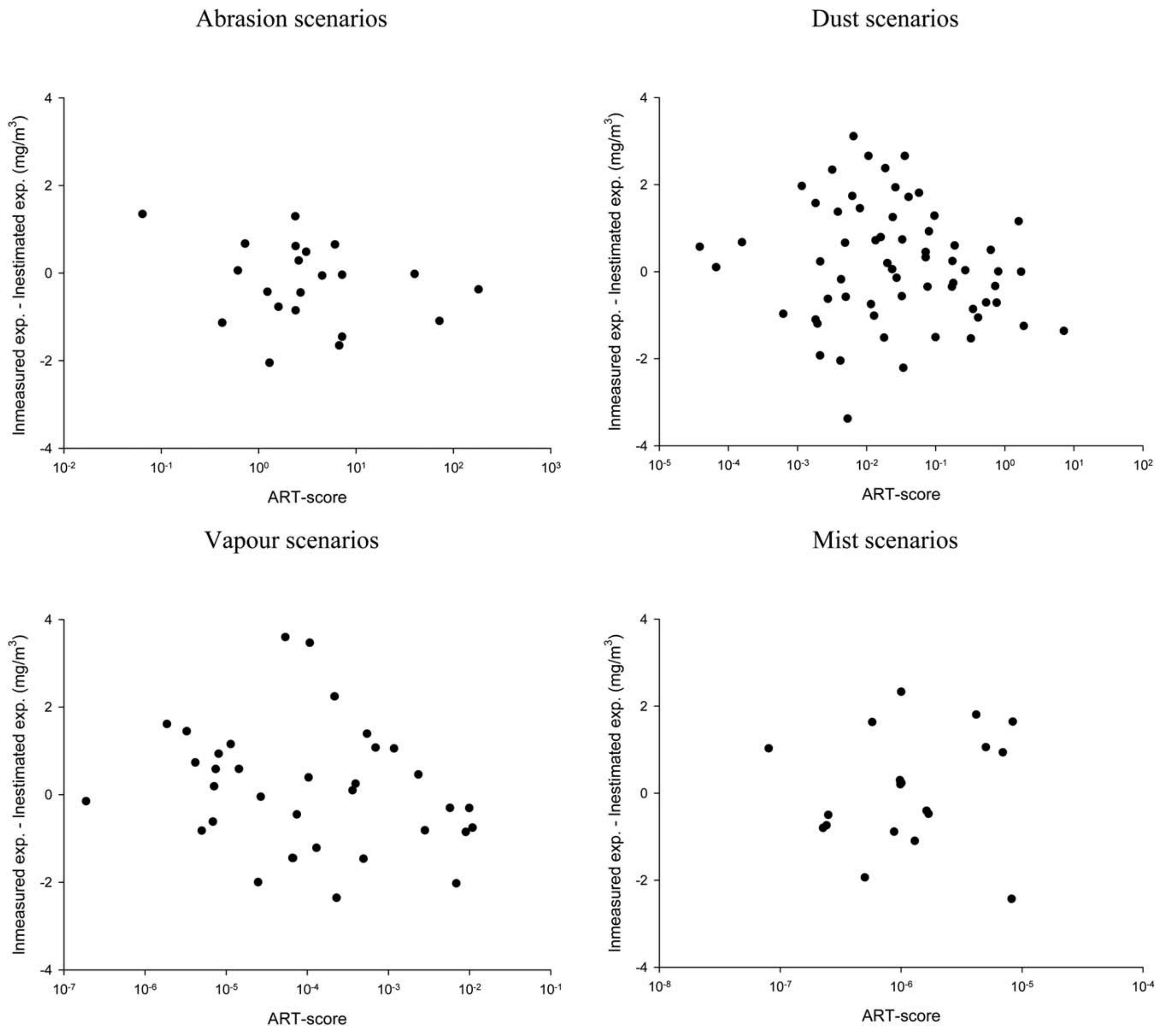

Fig. 2 Residuals per scenario, for the different forms of exposure.

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