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PAPER

Validation of the inhalable dust algorithm of the Advanced REACH Tool using a dataset from the pharmaceutical industry

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As it is often difficult to obtain sufficient numbers of measurements to adequately characterise exposure levels, occupational exposure models may be useful tools in the exposure assessment process. This study aims to refine and validate the inhalable dust algorithm of the Advanced REACH Tool (ART) to predict airborne exposure of workers in the pharmaceutical industry. The ART was refined to reflect pharmaceutical situations. Largely task based workplace exposure data ($n = 192$) were collated from a multinational pharmaceutical company with exposure levels ranging from 5×10^{-5} to 12 mg m^{-3}. Bias, relative bias and uncertainty around geometric mean exposure estimates were calculated for 16 exposure scenarios. For 12 of the 16 scenarios the ART geometric mean exposure estimates were lower than measured exposure levels with on average, a one-third underestimation of exposure (relative bias −32%). For 75% of the scenarios the exposure estimates were, within the 90% uncertainty factor of 4.4, as reported for the original calibration study, which may indicate more uncertainty in the ART estimates in this industry. While the uncertainty was higher than expected this is likely due to the limited number of measurements per scenario, which were largely derived from single premises.

1.0 Introduction

Pharmaceutical manufacturing processes frequently involve highly potent active pharmaceutical ingredients (APIs) and exposure assessment is fundamental to protecting the workers health in this industry. However due to the often intermittent nature of pharmaceutical processes it can often be difficult to obtain sufficient numbers of measurements to adequately characterise exposure levels, as required by the Chemical Agents Directive 98/24/EC. Furthermore a case-by-case assessment of exposure levels based on exposure measurement data is generally considered impracticable and expensive.[1]

The introduction of the Registration Evaluations Authorisation and Restriction of Chemicals (REACH) Regulations 2006 has placed an onus on the manufacturers of chemicals to produce chemical safety reports (CSR) containing 'exposure scenarios', which should detail how their products are manufactured or used during their life cycle. The REACH guidance recommends a tiered approach to exposure assessment, involving the use of tier 1 generic screening tools or exposure models to distinguish between substances in exposure scenarios of concern and those which are not[1] *e.g.* ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals) Targeted Risk Assessment (TRA),[2] Stoffenmanager[3] and the EMKG-Expo-Tool (http://www.reach-helpdesk.de/en/Exposure/Exposure.html). More sophisticated tier 2 exposure models, such as the Advanced REACH Tool (ART),[4] may be employed to provide more

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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 which can be combined using Bayesian statistics. The ART is freely available (www.advancedreachtool.com) for assessing worker exposure in the registration processes in the scope of REACH. This manuscript presents the refinements of the ART for the pharmaceutical industry and the validation of the inhalable dust model with a dataset collated from this industry. We believe that this study will stimulate further evaluation of exposure assessment models.

confidence, sensitivity and scientifically justified exposure estimates compared to tier 1 tools. The ART combines mechanistically modelled exposure estimates with available relevant exposure data using a Bayesian approach. The ART mechanistic model was developed and calibrated for the purposes of REACH exposure scenarios and estimates a geometric mean (GM) exposure level for any given exposure scenario from across many companies and countries.[5] Where traditional exposure assessment methods are not available, exposure models such as the ART may be the most viable option for derivation of REACH exposure scenarios.

Exposure variability and uncertainty are clearly distinct entities with different implications for exposure assessment. Regarding exposure models, uncertainty reflects our lack of knowledge of the exposure process and/or limitations of the model, while variability reflects the natural diversity over time, space and between the individuals and circumstances in the exposure scenario.[1,6] The ART provides separate estimates for variability and uncertainty. The user can select a percentile of the exposure distribution (*i.e.*, 50th, 75th, 90th, 95th, or 99th) and the difference between the 50th and a higher percentile level is a reflection of the variability in the scenario. In addition, a level of uncertainty around the estimated percentile is given (*i.e.*, interquartile, 80%, 90% or 95% confidence intervals). The ART provides an incentive to collect exposure measurements as by using the Bayesian application of the tool, the uncertainty of the exposure estimates will gradually decrease as representative exposure data become available.

Limited validation studies have been carried out on 1st tier exposure models.[7–9] ART is the only 2nd tier model currently available and a full evaluation is vital to ascertain its accuracy or validity and precision for its intended use. While the pharmaceutical industry is largely exempt from the requirements of REACH (as per Article 2 (5) (a) of the Regulations), and the objective of the ART was not to estimate workplace specific exposures, it was anticipated that ART could have potential applications for exposure assessment and risk management within this industry.

During the development of the ART mechanistic model, refinements were incorporated to increase the applicability of ART for exposure assessment in the pharmaceutical industry. A previous calibration of the ART mechanistic model showed that it was able to estimate GM exposures of a scenario with 90% confidence to within an uncertainty factor (UF) of 4.4 of the true GM exposure for the dust exposure form.[5] Using a dataset collated from the pharmaceutical industry, the aims of this study were twofold: to investigate the bias in model GM estimates by comparing with the GM of measurement data; and to validate the UF around the inhalable dust model GM exposure estimates by comparing with the results of the calibration study. This paper also describes the ART model refinements that were incorporated for the pharmaceutical industry and the results of the investigation of the validity of the inhalable dust model GM exposure estimates.

2.0 Materials and methods

2.1 ART exposure algorithm

The ART mechanistic model is based on a source-receptor model[10,11] which describes a stepwise transport of a contaminant from the source to the receptor, and incorporates seven independent principal modifying factors (MF) (*e.g.*, substance emission potential, activity emission potential and localised controls). Relative multipliers have been assigned to the underlying categories of each MF which are used as multipliers in the model algorithms. The model consists of one equation to estimate the contribution from NF [eqn (1)] and one for estimating the contribution from FF sources [eqn (2)]. Personal exposure from a NF source (C_{nf}) is a multiplicative function of substance emission potential (E), activity emission potential (H), (primary) localised control (LC_1), secondary localised control (LC_2), and dispersion (D). The equation for a FF source (C_{ff}) also includes segregation (Seg) and separation (Sep).

$$C_{nf} = (E_{nf}H_{nf}LC_{nf1}LC_{nf2})D_{nf} \quad (1)$$

$$C_{ff} = (E_{ff}H_{ff}LC_{ff1}LC_{ff2}Seg_{ff})D_{ff}Sep_{ff} \quad (2)$$

The level of surface contamination (Su) for each activity depends on the location of the source and is also taken into account. Subsequently, the overall exposure is estimated [eqn (3)]:

$$C_t = \frac{1}{t_{total}}\sum_{tasks}\left\{t_{exposure}\left(C_{nf} + C_{ff} + Su\right)\right\} + t_{non\text{-}exposure} \times 0 \quad (3)$$

The algorithm considers multiple activities (and exposure time ($t_{exposure}$)) within an 8 hour work shift (t_{total}) and also allows periods with assumingly zero exposure ($t_{non\text{-}exposure}$). This results in dimensionless relative exposure scores, which were calibrated using exposure measurements, enabling the mechanistic model to estimate the GM exposure level of an exposure scenario in mg m^{-3}.[5] Linear mixed effects models were used to evaluate the association between relative ART model scores and measurements. A random scenario component of variance was introduced to reflect the model uncertainty. The model was calibrated separately for the following exposure forms: vapour, mist, abrasive dust and dusts resulting from handling powders or granules; fumes, gases and fibres are outside the current applicability domain of the ART. Exposure data collected from across many industries, including the pharmaceutical industry ($n = 291$; 34% of the overall dataset), were used to calibrate the dust exposure form (resulting from handling powders or granules) of the mechanistic model. A detailed description of the ART mechanistic model, its underlying assumptions, assignment of model scores, and calibration can be found elsewhere.[4,5]

2.2 Refinement of ART MF for the pharmaceutical industry

In order to ensure that the ART was applicable for exposure scenarios from the pharmaceutical industry, it was necessary to review some of the ART MFs during the development of the ART and prior to the calibration of the mechanistic model, namely: activity emission potential, localised controls and dispersion. Proposed classifications were developed by the authors based on the review of published literature[4] and GlaxoSmithKline (GSK) data. The classifications and assigned efficacy multipliers were reviewed by health and safety experts from the pharmaceutical industry based on their experience in this industry and many of whom had access to their own

measurement data to justify their decisions. A workshop was held in the UK in October 2009 to discuss the refinements of the localised control and dispersion MFs with 11 experts, including occupational hygienists, containment experts and researchers, from GSK and the broader pharmaceutical industry. The classifications were discussed until a consensus was reached.

2.3 Collation of exposure data for the validation of the ART mechanistic model

Occupational exposure data were collected from the GSK pharmaceutical and consumer healthcare company from premises ($n = 11$) across Europe and Asia. The validation dataset included activities, local controls, sampling durations, *etc.* that were largely similar to the pharmaceutical dataset used in the calibration of the dust algorithm of the ART mechanistic model.[5] However the data were collected from six additional GSK premises that were not included in the calibration dataset. Exposure samples were analysed using validated methods (either GSK in-house methods or methods accredited by the United Kingdom Accredited Services (UKAS)), and included a range of analytical data for various APIs ($n = 130$) and gravimetric analysis for the total inhalable dust (TID) ($n = 62$). The data were collected using the following strategies: data were abstracted from existing occupational hygiene reports; and by collating monitoring record sheets from GSK occupational hygienists. All of the exposure data reflect personal inhalation exposure measurements and comprised either single or multiple activities. The data were collected by experienced occupational hygienists or occupational hygiene technicians. All of the data were reviewed by two of the authors (PMD and JS) whom had confidence that it was collected and recorded satisfactorily. Where necessary, to help clarify any ambiguities, further contextual information and photographs of the worker and the process were obtained from site occupational hygienists. The data requirements for this study were slightly less strict compared to those followed for the calibration of the ART *i.e.* assessments ($n = 90$) which did not have information available on sample duration, sampling methods or analytical methods were also included. However importantly all assessments were collated and analysed using GSK validated methods and all information required for the assessment of all ART MFs was available. In cases where sampling duration was not reported ($n = 65$), information on the relative durations of individual tasks were obtained by consultations with the site occupational hygienists. The majority of the measurements were task-based with a median sampling time of 28 min (range 5.4–286 min; $n = 127$) and 90% of measurements had sampling times <68 min in duration.

2.4 Assignment of ART model scores

Based on the contextual information documented in the survey reports, ART scores for each MF were assigned by one member of the project team (PMD) and subsequently reviewed by two project team members (JS and WF). In cases of inconsistencies the assessments were discussed until consensus was reached. When multiple activities occurred during a single measurement, ART scores were calculated per activity and then combined as a time-weighted average for all of the activities that occurred during the measurement period.

2.5 Data processing and statistical analysis

Both the measured exposure data and the contextual information required to derive ART scores were stored in Microsoft Office Excel 2007. The data were analysed using SAS Statistical Software (version 9.1.3; SAS Institute, Cary, NC, USA).

Measured exposure concentrations were found to approximate to a log-normal distribution and ART was developed to estimate GM exposure levels hence descriptive statistics are presented as GM levels, with geometric standard deviation (GSD) and range of the exposure distribution also presented. As measurement error may have more impact on measurements of short duration, measurements with sampling duration less than five minutes were excluded ($n = 5$). In order to accurately compare the measured GM exposure levels with the estimated GM exposure levels, exposure scenarios with greater than 50% of the measurements below the limit of detection (LOD) of the analytical technique ($n = 62$ measurements) and exposure scenarios with less than three measurements ($n = 45$ measurements) were excluded. After applying these exclusion criteria a dataset of $n = 192$ measurements from GSK primary ($n = 72$), secondary ($n = 67$), healthcare ($n = 17$) and Research and Development (R&D) ($n = 36$) sites remained. The measurements ($n = 192$) were grouped to exposure scenarios ($n = 16$). Exposure scenarios were defined by the main MFs: activity emission potential (based on activity class and quantities/level of contamination); substance emission potential (categories grouped to dust or granules); localised controls (categories grouped to class or subclass level) *e.g.* dumping of 1–10 kg granules with and without local exhaust ventilation (LEV) were considered to be two separate exposure scenarios. Similarly, data from scooping of <1 kg granules and <1 kg powders were included as two different exposure scenarios.

The maximum likelihood estimation (MLE) procedure[12] was used to treat measurement results that were below the LOD ($n = 36$). For all measurement results below the LOD the overall exposure distribution was used to randomly impute values between 0 and the LOD value taking into account the mean exposure for that individual scenario. To fully account for the variance from the imputation, 30 imputations were performed resulting in 30 datasets. Subsequently, PROC MIANALYZE was used to combine the imputed values from the multiple datasets.

As we were interested in the accuracy of the ART to estimate GM exposure levels, bias was calculated at scenario level as the difference between ART GM estimates and the GM of the measured exposure.[13] Overall bias for the scenarios was defined as the mean difference between GM estimates of the ART and the GM of measured exposure.

A positive bias indicates an overestimation of exposure while a negative bias indicates an underestimation of exposure by the ART model. The bias presents the systematic error of the model and shows the capability of the model to estimate the 'true value'. The relative bias was defined as the difference between the bias and GM of measured exposure multiplied by 100% [eqn (4)].

$$\text{Relative bias} = \left(\frac{\text{bias}}{\text{measured GM}}\right) \times 100\,\% \qquad (4)$$

The mechanistic model was developed to estimate GM exposure levels of an exposure scenario. Schinkel and colleagues (accepted) reported an overall UF of 4.4 for ART mechanistic model estimates of exposure to dusts resulting from handling powders or granules. This UF indicates that, with 90% confidence, the estimated GM exposure levels are within a factor 4.4 of the measured GM. The difference between estimated and measured GM exposure levels was calculated per scenario in this paper, and referred to as factor difference (*i.e.* estimated GM/measured GM). If the previously reported UF of 4.4 was true for this validation dataset, 90% of these factor differences should lie between 0.23 and 4.4 (derived from: 1/4.4 and 1 × 4.4).

3.0 Results

3.1 Refinement of ART for the pharmaceutical industry

To incorporate manufacturing activities and processes that are common in the pharmaceutical industry within the ART, the following amendments were incorporated into the activity emission potential MF classification:

- For all activity classes, with the exception of the activity class 'handling of contaminated objects' and 'impaction on contaminated objects', additional categories were added in the lower quantity ranges *i.e.* 10–100 g and <10 g.
- For the activity classes 'handling of contaminated objects' and 'impaction on contaminated objects', a category for 'handling of (or impaction on) apparently clean objects' was added.
- A separate activity subclass was incorporated into the transfer activity class to account for when the material is transferred through a hose or tube using pressure (*i.e.* vacuum transfer of powders).

To include local control measures common in the pharmaceutical industry, the following amendments were incorporated into the localised control MF categorisation:

- Glove-boxes (low, medium and high specifications).
- Glove-bags (non-ventilated and ventilated or kept under negative pressure).
- Horizontal or downward laminar flow booths (containing the source only) were added as an additional class within localised control by LEV enclosing hoods.
- Physical containment—no extraction (low, medium and high level specifications).

Table 1 shows the classification of localised controls, descriptions of the classes and assigned efficacy multipliers for reducing inhalation exposures.

Dual local control systems are sometimes used within the pharmaceutical industry and to allow the efficacy of two specific localised control measures to be accounted for, an option for selecting two local control measures was introduced within the ART localised control MF *e.g.* low level containment (multiplier = 0.1) with local exhaust ventilation (LEV) (multiplier = 0.1); multipliers are treated multiplicatively to result in a local control MF multiplier of 0.01.

To incorporate ventilation environments common in the pharmaceutical industry, downward laminar flow booths (containing the worker and the source) were added to the dispersion MF. These flow booths can be equipped with partial or full screens with glove ports, potentially offering a further level of containment. These screens were classified as follows: partial screen; partial screen fitted with glove ports; full screen fitted with glove-ports. Table 2 shows the classification of downward laminar flow booths and assigned multipliers.

3.2 Dataset used for validation of the ART mechanistic model

The overall validation dataset consisted of 192 personal inhalation exposure measurements that were collected over the period 2002–2009. They included a wide range of handling activities and local control measures that are representative of exposure scenarios found in the pharmaceutical industry. The measured exposure levels ranged from 5×10^{-5} to 12 mg m^{-3}, representing a large range of exposure levels from exposure scenarios such as small scale R&D activities and large scale bulk manufacturing (scenario GSD range = 1.2–6.0). There was a median of 6 exposure measurements per exposure scenario (range = 3–66), and the exposure scenarios were derived from a median of 1 company (range = 1–3). Table 3 presents the descriptive statistics for the exposure scenarios. The lowest detectable exposure level (5×10^{-5} mg m^{-3}) was found during an exposure scenario that involved scooping a few milligrams of material inside a fume cupboard. The highest exposure level (12 mg m^{-3}) was found during an exposure scenario which involved scraping of material off the surfaces of a mixer, with no localised controls (the worker wore RPE). It is important to note that this high exposure was based on a relatively short task-based measurement (33 min) that was analysed for the total inhalable dust (TID).

3.3 Validation of the ART mechanistic model

Results of the validation analysis for bias, relative bias and the factor difference between measured and estimated GM exposure levels are presented in Table 3. Relative bias values were between −94% and 700% indicating that for some exposure scenarios the estimated GM exposure was only 6% of the measured GM exposure while in other extreme cases the estimated GM exposure was 7 times higher than the measured GM exposure. The difference between estimated GM and measured GM exposure levels resulted in a maximum factor difference of 8. For 75% of the scenarios the uncertainty in exposure estimates was within the UF of 4.4, which is less than the 90% of scenarios found in the original calibration study[5] and indicates more uncertainty in the ART estimates in this industry. 90% of the scenarios had a factor difference of less than 5.5. In general (12 out of the 16 scenarios) the ART underestimated GM exposure levels. An overall relative bias of −32% for estimated *versus* measured GMs indicated on average a one-third underestimation of GM exposure levels.

Fig. 1 presents a scatter plot of the estimated GM exposure levels in relation to the GM measured exposure levels for the exposure scenarios plotted on log–log scales.

4.0 Discussion

This paper presents the refinements of the ART and the results of the validation of the dust exposure form of the mechanistic model using a pharmaceutical dataset. It was necessary to make

Table 1 Classification of the localised control MF and assigned efficacy multipliers[a]

Local control class	Localised control subclass	Description	Assigned efficacy multiplier
No localised controls			1
Containment—no extraction	General description	Physical containment or enclosure of the source of emission. The air within the enclosure is not actively ventilated or extracted. The enclosure is not opened during the activity. This class reflects "add on" enclosures and does not include inherently closed systems (like pipelines)	
	- Low specification containment	**Physical containment or enclosure of the source of emission. The air within the enclosure is not actively ventilated or extracted. The enclosure is not opened during the activity.** **The process is contained with a loose lid or cover, which is not air tight. This includes tapping molten metal through covered launders and placing a loose lid on a ladle.** **This class also includes bags or liners fitted around transfer points from source to receiving vessel. These include Muller seals, Stott head and single bag, and associated clamps and closures.**	0.1
	- Medium specification containment	**Physical containment or enclosure of the source of emission. The air within the enclosure is not actively ventilated or extracted. The enclosure is not opened during the activity.** **The material transfer is enclosed with the receiving vessel being docked or sealed to the source vessel.** **Examples include sealing heads, transfer containers and multiple o-rings. Inflatable packing head with continuous liner ensures a seal is maintained during the powder transfer and the continuous plastic liner prevents direct contact with the product. The correct type of tie off must be used.**	0.01
	- High specification containment	**Physical containment or enclosure of the source of emission. The air within the enclosure is not actively ventilated or extracted. The enclosure is not opened during the activity.** **The substance is contained within a sealed and enclosed system. This class includes metal smelting furnaces or atomisation units.** **The material transfer is entirely enclosed with high containment valves (*e.g.* split butterfly valves and direct couplings, which consist of two sections which connect together to allow the opening of the valve). At the end of the material transfer the two halves are separated, forming a seal on both the process equipment and the material container. The system is designed to minimise the surface area which can contact the material or pairs of valves with wash space between them.**	0.001
Receiving hoods	Canopy hoods	A canopy hood placed over a hot process to receive the plume of contaminant-laden air given off. For cold processes with no thermal uplift, canopy hoods are ineffective (HSE, 2008).	0.5
	Other receiving hoods	A receiving hood can be applied wherever a process produces a contaminant cloud with a strong and predictable direction (*e.g.* a grinding wheel). The contaminant cloud is propelled into the hood by process-induced air movement. The face of the hood must be big enough to receive the contaminant cloud and the extraction empties the hood of contaminated air at least as fast as it is filled.	0.2
Capturing hoods	Fixed capturing hoods	Fixed capturing hoods located in close proximity of and directed at the source of emission. The design is such that the work is performed in the capture zone of the ventilation system and the capture is indicated at the workplace.	0.1
	Movable capturing hoods	Movable LEV systems such as hoods with extendable arms. The design of the system does not prevent work being performed outside the capture zone of the system and worker behaviour can influence the effectiveness of the system.	0.5
	On-tool extraction	LEV systems integrated in a process or equipment that cannot be separated from the primary emission source.	0.1
Enclosing hoods	Fume cupboard	Any form of permanent encapsulation or encasing of the source of which maximally one side is open with a well designed local exhaust ventilation system (*e.g.* laminar air flow). The design of both the enclosure and the ventilation system is such that the influence of worker behaviour is minimal (*e.g.* an alarm system prevents the worker from using the fume cupboard in case the system is not working properly).	0.01
	Horizontal/downward laminar flow booth	**In a horizontal laminar flow booth, contaminated air is extracted through holes situated at the rear of the booth which creates a horizontal laminar air flow. The air is filtered prior to being discharged to the atmosphere. The booth contains the source and has maximally one side open.** **In a downward laminar flow booth, a curtain of descending laminar air flow is created between the ceiling and the rear of the booth where exhaust grills are located in the lower section. The booth contains the source and has maximally one side open.**	0.1

Table 1 (*Contd.*)

Local control class	Localised control subclass	Description	Assigned efficacy multiplier
		Spray rooms and laminar down-flow booths (with the size of a room which contains both the source and the worker) are not considered to be a localised control and will be treated together with the dispersion MF.	
	Other enclosing hoods	Any form of permanent encapsulation or encasing of the source of which maximally the front side is open with a proper local exhaust ventilation system.	0.1
	Other LEV systems	In case the type of the LEV system is unknown or not specified, this default LEV category can be selected. Note that this default category results in a low reduction of the estimated personal exposure level. An attempt should be made to more specifically define the type of local exhaust ventilation.	0.5
Glove bag	**General description**	**Large plastic bags, available in different designs and sizes are fitted with gloves which allow products to be handled in a contained way.** **An adaption piece is necessary between the glove bag and the process equipment.** **The glove bag must be designed specifically for the task and the quantity of material to be handled.** **Various other items such as pass-out boxes, inlet filters, and drains are added to meet specific needs.** **Note: use of glove bags does not negate the need to implement a long term permanent technological solution.**	
	>Glove bag (non-ventilated)	**Large plastic bags, available in different design and sizes are fitted with gloves which allow products to be handled in a contained way without exhaust ventilation.**	0.01
	>Glove bag (ventilated or kept under negative pressure)	Large plastic bags, available in different design and sizes are fitted with gloves which allow products to be handled in a contained way. The glove bag is maintained with filtration and ventilation at specific flow rates	0.001
Glove box	**General description**	**Any form of permanent encapsulation or encasing of the source (which are not opened during the given activity) with a well designed local exhaust ventilation system.** **The design of both the enclosure and the ventilation system is such that the influence of worker behaviour is minimal (*e.g.* the enclosure cannot be opened before the substance is properly vented).**	
	>Low specification glove box	**A low specification glove box is specified as:** **• Single chamber, simple access doors or pass box** **• Not safe change glove** **• Single HEPA filtered extract air** **• Not safe change filters** **• Manual cleaning**	0.001
	>Medium specification glove box	**A medium specification glove box is specified as:** **• Two or more chambers if large area bin docking or high dust levels expected** **• Safe change or push through filters are required** **• Solid (stainless steel) construction for durability** **• Size is dependent on the task to be carried out** **• Safe change filters are required** **• Air should be single or double HEPA filtered and or exhausted directly to the atmosphere after single HEPA filtration.** **• The equipment should be maintained under negative pressure and the air flow and filter condition continuously monitored.** **• Emergency air extraction should start up automatically in the event of a leak or a damaged glove.** **• Interlocked air locks should be used to prevent high dust concentrations in the area of the transfer ports and reduce risk. (Of escape of the contaminant during transfer of materials into and out of the glove box).** **• Glove changes should be able to be carried out without breaking containment** **• Waste disposal ports are required.** **• Correct sealing of continuous liners.** **• Manual cleaning**	0.0003
	>High specification glove box	**A high specification glove box is specified as:** **• Two or more chambers** **• Safe change filters are required** **• Stainless steel construction** **• Size is dependent on the task to be carried out** **• Safe change filters are required** **• Air should be single or double HEPA filtered and or exhausted directly to the atmosphere after single HEPA filtration.**	0.0001

Table 1 (*Contd.*)

Local control class	Localised control subclass	Description	Assigned efficacy multiplier
		• The equipment should be maintained under negative pressure and the air flow and filter condition continuously monitored. **• Emergency air extraction should start up automatically in the event of a leak or a damaged glove.** **• Interlocked air locks should be used to prevent the escape of the contaminant during transfer of materials into and out of the glove box.** **• Glove changes should be able to be carried out without breaking containment** **• Waste disposal ports are required.** **• Integrated sampling and contained drum charging** **• Sealed and high containment transfer ports (contained transfer couplings, rapid transfer ports (RTPs), alpha/beta valves, *etc.*)** **• Including waste removal and change parts** **• Wash in place** **• Alarmed**	

[a] Classifications shown in bold type were incorporated as a result of the pharmaceutical industry refinements but are applicable to other industries.

Table 2 Classification of the dispersion MF and assigned multipliers

Dispersion class	Description	Assigned multiplier
Downward laminar flow booth	Room enclosures can also be partially enclosed, which are a compromise between containment and accessibility. These so-called downward laminar flow booths (or 'walk-in' booths) can be very effective, and are defined as a booth, in which a curtain of descending laminar air is created between the ceiling and the rear of the booth where exhaust grilles are located at the lower section. To be effective in reducing personal exposure levels the worker must not stand at the exhaust grilles and standing in-between the source and the grilles will reduce the effectiveness of the booth. The exhaust volume is typically between 3500 and 4000 m^3 h^{-1} (per 1 m width). Other conditions that make the booth effective are: • The booths must completely enclose the work task and the worker. • Booth sizes are adaptable to the work task and process equipment and can have varying levels of filtration. • The filter should have high dust holding capacity, and performance and volume air flow need to be checked regularly. • For downward laminar flow booths the capture velocity should be approximately 0.5 m s^{-1}. • A safe work line (SWL) marks the limit of effective containment and dust capture.	0.2
- With partial screen	Partial screens covering the majority of the front of the process/booth; however, there may be relatively small openings for operator hands and/or gaps at the top and bottom of the booth.	0.15
- With partial screen fitted with glove ports	Partial screen covering the majority of front of process/booth and is fitted with glove ports to allow the operator to handle the product; however, there may be relatively small gaps at the top and/or bottom of the booth.	0.1
- With full screen fitted with glove ports	Full screen covering the entire front of the process/booth and is fitted with glove ports.	0.01

refinements to some of the ART MFs so that it would be applicable for exposure scenarios common to the pharmaceutical industry *e.g.* to include activities within glove-bags, glove-boxes and downward laminar flow rooms. As further information becomes available on the efficacy of local control measures it is possible that further refinements to ART may be warranted. The

Table 3 Descriptive statistics of available measured exposure data at scenario level and validation results[a]

Scenario	N	$N <$ LOD	K	GM/ mg m^{-3}	GSD	Min/ mg m^{-3}	Max/ mg m^{-3}	Estimate GM/ mg m^{-3}	Bias	Relative bias (%)	Factor difference (estimate GM/GM)
Cleaning 1–10 kg (dust)	7	0	1	5.03	2.3	1.83	12.33	2.42	−2.62	−51.97	0.48
Dumping 1–10 kg (dust) (DF room)	4	2	1	1.768	2.1	0.76	4.80	1.785	0.017	0.94	1.01
Dumping 1–10 kg (dust) (GB)	66	6	3	0.002	5.3	1×10^{-4}	0.10	0.001	−0.001	−50.00	0.50
Dumping 1–10 kg (dust) (LEV)	5	1	3	1.87	1.6	0.84	2.50	0.46	−1.41	−75.50	0.25
Dumping 1–10 kg (granules)	6	0	2	0.227	6.0	0.01	0.91	0.078	−0.149	−65.63	0.34
Dumping >10 kg (dust) (DF room)	6	0	1	2.115	1.3	1.60	2.97	1.0875	−1.03	−48.58	0.51
Dumping >10 kg (dust) (LEV)	12	4	2	3.09	2.2	0.82	7.79	1.18	−1.91	−61.77	0.38
Handling of slightly/limited contaminated (granules) (LEV)	7	0	1	0.005	2.0	0.002	0.011	0.0014	−0.0036	−72.00	0.28
Handling of slightly/limited contaminated (paste)	3	0	1	0.441	3.3	0.11	0.92	0.086	−0.355	−80.43	0.20
Handling of visible/substantial contamination (dust) (none and LEV)	3	0	1	5.07	1.8	3.40	9.80	1.37	−3.69	−72.94	0.27
Movement and agitation >10 kg (dust) (containment)	6	0	1	2.011	2.1	0.55	4.73	1.456	−0.555	−27.59	0.72
Scooping 1–10 kg (dust) (DF room)	7	0	2	1.982	2.0	1.27	9.29	1.586	−0.396	−20.01	0.80
Scooping 1–10 kg (dust) (LEV)	4	0	1	8.11	1.2	6.67	9.50	0.47	−7.64	−94.20	0.06
Scooping <1 kg (dust) (enclosing hoods)	44	21	3	0.00033	3.8	5×10^{-5}	0.02	0.0026	0.00227	687.88	7.87
Vacuum cleaning 1–10 kg (dust)	4	0	1	3.072	1.2	2.47	3.67	8.4595	5.39	175.39	2.75
Vacuum cleaning <1 kg (dust)	8	2	1	0.68	3.1	0.15	4.99	3.73	3.05	450.30	5.50

[a] N = Number of samples; $N <$ LOD = number of samples below the limit of detection; K = number of premises; GM = geometric mean; and GSD = geometric standard deviation.

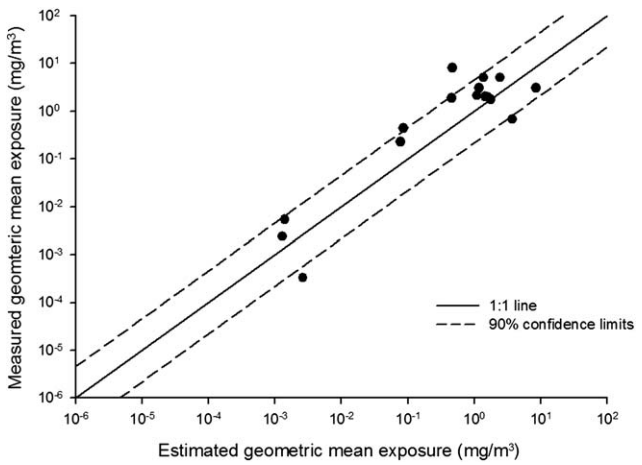

Fig. 1 The relationship between GM model scores and measured GM exposures per scenario for the pharmaceutical validation dataset.

exposure measurements used for the validation study ranged from 5×10^{-5} to 12 mg m^{-3} for 16 scenarios (individual scenario GSD range = 1.2–6.0). While the validation dataset covered a broad range of exposure situations typical of the pharmaceutical industry, not all exposure situations or possible ART MF combinations were included. This study gives an insight into the applicability of the ART for the pharmaceutical industry and the model uncertainty in exposure estimates. 75% of the scenarios had an estimated GM within the UF of 4.4 of the measured GM exposure levels, a smaller percentage than the 90% expected from the calibration study.[5] An overall relative bias of −32% for estimated *versus* measured GM exposure levels indicated on average a one-third underestimation of GM exposure levels for scenarios from the pharmaceutical industry.

A limitation of the dataset used in this validation study was the small sample size and the limited number of companies measured within a scenario. As exposure levels vary between scenarios, between premises and between and within workers[14,15] a precise estimate of the GM exposure levels could only be achieved with a dataset including a large number of representative measurements from many countries, companies, workers and days. Hence, the somewhat larger uncertainty observed in this study as compared to the calibration study might, in part, be due to the limited number of measurements and companies/premises included per scenario. The UF found in the calibration of the mechanistic model of ART showed the overall precision of the mechanistic model to estimate the GM exposure levels for a specific exposure scenario. Within the ART model it is possible to explicitly choose a level of conservatism (*i.e.* a higher percentile of the exposure distribution) to take into account the variability in exposure levels found between companies and between and within workers. Due to the limited number of measurements per scenario in this study, it was not possible to validate the mechanistic model estimates of the different percentiles of the exposure distribution.

The overall uncertainty of the ART exposure estimates is a consequence of a combination of model and model parameter uncertainty (our lack of knowledge of the exposure process, as discussed in [ref. 1]); exposure scenario uncertainty; and user or

input error. Exposure scenario uncertainty arises from inconsistencies between the scenario being modelled and the actual situation itself as it occurred in the workplace.[16] While the level of contextual information in the original survey reports was screened to obtain good quality data, in some cases it was still necessary for the assessors to employ some subjective judgement when interpreting the exposure scenarios. Field testing is an alternative method which could be used for testing the validity of exposure models, and may be the most direct measure of validity.[13] This would involve comparing the exposure model estimates to exposure levels of actual measurements made during an occupational hygiene survey specifically designed to collect all the data for the validation study, and would likely result in less subjective judgement and decreased exposure scenario uncertainty.

To the authors knowledge there have been no other comparably detailed validation studies of generic models with data specifically from the pharmaceutical industry. Several industry specific statistical models have been validated and as they were developed for specific scenarios, they are expected to be more accurate compared to the performance of generic models. However as the ART is based on a deterministic model it is not possible to compare the results of this study with any industry or exposure specific statistical models.[17,18] No other higher tier models are currently available for comparison of our study results and Stoffenmanager is the only generic 1st tier deterministic model with which the results of our study can be compared to. The validation study of Stoffenmanager showed a relative bias of −77% for scenarios resulting in dust exposure[9] indicating more bias than found in this validation study (overall bias −32%). However the relative bias value reported for Stoffenmanager was calculated on individual measurement level while the relative bias found in this study was on scenario level.

The categories of MFs in the validation dataset were largely similar to those in the pharmaceutical dataset that was used in the calibration of the ART,[5] with some differences. The calibration dataset only included one exposure scenario which included the use of a downward laminar flow room while the validation dataset included three of these exposure scenarios. The relative bias results (range 1 to −49%) indicate the ART mechanistic model underestimated the GM exposure by a factor two for these three scenarios within downward laminar flow rooms. As the dataset excluded all measurement series with greater than 50% of measurements less than the LOD, this largely resulted in exclusion of exposure scenarios with high specification localised controls such as glove-boxes and half suit isolators. Consequently only one exposure scenario with glove-boxes remained in the validation dataset. As glove-boxes are a very commonly used localised control in the manufacture of highly potent APIs it was important to investigate the accuracy of ART at estimating exposures for scenarios involving their use. The ART underestimated exposure for a scenario involving dispensing of API in a glove-box (n = 66 measurements) to within a factor of two of the measurement data value, which indicates that the tool may be useful for these scenarios.

Results from this study indicate that the ART may have useful applications for risk evaluations for example in the scope of REACH, as it is able to estimate GM exposure levels for exposure scenarios across companies and countries. The estimated exposure distribution gives an opportunity to choose more conservative exposure estimates to take into account uncertainty and variability in exposure situation. More precise estimates of the GM and the exposure distribution could be achieved by using the Bayesian application of the ART, whereby the information from a representative dataset can be used to reduce the uncertainty of the model exposure estimates.[19] Generally a more precise estimate of exposure could be achieved by increasing the number of measurements, and preferably from a range of companies with repeat measurements on a number of workers. ART is not applicable to assess a quantitative exposure level at a specific workplace. A comprehensive measurements study will be the most precise method to quantitatively estimate exposure at specific workplaces. In summary, this validation study indicates that the calibrated ART inhalable dust mechanistic model resulted in a one third underestimation of exposures (relative bias −32%). The uncertainty found for estimating GM exposure levels was bigger than the factor of 4.4 found in the calibration study. When interpreting these results one should take into account the relatively small dataset with scenarios largely derived from single premises. The lessons learned from the validation of ART for the pharmaceutical industry are relevant to the validation of ART for other industries as many of the exposure scenarios included in this study may be analogous to other industries. More validity studies focused on the exposure estimates and variability of the other exposure forms of the ART mechanistic model and user reliability studies should follow in the near future which will provide additional insight into the validity domain of ART.

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