Journal of Environmental Monitoring

Cite this: DOI: 10.1039/c0em00523a

www.rsc.org/jem

PAPER

Refinement and validation of an exposure model for the pharmaceutical industry

Patricia E. Mc Donnell,*[a] John W. Cherrie,[b] Anne Sleeuwenhoek,[b] Andy Gilles[c] and Marie A. Coggins[a]

Received 29th September 2010, Accepted 16th December 2010
DOI: 10.1039/c0em00523a

Objectives: Assessment of worker's exposure is becoming increasingly critical in the pharmaceutical industry as drugs of higher potency are being manufactured. The batch nature of operations often makes it difficult to obtain sufficient numbers of exposure measurements and occupational exposure models may be useful tools in the exposure assessment process. This paper aims to describe further refinement and validation of an existing deterministic occupational exposure model to predict airborne exposure of workers in this industry. Methods: Workplace exposure assessment data ($n = 381$) containing all the contextual information required for the exposure model were collated from a multinational pharmaceutical company. The measured exposure levels ranged from 5×10^{-7} to 200 mg m^{-3} for largely task based samples, and included a range of handling activities, local control measures and abnormal operating conditions. Model input parameters for local control measures and handling activities were refined to reflect pharmaceutical situations. Results: The refined exposure model resulted in good correlations between the log-transformed model predictions and the actual measured data for the overall dataset ($r_s = 0.61$, $n = 381$, $p < 0.001$) and at scenario level ($r_s = 0.69$, $n = 48$, $p < 0.001$). The model overestimated scenarios with measured exposure levels <0.1 mg m^{-3} ($r_s = 0.69$, bias = 0.71, $n = 46$, $p < 0.001$), and underestimated scenarios with higher measured concentrations (>0.1 mg m^{-3}) ($r_s = 0.59$, bias = −4.9, $n = 33$, $p < 0.001$). Including information on the refined sub-parameters improved the correlations, suggesting the uncertainty in the model parameters was partly responsible for the bias. Conclusion: Further scientific data from the pharmaceutical industry on model input parameters, particularly on the efficacy of local control measures, may help improve the accuracy of the model predictions. The refined exposure model appears to be a useful exposure assessment screening tool for the pharmaceutical industry.

Introduction

Many pharmaceutical manufacturing processes involve powder technologies and the control of solid aerosol emissions from these processes into the surrounding work environment poses an ongoing challenge for the occupational hygienist working in this industry.[1] In recent years the pharmaceutical industry has been developing more selective drugs of increasing potency. Due to

[a]*School of Physics, National University of Ireland Galway, University Road, Galway, Ireland. E-mail: patricia.mcdonnell@nuigalway.ie; Tel: +353 87 7928483*
[b]*Institute of Occupational Medicine (IOM), Research Park North, Riccarton, Edinburgh, EH14 4AP, UK*
[c]*Gillies Associates Ltd, 34 Holman Road, Aylsham, Norfolk, NR11 6BZ, UK*

Environmental impact

This paper describes the refinement and validation of an occupational exposure model, based on the determinants of exposure, for predicting inhalation exposures in the pharmaceutical environment. The methodology explains the source–receptor approach that incorporates parameters related to the contaminant, work process, workplace control measures and dispersion of contaminant into the workplace, which improves understanding of exposure assessment. It also describes the refinement of model parameters related to local control measures and handling activities and highlights the importance of collecting sufficient contextual information on the determinants of exposure. Results show that inclusion of this information improved correlations between model predictions and measurement data. The model is likely to have useful applications in selecting high risk exposure scenarios that warrant further investigation or to screen low risk exposure scenarios.

limited toxicity data for early life cycle pharmaceutical products, it is often difficult to specify appropriate in-house occupational exposure limits (OELs), and this has led to the use of control banding or performance-based exposure control approaches for setting exposure limits and managing worker exposure.[2] Once sufficient toxicological data become available pharmaceutical companies typically develop in-house exposure limits for their products. Exposure measurements are fundamental to the risk assessment process, however, due to the batch nature of pharmaceutical manufacturing, it is often difficult to obtain a sufficient number of measurements to adequately characterise worker exposure and verify controls.[3] Furthermore the collection and subsequent analysis of exposure measurements can be costly and labour intensive.

Modelling techniques, based on the underlying determinants of exposure,[4] provide an alternative or complementary approach to exposure measurements. There are many potential applications for exposure models, including assessing historical exposures for epidemiological studies, prediction of exposures before a process has been commissioned and using Bayesian statistics to combine modelled and measured exposures.[5,6] Importantly exposure models can reduce the number of occupational hygiene samples that are required to adequately characterise exposure, enabling more cost-effective targeted exposure assessment strategies.

The recent introduction of the Registration, Evaluation, Authorisation and restriction of Chemicals (REACH) Regulations places an additional requirement for employers to collect exposure data for the compilation of Exposure Scenarios as part of the Chemical Safety Assessments (CSA). Although chemicals used in finished pharmaceutical products (*e.g.* drug actives and excipients) are exempt from the requirements of REACH (as per Article 2 (5) (a) of the Regulations), exposure models developed for REACH may be useful in the pharmaceutical industry for risk management, as required by the Chemical Agents Directive 98/24/EC and the relevant national legislation.

Several generic or first tier exposure models are available including ECETOC TRA,[7] the Estimation and Assessment of Substance Exposure (EASE),[8] the Easy-to-use workplace control scheme for hazardous substances (EMKG)[9] and Stoffenmanager.[10] While models have been validated to differing extents for use with specific chemicals and industries,[11–14] there have been few studies that have validated their use to predict exposures to active pharmaceutical ingredients (APIs). Many of the local control measures and handling activity parameter classifications within these models are too vague to generate precise estimates of exposure for the pharmaceutical industry. Furthermore few models are capable of assessing worker behavioural effects on exposure, and this may be a significant exposure determinant.[15]

A deterministic exposure model developed by Cherrie and coworkers[16,17] has been validated to a limited extent for predicting inhalation exposures to API's.[18] The model algorithm incorporates a parameter to consider the potential effect of worker behaviour on exposure and also allows consideration of the proportion of API in the material being handled. The objective of this study was to refine this exposure model to accurately predict inhalation exposures to pharmaceutical APIs. Model input parameters for local control measures and handling activities were refined to incorporate manufacturing and control technologies relevant to exposure scenarios found in the pharmaceutical industry. A broad range of exposure assessments from scenarios in the pharmaceutical industry were then used to validate the refined version of the exposure model.

Methods

Exposure algorithm

The exposure estimates were calculated using a deterministic model, which has been extensively described elsewhere.[16–18] The model uses a source–receptor approach that incorporates parameters related to the contaminant, the work process, workplace control measures and dispersion of contaminant into the workplace. Exposure is estimated by assessing each sub-task individually and combining them to produce a time-weighted average estimate of exposure for the complete work task or scenario.

The exposure algorithm is presented below:

$$C = (\varepsilon_i h(1 - \eta_{lv})t_a + \varepsilon_p) \times (1 - \eta_{ppe})d_{gv}$$

where ε_i = intrinsic emission of the contaminant (dustiness × proportion of API in the material), h = manner in which the solid is handled (handling activity energy × quantity of the material handled × worker behaviour), $1 - \eta_{lv}$ = the efficiency of *local controls* at reducing exposure (efficiency of local controls × adjustment factor), t_a = the fractional time the source was active, ε_p = passive or fugitive emission, $1 - \eta_{ppe}$ = the efficiency of respiratory protection, d_{gv} = the effect of general ventilation *i.e.* a combination of room size and the no. of air changes per hour.†

Model parameters are divided into classes and numerical scores are assigned to the classes based on a logarithmic scale. Intrinsic and passive emissions have concentration units (*e.g.* mg m^{-3}) and the other parameters in the equation are dimensionless.

As the model assesses exposure to dust, the intrinsic emission (ε_i) parameter takes into account the dustiness of the material and the proportion of API in the dust. Few quantitative data are available on the dustiness characteristics of the powders being handled in the pharmaceutical industry and for the purpose of this study all materials were assigned the same model score. It is assumed that the proportion of API in the bulk product is the same as is found in the aerosol,[18] and the proportion of API in the material was multiplied by the intrinsic emission.

Collation of exposure data

GlaxoSmithKline (GSK) has over eighty pharmaceutical and consumer healthcare manufacturing facilities worldwide, involving approximately 2400 APIs. For this study occupational hygiene survey reports and survey monitoring record sheets were abstracted from GSK archives. To ensure that the descriptive information was sufficient for the model parameters, survey reports were analysed for data quality and those not containing information on all model parameters were rejected. To reduce the

† The terminology used here is the same as originally reported for the source–receptor algorithm[17] and slightly different to that used when the algorithm was developed for Stoffenmanager.[19]

influence of the measurement error, measurements with a sampling duration of less than 5 minutes were excluded. Where necessary to help clarify any ambiguities, further enquiries were made with site occupational hygienists. Where available, other contextual information and photographs of the worker and the processes were obtained. After checking for data quality, exposure data ($n = 381$) collected over the period 2002–2008 from GSK primary ($n = 77$) and secondary manufacturing ($n = 281$) and from consumer healthcare sites ($n = 23$) located across Europe and Asia were included in this study.

The exposure scenarios in the study included a wide range of handling activities and control technologies used in the pharmaceutical industry, and are considered to be representatives of exposure scenarios found in this sector. All of the exposure data were collected by experienced occupational hygienists or occupational hygiene technicians. Exposure samples were collected and analysed using GSK validated methods, and included a range of analytical data for various types of APIs ($n = 18$; names confidential), and gravimetric analysis results for total inhalable dust (TID) ($n = 74$). For measured results less than the limit of detection (LOD) of the analytical method, the substitution method of LOD/2 was employed ($n = 38$).[20] The majority of the measurements were task-based with a median sampling time of 30 min (range 5–240 min). In cases where sampling duration was not reported ($n = 10$), information on the relative durations of individual tasks were obtained by consultations with the site occupational hygienists. Exposure was estimated by assessing each sub-task within a scenario, and combining them to produce a time-weighted average estimate of exposure for the exposure scenario. Thus it is the relative duration of the '*n*' subtasks in the exposure scenario that is of importance and not the sample duration. Where identified as being required by risk assessment, workers wore respiratory protective equipment (RPE); however, as all exposure samples were collected in their breathing zone (*e.g.* on their lapel) outside the RPE, the protection afforded by the RPE was not taken into account when using the model to predict exposure, although this can be incorporated.

Prior to the refinement of the model parameters the reproducibility of the exposure model predictions was investigated. A selection of exposure scenarios ($n = 27$) from the dataset were assessed by three independent assessors (JC, AS and PMD); the results were found to be comparable between assessors, with an excellent correlation between the log-transformed estimates and the log-transformed arithmetic means from the corresponding scenario ($r_s = 0.88$, 0.93 and 0.97).[18]

Model parameter refinement

Further refinements to the model input parameters were necessary to include handling activities and local control measures that are used in the pharmaceutical industry. In order to make such refinements it was first necessary to compile a list of handling activities and local control measures that occur within the industry. Information on the efficacy of the local control measures in reducing inhalation exposures was also collected. This was done by reviewing the literature, reviewing GSK occupational exposure assessment reports, engineering design kits (EDKs), and consulting with occupational hygienists, professional organisations and consultants working in the pharmaceutical industry (*e.g.* Safebridge and International Society for Pharmaceutical Engineering). Further details of the refined local control measures, handling activity parameters, sub-parameters and assigned scores are given in the following sections.

Handling activity parameter

The handling activity parameter consists of three sub-parameters related to the energy input to the material during the task, quantity of the material handled per hour and the influence of worker behaviour on the task.

All new handling activities were subjectively assigned to a handling activity energy class, and scored on a logarithmic scale according to the level of energy that was considered to be transferred to the material during the activity. For example, sweeping product on the floor would produce a higher handling component ($h = 10$) than careful weighing of a powder in a weighing cabinet ($h = 0.001$). Table 1 shows the handling activity energy classes, corresponding model scores and example handling activities per class.

The sub-parameter related to the quantity of the material handled was categorised as tonne per h, kg h^{-1}, g h^{-1} or mg h^{-1} and scored on the logarithmic scale as 3, 1, 0.3 and 0.1 respectively.

The sub-parameter related to the influence of worker behaviour on the task was categorised as: exposure very prone to worker behaviour effects, exposure prone to worker behaviour effects, and exposure not prone to worker behaviour effects and scored using the logarithmic scale as presented in Table 2. For example the activity of sweeping a floor is very prone to worker behaviour, while automated processes are not affected by worker behaviour. Using the contextual information provided in the occupational hygiene survey report, the worker behaviour sub-parameter was adjusted to take account of any administrative measures, such as training or supervision, relevant to the task. The classifications of worker behaviour are quite subjective and in some cases handling activities may be more or less prone to worker behaviour than is presented in Table 2; hence if the information in the monitoring record sheet suggested otherwise, this would over-ride the general classification presented and the appropriate worker behaviour subclass was applied.

Local control measure parameter

The local control measure parameter consists of two sub-parameters related to: the efficacy of the local control measure, and an adjustment factor to take account of the condition and/or the performance of the control at the time of the exposure assessment. Using the GSK performance based occupational exposure limit (PB-OEL) approach to exposure control and information collected from professional experts working within the pharmaceutical industry, the efficacy of the local control measures was scored. An overview of the GSK control banding approach incorporating occupational hazard categories (OHC) and exposure control approaches (ECA), a list of local control measures and assigned model scores used in the study are presented in Table 3.

Using the contextual information recorded in the occupational hygiene survey reports the local control adjustment factor was

Table 1 Handling activity energy classes, corresponding model scores and examples of handling activities per class

Handling activity energy classes: model scores	Handling activities	
10	Sweeping	
3	Drying	Milling
	Material transfers (including vacuum)	Charging
	Filling materials (>0.5 m drop height)	Coating
	Blending	Cleaning with blowing tool/hose
	Mixing	
1	Tableting/compression	Brushing
	De-duster	Wash objects with water or power kettle (not power hose)
	Sieving/grating	De-lumping (>10 kg)
	Encapsulation	Disposal of filters, *etc.* with substantial contamination
0.3	Vibrating table	Handling of contaminated objects
0.1	Manipulate/poking of wand/hose	Tablet sorting machine
	Filling materials (drop heights <0.5 m)	Packaging (including blistering and de-blistering)
	Hand sieving	Disassemble machine
	Weighing and breaking up lumps (<10 kg)	Handling/disposal of objects with limited contamination
	Test hardness (crush)	Handling (connections/disconnections) big-bag/IBC/drum/keg
0.03	Handling (opening/closing) of bags/liners/boxes	Short transfer of materials (<1 kg) *e.g.* sampling, filling vials, probe samples
	Add liquid to powder	Seal and de-dock
0.01	Careful sampling for QC	Vacuum cleaning
	Fixing problems/hand cleaning inside machine	Sticking packs together
	Manual connections of liner/bottle bag	Moving containers/lids/bins
	Handling/checking capsules	
0.003	Handling of small potentially contaminated objects	Wet wiping
0.001	Weighing bottle bag	Count packages
	Careful laboratory weighing	

scored using the following categorisation: poorer than expected (3), typical of the control (1), with some additional control (0.3), or with good additional control (0.1).

Data processing

All of the exposure information collected was summarised and model scores were assigned to the model parameters in Microsoft Excel and analysed using SAS statistical software (version 9.1.3; SAS Institute, Cary, NC). Measured exposure concentration and model predictions were found to approximate to log-normal distributions and descriptive statistics are presented both as arithmetic and geometric mean levels with geometric standard deviation and range of the exposure distribution.

Spearman rank correlation coefficients were calculated to study the relationship between the model predictions and the actual measurement data and between the geometric mean (GM) model predictions and the GM of the measurement data when grouped to scenario level. Model bias *i.e.* the ratio of the geometric mean (GM) of the model predictions to the GM of the measured data was determined to assess accuracy of the model exposure predictions.

Results

Data were obtained for 381 exposure measurements across primary and secondary pharmaceutical manufacturing and healthcare sites. Exposure measurements and information on potential exposure determinants were collated. A summary of the descriptive statistics of the measurement data is presented in Table 4. The dataset included a wide range of exposure measurements. The lowest measured exposure level was found during a task involving dispensing an API in a negative pressure glove-box (5×10^{-7} mg m^{-3}) while the highest exposure level was found during a sack tipping operation (200 mg m^{-3}) in a downward laminar flow booth (the worker wore RPE). It is important to note that this measurement with the high exposure levels involved excipients and was based on a short (8 min) task based measurement for TID.

The Spearmans correlation (r_s) between model predictions and the measurement data appeared to be good ($r_s = 0.61$, $n = 381$, $p < 0.001$). Fig. 1 presents a scatter plot of the predicted exposure levels in relation to the measured exposure levels on a log scale. The figure shows a good degree of correlation with the predicted–measured data points falling close to the 1 : 1 agreement line and over half of the points are within one order of magnitude of the measured values.

The degree of accuracy of the model predictions or model bias was assessed using the ratio of the GM estimate to the GM of the measured value. A bias value of −3.2 indicates that the model underestimated exposure for this particular dataset.

Exposure measurements ($n = 381$) for the same or similar tasks, and collected from the same site were grouped to exposure scenarios. In order to calculate a GM exposure level per exposure scenario ($n = 48$), each scenario had a minimum of 3 measurements of exposure available (range 3–22). The mean exposure levels of the scenario groups ranged from 0.000003 to 64 mg m^{-3}. 18 scenarios had an average exposure level of less than 0.1 mg m^{-3}, 12 had average exposure levels between 0.1 and 1 mg m^{-3}, 14 scenarios had average exposure levels between 1 and 10 mg m^{-3} and 4 scenarios had average exposure levels above 10 mg m^{-3}.

The correlation between model predictions and the GM of measurement data per scenario was also good ($r_s = 0.69$, $n = 48$, $p < 0.001$). There was no clear trend of an improved correlation

Table 2 Description of the worker behaviour sub-parameter classes and associated administration measures, model scores and examples of handling activities per class

Worker behaviour class	Description	Administration measures	Model scores	Example handling activities
Not prone, exposure not affected by worker behaviour	Remote working or automatic process, worker is isolated from the process, may be occasional handling *e.g.* when fine adjustments are required	Process largely not affected by worker behaviour; if so extremely carefully carried out	0.3	Automated processes *e.g.*: drying, blending, discharging, tableting, vacuum transfers
Prone, exposure some-what influenced by worker behaviour	Semi-automatic process, worker occasionally/frequently intervenes in the process and involves some handling of products	Carried out as per standard operating procedures/training/supervised	1	Manipulation of wand/hose, handling (opening/closing) of bags/liners/boxes, transfer or weighing of materials
Very prone, exposure greatly affected by worker behaviour	Manual process, worker very frequently intervenes/is involved in the process and handling of products	Not carried out as per SOPs/no specific training/no supervision	3	Sweeping, cleaning with blowing tool/hose, brushing, manual processes *e.g.* sieving, cleaning or tipping of materials

between the mean measured and predicted exposures with an increasing number of measurements per scenario group (Table 5). Fig. 2 shows a scatter plot of the predicted exposure levels in relation to the mean measured exposure for each scenario group.

The model tends to overestimate exposure at lower exposure concentrations (<0.1 mg m^{-3}) and to underestimate exposure at the higher exposures concentrations (>0.1 mg m^{-3}). Limiting the correlation analysis to data above 0.1 mg m^{-3} caused a decrease in the association per exposure scenario ($r_s = 0.59$, bias = −4.9, $n = 33$, $p < 0.001$), and limiting the analysis to data below 0.1 mg m^{-3} resulted in a similar correlation coefficient per scenario ($r_s = 0.69$, bias = 0.7, $n = 19$, $p < 0.001$). There did not appear to be any trends in particular pharmaceutical products (API/TID), classes of handling activities or local controls resulting in improved correlations.

The availability of accurate information on many of the model parameters significantly improved model exposure predictions when compared to omitting the individual parameters from the algorithm and assigning the mean score for all of the other parameters. Including information on the energy input during the handling activity, the quantity of the material handled, and worker behaviour increased the Spearmans correlation by 19%, 12% and 4% respectively. Similarly, including information on local control measures and the local control adjustment factors increased the correlation by 12% and 5% respectively. It was also noted that inputting information on the proportion of API in the material increased the correlation by 1%. Table 6 shows the effect of omitting information on individual model sub-parameters on the correlation for the overall dataset.

Discussion and conclusion

This paper presents the refinement of an existing exposure model for use within the pharmaceutical industry. The handling activity and local control measure model parameters were refined to reflect work tasks and control technologies used within the pharmaceutical manufacturing and healthcare. The refined model was then validated using a dataset collected from within the pharmaceutical industry. The refined exposure model resulted in good correlations between the model predictions and the measured data for the overall dataset ($r_s = 0.61$, $n = 381$, $p < 0.001$) and at scenario level ($r_s = 0.69$, $n = 48$, $p < 0.001$).

The correlation coefficient ($r_s = 0.69$) between model predictions and the mean measured exposure levels at scenario level is slightly lower than that found when using the unrefined exposure algorithm for a smaller pharmaceutical dataset ($r_s = 0.88$–0.97 and $n = 278$).[18] This is most likely due to the fact that in the previous study the dataset included greater number of measurements per scenario, with on average eleven measurements per scenario compared with on average six measurements per scenario in this study. Using fewer measurement values to assess the accuracy and precision of the model exposure predictions compared to mean exposure levels per scenario ignores the fact that the individual measured exposure levels are likely to represent a point in an exposure distribution.

The correlation coefficient for the overall dataset ($r_s = 0.61$) reported in this study is within the range of the correlation values obtained using the original unrefined exposure algorithm for

Table 3 GSK control banding approach detailing OHC, performance band and ECA categories, with local control measure options and model scores

OHC	Performance band/μg m^{-3}		ECA	Local control measures	Model scores
1	>1000 ≤ 5000	Risk assessment	A	No special engineering containment is required, general room ventilation	1
2	>100 ≤ 1000		B	Local exhaust ventilation Partial enclosures Downward laminar flow booths Solids transfer using standard docking station or using slot LEV and transfer sock	0.1
3	>10 ≤ 100		C	Downward laminar flow booths (fitted with barriers or shower curtains) Containment with extraction Enclosed material transfer systems (*e.g.* split butterfly valves, flexible liners or inflatable heads) Vacuum transfers Shrouds	0.01
4	>1 ≤ 10		D	Slot LEV and transfer sock Enclosed processes Single chamber glove boxes Contained or Rapid Access Port (RAP)	0.001
5	≤1		E	Multiple compartment glove boxes Continuous liner systems in glove boxes Isolators Enclosed process plus additional containment	0.001

non-pharmaceutical agents such as asbestos, toluene, man-made mineral fibre, respirable dust and styrene (r_s = 0–0.93).[17] Correlation coefficients are also comparable to the results reported for other exposure models that were developed for specific industries. For example, results are comparable to those obtained when modelling dust exposures in saw mills (r_s = 0.70–0.79),[21] and slightly higher than those reported for cotton dust, endotoxin (r_s = 0.58) and asphalt paving (r_s = 0.28).[22,23] Correlation coefficients are also similar to those reported for Stoffenmanager (r_s = 0.2–0.69), a generic model which has been validated as a first tier exposure assessment tool for REACH.[24] Results from this study indicate that exposure models developed for specific scenarios or industries are more accurate than generic first tier models; however, it is acknowledged that when developing a first tier exposure model, there is generally a compromise between accuracy of the model predictions and broadness of the applicability domain.

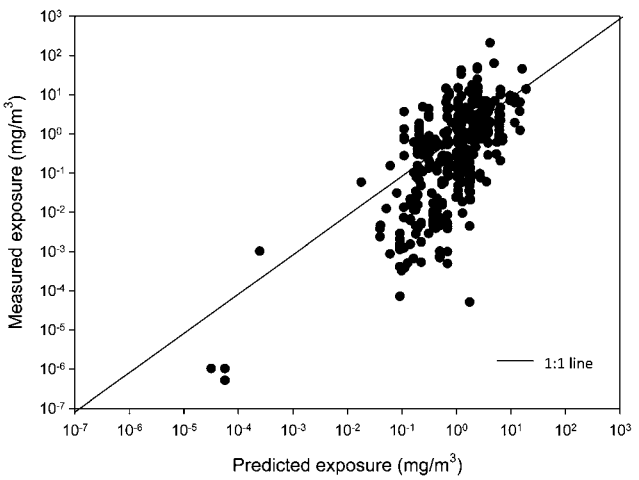

Fig. 1 Relationship between the model predictions and the measured concentrations (mg m^{-3}) for exposure assessments.

The availability of accurate information on model parameters such as handling activities and local control measures clearly improved exposure model predictions (Table 6). Including information on refined model sub-parameters of handling activity energy, quantity of the material handled, and worker behaviour increased the correlation coefficient by 19%, 12% and 4% respectively. Including information on local control measures and the local control adjustment factors was found to increase the model correlation coefficient by 12% and 5% respectively and including information on the proportion of API in the material increased the correlation coefficient by 1%. This highlights the importance of both handling activities and local control measures as exposure determinants for the pharmaceutical industry and further emphasises the importance of collecting comprehensive contextual information specific to each exposure assessment to enable more accurate model predictions.

The model tends to overestimate exposure at lower exposure concentrations (<0.1 mg m^{-3}) and to underestimate exposure at the higher exposures concentrations (>0.1 mg m^{-3}). Limiting the correlation analysis to data above 0.1 mg m^{-3} caused a decrease in the association per exposure scenario (r_s = 0.59, bias = −4.9, n = 33, p < 0.001), and limiting the analysis to data below 0.1 mg m^{-3} resulted in a similar correlation coefficient per scenario (r_s = 0.69, bias = 0.7, n = 19, p < 0.001).

Results from this study show that the exposure model tends to overestimate exposure scenarios with measured exposure levels <0.1 mg m^{-3} (r_s = 0.69, bias = 0.7, n = 19, p < 0.001), and

Table 4 Descriptive statistics of the measured exposure data[a]

N	AM/mg m^{-3}	GM/mg m^{-3}	Minimum/mg m^{-3}	Maximum/mg m^{-3}
381	3.1	0.21	0.0000005	200

[a] N = number of samples; AM = arithmetic mean; GM = geometric mean.

Table 5 The correlation coefficients between the model predictions and the mean measured concentrations with varying number of measurements per scenario group

Minimum no. of measurements per scenario	No. of scenarios	r_s
3	48	0.69
4	38	0.68
5	30	0.76
6	23	0.66
7	17	0.61
8	11	0.50

Table 6 The correlation coefficients between the model predictions and the mean measured concentrations when individual model parameters were omitted

Model parameter omitted	r_s
Handling activity energy	0.50
Quantity of material handled	0.57
Worker behaviour	0.65
Local controls	0.57
Effectiveness of local controls	0.64
% Active ingredient	0.78
Full model (all parameters)	0.69

underestimate scenarios with measured concentrations >0.1 mg m^{-3} ($r_s = 0.59$, bias = −4.9, $n = 33$, $p < 0.001$). Overall the refined exposure algorithm underestimated exposure to pharmaceutical dusts by a factor of 3, which is slightly higher than the bias values found when using this model for non-pharmaceutical agents (bias = 0.47–2.86).[17] The tendency of the model to overestimate scenarios with low exposure levels has also been observed in a previous study with a smaller subset of the current pharmaceutical dataset.[18] Also, previous studies have shown that the occupational hygienists tend to overestimate exposure when using exposure assessment tools.[25] In this study the model assessor was not a GSK occupational hygienist and thus was not very familiar with the exposure scenarios included in the study. It is likely that the following could improve the assessors understanding of the scenarios and the model correlations with measurement data: photographs or video clips of the scenario; provision of training on the identification and classification of model parameters, especially those requiring subjective assessment; reference material for the relevant industries; and development of a user interface for the model.

For all of the other exposure data with exposure levels <0.1 mg m^{-3} where the model overestimated exposure, this is probably related to the classification and scoring of the local control parameter within the model. In the pharmaceutical industry it is a common practice to use dual containment systems for handling activities involving potent APIs, for example glove-boxes fitted to contained enclosures or down flow booths fitted with full screens and glove-ports. While the model allows for a local control adjustment factor, it is only possible to select one specific local control measure which does not allow the combined efficacy of two local control measures to be assessed. It would be desirable to further refine the local control measure parameter to enable the efficacy of two specific local control measures to be accounted for *e.g.*, vacuum transfers within a down-flow booth. As there were only a small number of scenarios in the current dataset with double control systems, it was not possible to comprehensively test the effect of this proposed adaptation with the dataset. Furthermore it is possible that the efficacy of individual local control measures, such as high specification glove-boxes may be underestimated by the current scoring system and increased efficacy values may be warranted. This information is not available in the open literature and so further expert workshops and scientific data are necessary to develop more concise parameter classifications and to scientifically underpin the assigned model scores for local control measures. Work being undertaken in this area includes the development of an exposure control efficacy library (ECEL)[26] for use within the Advanced REACH tool.

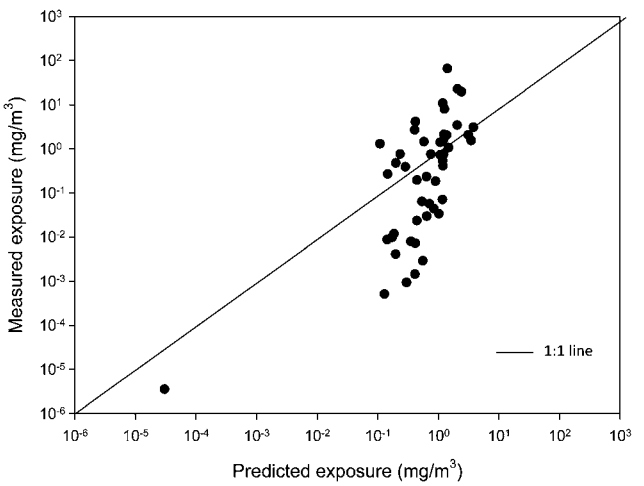

Fig. 2 Relationship between the GM model predictions and the GM measured concentrations (mg m^{-3}) per exposure scenario.

The tendency of the model to underestimate exposure scenarios with higher measured concentrations may be attributed to the fact that many of these scenarios involve manual handling activities with large quantities of material and are very prone to worker behaviour. One example is a scenario in which bags of material were manually tipped into an open vessel; the scenario took place within a downward laminar flow booth and had measured task-duration exposures ranging from 32–200 mg m^{-3}. Manual processes, or those where the worker frequently intervenes in the process, are prone to the effects of worker behaviour as they are dependent on the worker adhering to standard operating procedures and carrying out the tasks in a careful manner. Such manual processes often result in high exposure levels; hence the collection of observational information on worker behaviour and the manner in which manual tasks were carried out is pertinent. Further refinement of the worker behaviour parameter and scores is probably needed to provide more accurate model predictions for scenarios of this kind.

The purpose of this study was to refine an existing exposure model to predict inhalation exposures of workers in the pharmaceutical industry. This study builds on previous work[18] by including refinements on model parameters for local control measures and handling activities specific to the pharmaceutical and healthcare industry. In total 381 exposure assessments were collated from across pharmaceutical manufacturing and

healthcare and were used to validate the refined exposure model. Good correlations were found between the exposure model predictions and the measurement data for the overall dataset and also at scenario level. Model correlations were largely consistent with those found in previous studies of models developed for specific industries and were slightly greater than those reported for generic exposure models. Improved correlations were achieved by including information on the refined exposure model parameters. The model has a tendency to overestimate scenarios with low exposure levels and underestimate scenarios with high exposure concentration. Further improvements in the model predictions could be made by refining the local control measure and handling activity parameters, adjusting model scores and possibly by gathering additional information specific to the pharmaceutical industry. In future developments of the model the present dataset could be used to calibrate the model to provide more accurate exposure predictions. This study highlights the importance of recording contextual information during the exposure assessment process to enable more accurate exposure predictions to be made. The exposure predictions of this model should not be used in place of measurement data which have an important role in the exposure assessment strategy. The model is likely to have useful applications in selecting high risk exposure scenarios that warrant further investigation or to screen low risk exposure scenarios. This work also highlights the most significant exposure determinants within an exposure scenario and will allow the assessor to explore how changing the work situation, for example by introducing local exhaust ventilation, may alter the exposure. In conclusion, the refined exposure model appears to provide a useful basis for an exposure assessment tool for the pharmaceutical industry enabling improved targeting of exposure monitoring strategies.

Acknowledgements

This study was supported by a research grant from GlaxoSmithKline. We are very grateful to all of the GlaxoSmithKline employees who participated in this study. Steve Bailey and Erica Joseph of GlaxoSmithKline are acknowledged for their guidance during the research project and for their helpful suggestions in compiling this paper. Jody Schinkel of TNO Quality of Life is gratefully acknowledged for his help with SAS statistical software. Dr Martie von Tongeren of the Institute of Occupational Medicine is also acknowledged for his guidance on the statistical analysis of study results.

References

1 J. Muzzio, T. Shinbrot and J. Glasser, Powder technology in the pharmaceutical industry: the need to catch up fast, *Powder Technol.*, 2002, **124**, 1–7.
2 N. Nauman, E. Sargent, B. Starkman, W. Fraser, G. Becker and D. Kirk, Performance-based exposure control limits for pharmaceutical active ingredients, *Am. Ind. Hyg. Assoc. J.*, 1996, **57**, 33–42.
3 H. Kromhout, E. Symanski and M. Rappaport, A comprehensive evaluation of within- and between-worker components of occupational exposure to chemical agents, *Ann. Occup. Hyg.*, 1993, **37**(3), 253–270.
4 A. Burdorf, Identification of determinants of exposure: consequences for measurement and control strategies, *Occup. Environ. Med.*, 2005, **62**(5), 344–350.
5 I. Burstyn and H. Kromhout, A critique of Bayesian methods for retrospective exposure assessment, *Ann. Occup. Hyg.*, 2002, **46**(4), 429–432.
6 G. Ramachandran, Toward better exposure assessment strategies—the new NIOSH initiative, *Ann. Occup. Hyg.*, 2008, **52**(5), 297–301.
7 ECETOC, *Targeted Risk Assessment, Technical Report no 93*, European Centre for Ecotoxicology and Toxicology of Chemical, Brussels, Belgium, 2004.
8 J. Tickner, J. Friar, S. Creely, J. Cherrie, E. Pryde and J. Kingston, The development of the EASE model, *Ann. Occup. Hyg.*, 2005, **49**(2), 103–110.
9 REACH, CLP.helpdesk, *Exposure Estimate at the Workplace*, 2008, www.reach-clp-helpdesk.de/en/Exposure/Exposure.html, cited 2010 11/05.
10 H. Marquart, H. Heussen, M. Le Feber, D. Noy, E. Tielemans, J. Schinkel, J. West and D. Van Der Schaaf, 'Stoffenmanager', a web-based control banding tool using an exposure process model, *Ann. Occup. Hyg.*, 2008, **52**(6), 429–441.
11 J. Cherrie and G. Hughson, The validity of the EASE expert system for inhalation exposures, *Ann. Occup. Hyg.*, 2005, **49**(2), 125–134.
12 R. Jones and M. Nicas, Margins of safety provided by COSHH essentials and the ILO chemical control toolkit, *Ann. Occup. Hyg.*, 2006, **50**(2), 149–156.
13 E. Lee, M. Harper, R. Bowen and J. Slaven, Evaluation of COSHH essentials: methylene chloride, isopropanol, and acetone exposures in a small printing plant, *Ann. Occup. Hyg.*, 2009, **53**(5), 463–474.
14 R. Jones and M. Nicas, Evaluation of COSHH essentials for vapor degreasing and bag filling operations, *Ann. Occup. Hyg.*, 2006, **50**(2), 137–147.
15 A. Stewart-Taylor and J. Cherrie, Does risk perception affect behaviour and exposure? A pilot study amongst asbestos workers, *Ann. Occup. Hyg.*, 1998, **42**(8), 565–569.
16 J. Cherrie, T. Schneider, S. Spankie and M. Quinn, A new method for structured, subjective assessments of past concentration, *Occup. Hyg.*, 1996, **3**, 75–83.
17 J. Cherrie and T. Schneider, Validation of a new method for structured subjective assessment of past concentrations, *Ann. Occup. Hyg.*, 1999, **43**(4), 235–245.
18 J. Cherrie, A. Gillies, A. Sleeuwenhoek, M. van Tongeren, P. Mc Donnell and S. Bailey, *Modelling Exposure to Pharmaceutical Agents*, IPX, 2009.
19 E. Tielemans, D. Noy, J. Schinkel, H. Heussen, D. Van Der Schaaf, J. West and W. Fransman, Stoffenmanager exposure model: development of a quantitative algorithm, *Ann. Occup. Hyg.*, 2008, **52**, 443–454, p. men033.
20 R. Hornung and L. Reed, Estimation of average concentration in the presence of nondetectable values, *Appl. Occup. Environ. Hyg.*, 1990, **5**(1), 46–51.
21 M. Friesen, H. Davies, K. Teschke, S. Marion and P. Demers, Predicting historical dust and wood dust exposure in sawmills: model development and validation, *J. Occup. Environ. Hyg.*, 2005, **2**(12), 650–658.
22 G. Astrakianakis, N. Seixas, J. Camp, D. Christiani, Z. Feng, D. Thomas and H. Checkoway, Modeling, estimation and validation of cotton dust and endotoxin exposures in chinese textile operations, *Ann. Occup. Hyg.*, 2006, **50**(6), 573–582.
23 I. Burstyn, P. Boffetta, G. Burr, A. Cenni, U. Knecht, G. Sciarra and H. Kromhout, Validity of empirical models of exposure in asphalt paving, *Occup. Environ. Med.*, 2002, **59**(9), 620–624.
24 J. Schinkel, W. Fransman, H. Heussen, H. Kromhout, H. Marquart and E. Tielemans, Cross-validation and refinement of the Stoffenmanager as a first tier exposure assessment tool for REACH, *Occup. Environ. Med.*, 2010, **67**, 125–132, p. oem.2008.045500.
25 N. Hawkins and J. Evans, Subjective estimation of toluene exposures: a calibration study of industrial hygienists, *Appl. Ind. Hyg.*, 1989, **6**, 61–68.
26 W. Fransman, J. Schinkel, T. Meijster, J. Van Hemmen, E. Tielmans and H. Goede, Development and evaluation of an exposure control efficacy library (ECEL), *Ann. Occup. Hyg.*, 2008, **52**(7), 567–575.

