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Modelling exposure to pharmaceutical agents

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Abstract. Aerosol exposure to the active ingredients of pharmaceuticals arises in research, development and manufacturing. In most instances it is only possible to make small numbers of measurements of exposure and given the inter- and intra-individual variability it is often difficult to obtain sufficient objective data to make reliable decisions about the appropriateness of control measures. This paper describes the development and validation of an exposure model with the potential to predict airborne exposure from both new and existing operations. The model could be used to more efficiently target exposure measurement resources.

1. Introduction

There is widespread handling of powders in the pharmaceutical industry. Manufacturing is divided into two major stages: the production of the active pharmaceutical ingredients (APIs) and secondary processing, involving the addition of other substances to the active ingredients and conversion into medicines. The manufacturing process is largely “powder technology” and the control of aerosol emissions from these processes into the surrounding work environment poses an ongoing challenge [1].

While the effects of pharmaceutical agents may be beneficial for the individuals to whom they are prescribed, it is not desirable or acceptable for workers manufacturing such products to be excessively exposed to these APIs. Heron and Pickering [2] reviewed the published evidence for the presence of adverse occupational health effects from APIs and categorized them as: acute pharmacological effects; chronic effects from potent compounds; respiratory sensitisation and bronchoconstriction; and skin sensitisation. Also drug exposures in the workplace can add to, be synergistic with, or even potentiate drugs the employees take therapeutically [3]. New APIs are increasingly potent, with many having exposure limits less than $1\mu\text{g}/\text{m}^3$

Many pharmaceutical companies develop in-house occupational exposure limits (OELs) for the APIs in their products. For new pharmaceuticals, it is difficult to specify OELs because of limited toxicity data and this has led to the development of “banding systems” that provide performance-based occupational exposure limits (PB-OEL) systems [4]. These approaches offer systematic methods of assigning compounds to a particular Occupational Hazard Category (OHC) based on the potency,

pharmacological and toxicological effects of the API. An Exposure Control Approach (ECA) is then chosen to achieve the performance specification, taking into account exposure factors such as physical form, dustiness, energy input, and volume of material. This is illustrated in Table 1, which summarises the classifications used by GlaxoSmithKline (GSK).

Table 1. An example of a Banding System

OHC	Performance Band ($\mu\text{g}/\text{m}^3$)	Assessment	ECA	Summary Description of Control Options
1	$> 1000 \leq 5000$		A	Room ventilation
2	$> 100 \leq 1000$		B	Local extract ventilation
3	$> 10 \leq 100$		C	Partial enclosure
4	$> 1 \leq 10$		D	Enclosed processing and isolation
5	≤ 1		E	Enclosed processing plus additional containment

Exposure measurements show substantial variation within- and between-workers. Kromhout and coworkers investigated data from about 14,000 measurements from more than 1,500 workers in 165 occupational groups in general industry, defined by job title and factory [5]. Only 25% of the occupational groups had 95% of the individual mean exposures within a factor of 2, while almost 30% of the groups had greater than a 10-fold range in individual mean exposures. In most cases the within-worker variability exceeded the between-worker variability, and the within-worker exposures were much greater for intermittent processes, such as those typical of the pharmaceutical industry, when compared to continuous processes. This variability makes it difficult to reliably characterize exposure in a specific scenario with a reasonable number of personal exposure samples, e.g. less than about 5 to 10.

An alternative approach to assess exposure is to use modeling techniques based on the underlying determinants of exposure. There are many benefits that can arise from exposure models, including prediction of exposures before the process has been commissioned, maximizing the benefit of existing data by combining with modelled exposures, and reducing the number of occupational hygiene samples required to characterize and monitor exposure. This type of model could also be useful in implementing the new European REACH regulations for chemicals.

In this paper we describe the adaptation of an existing deterministic model to predict the mean inhalation exposure to an API in a given scenario and describe a series of exposure assessments from scenarios in the pharmaceutical industry that have been used to validate the model output.

2. Methods

Estimates of exposures for pharmaceutical scenarios were based on the methods originally described by Cherrie and his co-workers [6-7], with a small number of adaptations to reflect the approach to risk management taken in this industry.

The exposure estimates were based on a simple theoretical model, which comprises a source term that is dependent on the *intrinsic properties* of the contaminant (ϵ_i), e.g. the dustiness of a solid and the proportion of API in the mixture, the way the material is *handled* (h), e.g. careful scooping of a powder, and finally, the efficiency of *local controls* ($1-\eta_v$). The three parameters (i.e. ϵ_i , h and $(1-\eta_v)$) were multiplied together to provide the active emission of the source (e_a). We assume that the proportion of the API in the bulk product will be the same as is found in the aerosol, and therefore multiply the total emission by the percent API present.

Three further parameters were incorporated into the basic model. These are the passive or fugitive emission (ε_p), the fractional time the source was active (t_a) and the efficiency of any respiratory protection ($1 - \eta_{ppe}$). So for a single source close to a worker, i.e. in their near-field, the estimated exposure level (C) would be:

$$C = (\varepsilon_i \cdot h \cdot (1 - \eta_{lv}) \cdot t_a + \varepsilon_p) \cdot (1 - \eta_{ppe}) \quad (1)$$

The passive emission term is shown as an additive term unrelated to the active source.

The model simplifies the dispersion of contaminants away from sources using two notional spatial regions: the *near-field*, which comprises a volume of 8m^3 (a $2\text{m} \times 2\text{m} \times 2\text{m}$ cube) around the worker whose exposure is being investigated; and the *far-field*, which comprises the remainder of the work environment. General ventilation in a workroom will have an impact on the contaminant concentration in both the near-field and the far-field. Equation 1 should therefore more correctly be written with suffixes for the near-field, i.e. “NF” and where the source is in the far-field with “FF”, as in equations 2 and 3. The term d_{gv} accounts for the dilution effect of general ventilation in the work room or area.

$$C_{NF} = ((\varepsilon_i \cdot h \cdot (1 - \eta_{lv}))_{NF} \cdot t_{a,NF} + \varepsilon_{p,NF}) \cdot (1 - \eta_{ppe}) \cdot d_{gv,NF} \quad (2)$$

$$C_{FF} = ((\varepsilon_i \cdot h \cdot (1 - \eta_{lv}))_{FF} \cdot t_{a,FF} + \varepsilon_{p,FF}) \cdot (1 - \eta_{ppe}) \cdot d_{gv,FF} \quad (3)$$

In this scheme the intrinsic and passive emissions have concentration units (e.g. $\mu\text{g}/\text{m}^3$). This would correspond to the airborne concentration generated with a certain “standardised” handling. The other terms in these equations are dimensionless.

To take account of some of the specific issues associated with pharmaceutical manufacturing we subdivided the model terms of handling activities and local controls to make more explicit some of the contributing factors. For handling we had factors for the energy input during the activity, the quantity being handled per hour and the likelihood that the workers behaviour could influence their actual exposure. For local control we assigned the control factor illustrated in Table 2. In addition if the information suggested that the design of the controls was better or worse than the general requirements for that level of control the assessor could apply an adjustment local control factor (3, or 0.3).

Table 2. Control factors used in the model

ECA	Summary Description of Control Options	($1 - \eta_{lv}$)
A	Room ventilation	1
B	Local extract ventilation	0.1
C	Partial enclosure	0.01
D	Enclosed processing and isolation	0.001
E	Enclosed processing plus additional containment	0.0001

To estimate exposure levels, the assessor must assign numeric values to each of the parameters. These parameters were based on the descriptive information obtained during exposure measurements in the exposure scenarios of interest. The information was summarised by one of the authors (AG) and any clarification was obtained by telephone or email correspondence. The reconstructions were undertaken by three independent assessors (JWC, AS and PMcD) who were blinded to the results from the exposure measurements at the time of the assessments. Guidance on the values of the parameters was developed by JWC, who trained AS in the methodology, who subsequently trained PMcD. The parameters were then adjusted by the assessors as they completed the set of scenarios to ensure that the allocation of numeric values to parameters was consistent across all situations.

Little quantitative data is available about the dustiness characteristics of the powders being handled in the pharmaceutical industry. In the modelling work described in this paper we used a single factor for intrinsic emission for almost all products.

Data for the validation exercise was abstracted from the occupational hygiene records of GSK. All of the measurements were collected during the scenario rather than over a full-shift. In addition to the measurement results details of the process, work tasks, control measures, materials being handled, the size of the workroom and other relevant contextual information was summarised. Where available photographs of the operator carrying out their work tasks were obtained. The exposure scenarios were deliberately selected to cover a wide range of handling operations and containment levels, and hence represent a broad range of exposure levels. Abnormal operating conditions (e.g. mixer with and without leaks) were also included in the list of scenarios. Also, where possible the same or similar jobs from different sites were included.

3. Results

Data were obtained for 27 scenarios across five pharmaceutical manufacturing sites. These ranged from dispensing gram quantities of API in a negative pressure glove box through to dispensing about a tonne of API into 25kg quantities in kegs. Most of the operators wore respiratory protective equipment (RPE) although all samples were collected on the lapel of the operator and so for the purposes of this exercise we did not take account of the protection afforded by the RPE. There were between two and 31 measurements of exposure available for each scenario; in some cases only the arithmetic mean measured exposure and the range was available, while in others all of the measurement results were retrieved. The scenario mean exposure levels ranged from <0.005 to 20,000 $\mu\text{g}/\text{m}^3$. Six scenarios had an average exposure level less than 100 $\mu\text{g}/\text{m}^3$, eight were between 100 and 1,000 $\mu\text{g}/\text{m}^3$, 10 scenarios were between 1,000 and 10,000 $\mu\text{g}/\text{m}^3$ and three above 10,000 $\mu\text{g}/\text{m}^3$.

Table 3 summarises the geometric mean level for all of the scenarios from the three assessors along with the bias, i.e. the ratio of the geometric mean level from the assessor to the geometric mean of the scenario means and the correlation between the log-transformed assessments and scenario means.

Table 3. Summary data from the exposure assessments and measurements

	Exposure measurements	JWC	AS	PMcD
Geometric mean (GM) of scenario estimates ($\mu\text{g}/\text{m}^3$)	278	360	220	400
Bias, i.e. ratio of assessor GM to data GM	-	1.3	0.8	1.4
Correlation between log-transformed estimates from assessor and exposure measurements	-	0.97	0.93	0.88
Correlation between log-transformed estimates from assessor and exposure measurements (excluding data below 100 $\mu\text{g}/\text{m}^3$)	-	0.84	0.76	0.80

The assessors showed a small positive bias (between 30 and 40% high on average) or a small negative bias (20% low). There was an excellent correlation between the log-transformed estimates and the log-transformed means from the corresponding scenario (between 0.88 and 0.97). Limiting the correlation analysis to data above 100 $\mu\text{g}/\text{m}^3$ caused a slight decrease in the association.

Figure 1 shows a scatter plot of the assessed exposure levels in relation to the mean measured exposure for each scenario.

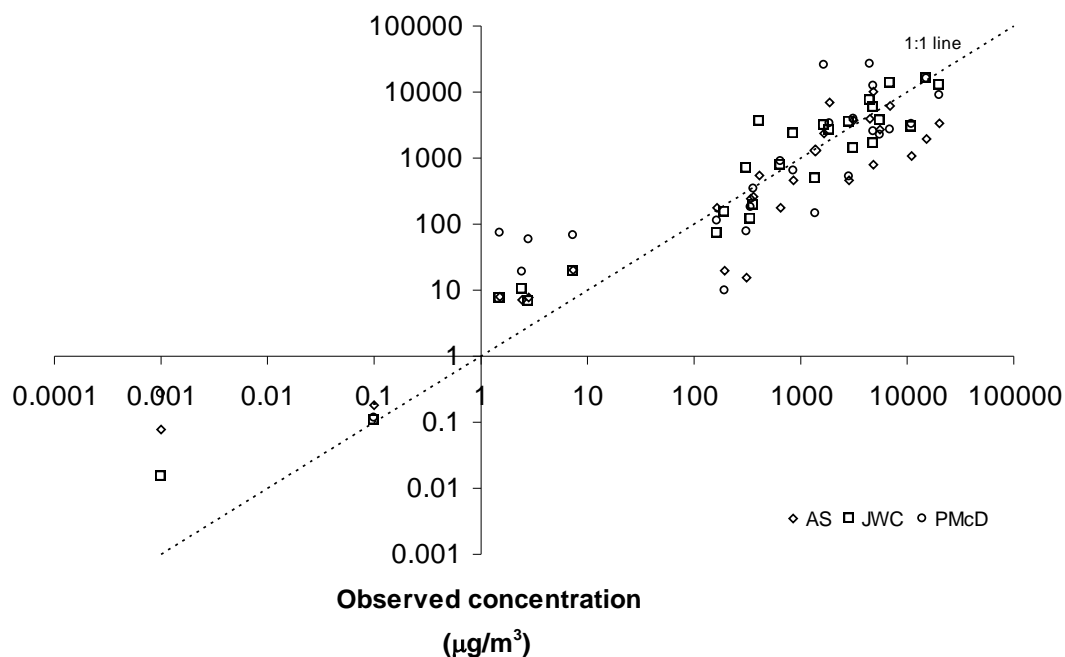


Figure 1. Scatter plot of assessed exposure level in relation to the scenario mean exposure level.

The results from this validation exercise are comparable to that which was obtained when this methodology was validated for non-pharmaceutical scenarios [7-8]. Results suggest that the exposure estimates are of comparable accuracy and precision to the available measurement data. Individual estimates from the assessors were generally no more than an order of magnitude different from the average measured value, which was comparable to the variation in the measurement data from the same scenario. There is some possible overestimation of exposure at lower exposure levels, but this may be partly related to potential bias in the measured exposure data, particularly because of the relatively small number of measurements available for most scenarios.

4. Discussion

The exposure model appears to provide a useful way of estimating the mean exposure to airborne APIs in pharmaceutical manufacturing operations using descriptive information on key contextual variables. It could certainly be used to more effectively target and prioritise monitoring efforts to focus on scenarios where there is a greater probability that exposure could be high in relation to the relevant occupational exposure limit.

The validation exercise produced results that are comparable to those previously produced for non-pharmaceutical agents. Cherrie and Schneider [7] reported bias between 0.47 and 2.86 and correlation coefficients between the log-transformed data of zero to 0.93 for asbestos, toluene man-made mineral fibre, respirable dust and styrene. They noted that the correlation coefficients between the assessments and the measurements were greater when the span of the data (ratio of the highest to lowest mean scenario measurement) was relatively large, i.e. greater than about 100. In the present study we also noted that the correlation between the measurements and assessments decreased when the lower exposure level scenarios were excluded from the comparison, although this did not substantially reduce the association. Semple and colleagues [8] quoted the mean correlation coefficients between the scenario mean measured and estimated levels for a variety of agents of 0.82 with a range of 0.73 to 0.85 for five assessors.

Preliminary data that we have obtained suggests that the range of dustiness of the pharmaceutical products included in this evaluation may be relatively small, which may explain the good correlation obtained without taking variation in dustiness into account. Additional data on the dustiness of pharmaceutical powders, the generation of airborne dust from pharmaceutical processes and the effectiveness of control measures used in the industry would further aid the accuracy of the model predictions. Boundy and co-workers [9] developed a small-scale apparatus for testing the dustiness of pharmaceutical powders, which would minimize the mass of API handled. However, data on the magnitude of the dustiness of pharmaceutical powders was not provided by the authors.

It would be advantageous to develop a user-friendly interface for the model and to remove some of the professional judgment needed in assigning the model input parameters. This model could be implemented as an integrated exposure assessment tool by extending it to incorporate a probabilistic approach using Monte Carlo simulation and then to use Bayesian statistics to update the modelled estimates with measurements contained in a linked exposure database, as suggested previously [10]. Importantly, this approach would allow an iterative exposure assessment process, whereby an initial appraisal is obtained using the exposure model results and when further data becomes available the model estimates can be updated to account for the increased understanding of the exposure in the scenario.

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