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Acknowledgements

I would like to express my sincere thanks and appreciation to the following, without whom, this work would not have been possible:

My supervisor Dr. Marie Coggins for her help, insightful guidance and ready availability throughout the duration of my project.

GlaxoSmithKline for funding this research.

Jody Schinkel, for his invaluable knowledge, patience, direction and relentless support. I am sure neither of us will miss the eight hour phone conversations discussing our SAS scripts and assessments!

Dr. Erik Tielemans, Dr. Wouter Fransman, Prof. Hans Kromhout and Dr. John Cherrie for their ever-helpful advice, constructive input and assistance on compilation of our published papers.

All the GSK occupational hygienists, engineers and health and safety professionals, and those from the broader health and safety community, who participated in this study, while there are too many to name here, I am extremely grateful and indebted for their time and cooperation.

Steve Bailey and Erica Joseph of GlaxoSmithKline, I would like to express my gratitude for their help throughout this research.

To all the girls, my friends from the West, for their encouragement and friendship, throughout what has proven to be a challenging, but more importantly, a thoroughly enjoyable and memorable experience.

To my family, especially my parents Anthony and Joan, I would like to express my sincere appreciation, for their constant support throughout my years at college... I promise I am now finished being a student!

And lastly but by no means least, Jamie, thank you for everything!

Abstract

Assessment of worker's exposure is becoming increasingly critical in the pharmaceutical industry as drugs of higher potency are being manufactured. Also the batch nature of operations often makes it difficult to obtain sufficient numbers of exposure measurements to adequately characterise exposure levels. This research aims to investigate the ability of two occupational exposure models to predict inhalable dust exposures in this industry and specifically to: refine and validate an existing deterministic source-receptor exposure model; and to refine, calibrate, validate and investigate the reliability of the inhalable dust exposure form of the newly developed Advanced REACH Tool (ART).

A broad range of workplace exposure assessment data containing all the contextual information required for the exposure models was collated from a multinational pharmaceutical company. Within both exposure models, input parameters such as localised controls and handling activities, were refined to reflect pharmaceutical situations. The source-receptor model was validated and the relationship between model estimates and measured pharmaceutical data was investigated (n=381 measurements). The inhalable dust exposure form of the ART was calibrated with a pharmaceutical dataset and linear mixed effects regression analysis was used to translate the relative model scores to quantitative exposure levels (in mg/m^3). The pharmaceutical dataset was also included in the generic dataset for the calibration of the inhalable dust model and results of both calibrations are compared to investigate the applicability of the generic model for pharmaceutical scenarios. As part of the validation of the generically calibrated ART, relative bias and uncertainty around geometric mean exposure estimates were calculated for 16 pharmaceutical exposure scenarios (n=192 measurements). To investigate the reliability of the online ART, 18 health and safety professionals assessed four exposure scenarios representative of the industry; information and a demonstration of the ART were provided at two stages during the one-day workshop. Inter-rater agreement was investigated and also the participants' assessment per determinant and their ART exposure estimates were compared with the corresponding gold-standard assessments.

The refined source-receptor exposure model resulted in good correlations between the log-transformed model predictions and the actual measurement data 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. The pharmaceutical and generically calibrated ART were able to estimate geometric mean exposure levels (with 90% confidence) for a given workplace exposure scenario within a factor of 4.6 and 4.4 respectively of the measured geometric mean exposure level. The calibrations resulted in comparable models which were able to explain similar levels of total exposure variance (69 and 64% respectively). The validation of the generic model showed that 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. Results from the reliability study showed that the average not-chance corrected agreement values of the determinants with gold standard for the increased information stages were 58, 67, and 83% respectively. While the provision of information on ART improved inter-rater agreement and agreement with the gold-standard for most determinants, there was a broad range between the participants and gold-standard exposure estimates, with approximately 60% within ten-fold of the gold-standard.

The source-receptor model provides a useful basis for an exposure assessment tool for the pharmaceutical industry; however the ART will likely have more useful applications for the this industry where it is anticipated that it can be used as part of the exposure assessment strategy under the Chemical Agents Directive (98/24/EC) or to assist with developing risk evaluations within the scope of REACH. The ART is not recommended as a suitable tool to assess a quantitative exposure level at a specific workplace. It is an expert tool and extensive user training in required. As models are increasingly used in the context of REACH and beyond, this study emphasises that proper validation and reliability studies are required.

Keywords: *pharmaceutical industry, exposure assessment, worker exposure, exposure model, Advanced REACH Tool, calibration, validation, reliability.*

Abbreviations

ACGIH = American Conference of Governmental Industrial Hygienists

AIHA = American Industrial Hygiene Association

ACH = Air Changer per Hour

APF = Assigned Protection Factor

API = Active Pharmaceutical Ingredient

ART = Advanced REACH Tool

BEAT = Bayesian Exposure Assessment Tool

BEI = Biological Exposure Indices

BOHS = British Occupational Hygiene Society

BSI = British Standards Institute

CDC = Centre for Disease Control

CEMAS = Chemical Exposure Management and Assessment System

CEN = Comite European de Normalisation

COSHH = Control of Substances Hazardous to Health

CSR = Chemical Safety Report

DNEL = Derived No Effect Level

DMEL = Derived Minimal-Effect Level

EASE = Estimation and Assessment of Substance Exposure

EC = European Community

ECA = Exposure Control Approach

ECHA = European Chemcials Agency

ECEL = Exposure Control Efficacy Library

ECETOC = European Centre for Ecotoxiciology and Toxicology of Chemcials

EN = Norme Européenne (European Standard)

ES = Exposure Scenario

EU=European Union

EUROPOEM = European Predictive Operator Exposure Model

GMS = Global Manufacturing and Supply

GSK = GlaxoSmithKline

HEPA = High Efficiency Particulate Arrestor

HSA= Health and Safety Authority

HSE = Health Safety Executive

HSL = Health Safety Laboratory

IOM = Institute of Occupational Medicine

ISO = International Organization for Standardization

ISPE = International Society of Pharmaceutical Engineering

LEV = Local Exhaust Ventilation

MLE = Maximum Likelihood Estimation

MF=Modifying Factors

MRS = Monitoring Record Sheet

MSDS = Material Safety Data Sheet

NEDB = National Exposure Database

OC = Operating Conditions

OELV = Occupational Exposure Limit Value

OHC = Occupational Hazard Categories

OHSI = Occupational Hygiene Society of Ireland

PB-ECL = Performance-Based Exposure Control Level

POEM = Predictive Operator Exposure Model

PPE = Personal Protective Equipment

RAP = Rapid Access Port

R&D = Research and Development

REACH = Registration Evaluation Authorisation of Chemicals

RISKOFDERM = Risk Assessment for Occupational Dermal Exposure to Chemicals

RMM = Risk Management Measures

RPE=Respiratory Protective Equipment

SEG = Similarly Exposed Group

SME = Small and medium-sized enterprises

STEL = Short Term Exposure Limit

SWL = Safe Work Line

UK = United Kingdom

USA = United States of America

TID = Total Inhalable Dust

TLV= Threshold Limit Value

WEL = Workplace Exposure Limits

WHO = World Health Organisation

1.0 Introduction

This thesis presents research which aims to investigate the applicability of occupational exposure models to predict inhalable dust exposures of workers in the pharmaceutical industry.

This research project was funded by and carried out in conjunction with GlaxoSmithKline (GSK), a leading healthcare and pharmaceutical company with over eighty manufacturing facilities worldwide. Besides its enormous economic value, the pharmaceutical industry is important for ensuring and further improving public health and generating the medicines that society needs to cure diseases and minimise health risks. In recent years this industry has been developing more selective drugs of increasing potency. While the effects of such drugs are desirable for the people who take them, it is not desirable for the workers manufacturing these products to be exposed to their toxicological effects. Exposures to active pharmaceutical ingredients (APIs) can cause acute pharmacological effects such as insomnia, chronic effects (including steroid hormones effecting endocrine system and cytotoxic anti-cancer drugs effecting cell growth), respiratory sensitisation, bronchoconstriction, and skin sensitisation (Heron and Pickering (2003). Also such exposures can add to, be synergistic with, or even potentiate drugs the employees take therapeutically (Heidel, 2001). Accordingly this industry is highly regulated and health and safety legislation, such as the Chemical Agents Directive (98/24/EC), requires that employers, prepare a chemical risk assessment, and demonstrate that their products are manufactured and controlled in a manner that is safe for their workers. The introduction of the Registration Evaluation and Authorisation and restriction of Chemicals (REACH) Regulations 2006 (1907/2006/EC) places an additional requirement on employers for risk assessment of chemicals; this includes the compilation of exposure scenarios which requires information on all potential occupational exposure levels throughout the life cycle of each chemical of concern.

While personal exposure measurements are fundamental to the chemical exposure assessment process, there are several limitations associated with this approach, e.g.: monitoring can be expensive and labour intensive; and due to the sometimes intermittent nature of pharmaceutical manufacturing, it is often difficult to obtain a sufficient and robust number of measurements to adequately

characterise worker exposure and verify controls (Kromhout *et al,* 1993). Therefore the scale and complexity of the monitoring requirements within the pharmaceutical industry necessitates much targeted occupational hygiene measurement efforts.

Exposure modelling techniques, based on the underlying determinants of exposure (Burdorf, 2005) provide an alternative or complimentary approach to personal exposure measurements. In addition to the derivation of REACH exposure scenarios, there are many other potential applications for exposure models, including: assessing historical exposures for epidemiological studies; prediction of hypothetical or future exposures before a process has been commissioned; and strengthening exposure estimates by incorporating existing data with modelled exposure estimates (Burstyn and Kromhout, 2002; Friesen *et al.,* 2005; Friesen *et al.,* 2006; Hewitt *et al.,* 2006; Meijster *et al.,* 2007; Ramachandran, 2008).

While the pharmaceutical industry is largely exempt from the requirements of the REACH Regulations, (as per Article 2 (5) (a) of the Regulations), as part of their initiative to improve their exposure assessment strategy, GSK recognised the potential applications of exposure modelling techniques for exposure assessment and risk management. Importantly exposure models may reduce the number of occupational hygiene samples that are required to adequately characterise exposure, enabling more targeted cost-effective exposure assessment strategies. While several generic exposure models are available, few or no published studies have validated their use to predict exposures to APIs. Also regarding the pharmaceutical industry several limitations were associated with these models e.g. the classifications of parameters were considered too vague to generate precise estimates of exposure for this industry.

This research aims to investigate the applicability of two occupational exposure models for predicting inhalable dust exposures in the pharmaceutical industry. This involves exploring an existing source-receptor exposure model (Cherrie *et al.,* 1996; Cherrie and Schneider 1999) and the newly developed Advanced REACH Tool (ART) (Tielemans *et al.,* 2007) for their possible applications in this industry.

2.0 Overview of Chapter

This objective of this research is to investigate the applicability of occupational exposure models for predicting inhalable dust exposures in the pharmaceutical industry. In this chapter an overview of the literature relevant to this study will be discussed under the following themes: chemical exposure assessment in the pharmaceutical industry (Section 2.1); exposure modelling techniques (Section 2.2); the source-receptor exposure model (Section 2.3); the Advanced REACH Tool (Section 2.4); research needs in the area of occupational exposure modelling (Section 2.5); and objectives of research project (Section 2.6). The following section provides an overview of chemical exposure assessment in the pharmaceutical industry and includes a discussion of the various strategies currently available for assessing occupational exposure. Exposure assessment requirements imposed on the pharmaceutical industry under European chemical legislation that are relevant to this research are also discussed.

2.1. Chemical exposure assessment in the pharmaceutical industry

In addition to moral and economic reasons, health and safety legislation provides the main impetus for the assessment of worker exposure to chemicals that are manufactured or used in the workplace. In the case of chemicals, the process of occupational exposure assessment involves the determination of the potential routes of entry to the human body and of the magnitude, duration and frequency of contact with the body. As most of the materials involved in pharmaceutical manufacturing are in powder form, the inhalation route of exposure is the exposure route of most importance followed by, dermal exposure and to a lesser extent ingestion and injection exposure. Inhaled particles may cause adverse health effects either directly on the respiratory system, or indirectly, as the particles may be absorbed from the respiratory system to produce effects in other parts of the body (Ayres, 2005).

In recent years the pharmaceutical industry has been developing more selective drugs of increasing potency. Due to limited potency and toxicity data for early life cycle pharmaceutical products, it is not possible initially to specify appropriate in-house occupational exposure limits (OELs), and this has led to the use of “control banding” or performance-based occupational exposure limit (PB-OEL) approaches for managing worker exposure (Nauman *et al.,* 1996). These

approaches offer a systematic method of assigning compounds to a particular hazard category or band based on their anticipated potency, pharmacological and toxicological effects. Each band or category corresponds to appropriate facilities and process containment technologies effective in controlling exposure to a range of concentrations or OELs (Wood, 2001). While most of these systems are uncomplicated and relatively easy to communicate, it has been cautioned that they are not a replacement for quantitative risk assessment, development of OELs or validated occupational hygiene air monitoring (Farris *et al.*, 2006).
Later in the life cycle of the pharmaceutical drug and once sufficient toxicological data becomes available, pharmaceutical companies typically develop in-house OELs for their products.
Various strategies exist for assessing and evaluating occupational exposures including:

- Exposure monitoring data - this can be further classified as personal exposure monitoring or screening measurements. Personal exposure monitoring involves measuring personal exposure at the time of contact with the hazard and has traditionally been used to measure exposure in the workplace to occupational hazards such as air contaminants and noise. Using personal monitoring techniques, the measured exposure level can be compared with OELs, regulatory or otherwise. Screening measurements can be used to check "worst case" tasks or typical exposure levels; techniques include direct measurement methods such as detector tubes, photo-ionization detectors and aerosol monitors.
- Surrogate exposure measurements involve using, with caution, exposure data from another agent e.g. lactose, or from another operation, to estimate exposure for another chemical that is used similarly in the workplace (Mulhausen and Damiano, 1998).
- Qualitative techniques include conducting interviews or dissemination of questionnaires to study participants. Questionnaires typically provide qualitative, often retrospective, information and may be used to categorise respondents into two or more groups with respect to potential exposure (e.g. exposed or unexposed, high exposure or low exposure) (World Health Organisation (WHO), 2000).

- Biological monitoring involves analysis of breath, urine or blood samples collected from individuals to measure the amount of a chemical or metabolite of concern that enters the body. While it does not directly measure exposure, it may be particularly useful where hazardous chemicals could be ingested, absorbed through the skin or where control of workers exposure relies on respiratory protective equipment (RPE) (Health and Safety Executive, 1997).

All of the above approaches for evaluating exposures have associated limitations. Traditionally, personal exposure monitoring is the most commonly employed approach for assessing occupational chemical exposure. However there are several limitations associated with this method: it is normally expensive and labour intensive; and sometimes difficult to quantify as often the act of measuring affects the parameter being measured (Semple *et al.,* 2001). Critically, exposure levels may vary from moment to moment, day to day, between processes and between and within workers (Kromhout *et al.,* 1993) and it is never going to be feasible to measure every potential exposure situation in every workplace. The intermittent or batch nature of most pharmaceutical operations often makes it difficult to obtain sufficient numbers of exposure measurements to assess occupational exposure. Furthermore, due to their wide spread geographical locations in continents such as Asia and South America, many pharmaceutical manufacturing facilities do not have access to, or have limited competent resources to facilitate such occupational hygiene monitoring and analysis.

As an alternative to the conventional occupational hygiene exposure assessment methods, expert judgement and exposure modelling techniques are often used to estimate workers' occupational exposure. Expert judgement involves using the professional judgement of experts, such as occupational hygienists, on its own, or using Bayesian techniques to combine their judgement with measurement data to assess workers exposure to chemical agents (Wild *et al.,* 2002; Tesche *et al.,* 2002; Van Wendel De Joode *et al.,* 2005). A study of expert judgement which employed 11 experts to estimate an exposure parameter in the nickel industry, reported encouraging results which suggested that there is indeed some broad body of specialised knowledge that experts from varied backgrounds draw on to reach similar judgments (Ramachandran *et al.,* 2003). However there are distinct

disadvantages associated with this approach. The experts may not be familiar with the jobs or industries, are unlikely to be aware of conditions present in the specific work sites or workers, and their background may influence how they assess exposure (Teschke *et al.,* 2002). As the experts' decision-making process is not defined it is difficult to replicate or scientifically justify their predictions or conclusions (Cherrie *et al.,* 1996). Also, there has been relatively little research into the accuracy of such subjective judgements (Ramachandran *et al.,* 2008). Exposure modelling techniques are acknowledged as having many potential applications and benefits in the occupational exposure assessment process. By structuring the decision-making process, an exposure model or algorithm based on the determinants of exposure, can allow exposure estimates to be derived in a transparent manner and are expected to be more reproducible and less subjective than expert judgement (Cherrie *et al.,* 1996). Exposure modelling techniques will be reviewed in more detail in Section 2.2.

As mentioned previously, compliance with chemical legislation provides a strong impetus for conducting occupational exposure assessments across all industries. In developing an occupational exposure model which is to be useful for the pharmaceutical industry, it is necessary to understand this industry's responsibilities for ensuring their compliance with chemical legislation. The following section offers a short overview of the European legislation pertaining to chemical hazards in the pharmaceutical workplace.

2.1.1. Occupational health and safety legislation pertaining to the pharmaceutical industry

European Directives have driven comprehensive legislation on the manufacturing and usage of chemicals across the European Union (EU) member states. Two of the most significant pieces of legislation pertaining to occupational exposure assessment across chemical industries are the Chemical Agents Directive (98/24/EC) and the Registration Evaluation and Authorisation and restriction of Chemicals (REACH) Regulations (1907/2006/EC). For the purpose of this review these two pieces of legislation are discussed in relation to how they legislate for occupational exposure assessment to protect the health of workers in the pharmaceutical industry. Hereinafter they will be referred to as the Chemical Agents Directive and the REACH Regulations respectively.

The Chemical Agents Directive legislates for the protection of the health and safety of workers from the risks related to chemical agents at work. This Directive has been transposed into national legislation in the EU member states: in Ireland as the Safety, Health and Welfare at Work (Chemical Agents) Regulations 2001 (S.I. No 619 of 2001); and in the United Kingdom (UK), as the Control of Substances Hazardous to Health (COSHH) Regulations, 2002. These Regulations will herein be referred to as the Chemical Agents Regulations, 2001 and COSHH Regulations 2002, respectively. The objectives of these Regulations are to protect the health of workers from chemicals and to set obligations on employers regarding implementation of chemical risk assessment, prevention and control of exposure, health surveillance and training programmes.

In Ireland, the Chemical Agents Regulations, 2001 legislates that employers must comply with occupational exposure limit values (OELVs), as listed in the 2010 Code of Practice for the Chemical Agents Regulation, 2001. The latter document defines OELVs as *'the maximum permissible concentration of a chemical agent in the air at the workplace to which a worker may be exposed, in relation to an 8 hour or 15 minute reference period'*; these limits are intended to be the levels of chemicals that healthy workers could inhale for up to 40 hours per week over a working lifetime, which would not result in any adverse health effects. The Scientific Committee on Occupational Exposure Limits (SCOEL) provides scientific advice to the European Commission to underline and strengthen their proposals on minimum exposure limits for chemicals in the workplace. This committee examines information on toxicological and other relevant properties of chemical agents, evaluates the relationship between the health effects of the agents and the level of occupational exposure, and recommends values for health-based OELs (European Commission, 2009). OELs are subsequently implemented into legislation by competent national authorities or other relevant national institutions, and industry must then comply with them and demonstrate such compliance. While OELs are referred to with different terminology across the various countries, e.g. in Ireland as OELVs and in the UK as workplace exposure limits (WELs) for the purpose of this review the term OEL is used. As statutory OELs are set for very few pharmaceutical products, where none are available, the Chemical Agents Directive encourages pharmaceutical companies to set their own OELs. Consequently most major

pharmaceutical companies develop in-house OELs and apply a similar regime of compliance assessment to that used for regulatory limits. Personal exposure monitoring is typically employed in the process of exposure assessment to demonstrate compliance with OELs. However due to the limitations of personal monitoring methods and the challenges in obtaining measurements in the pharmaceutical industry, exposure modelling techniques may be useful for predicting exposures and for demonstrating compliance in this industry.

The REACH Regulations, effective on July 1st 2007, is a major landmark in European chemical policy which streamlines and improves the former EU legislative framework on chemicals. REACH replaces more than 40 existing directives related to the use of chemicals (including the Safety Data Sheet Directive 91/115/EEC) and imposes greater responsibility on manufacturers and importers of chemicals for registering, assessing and managing the risks posed by their chemicals and for providing appropriate safety information to their users. One of the most pertinent objectives of REACH was that dangerous substances of concern (i.e. those manufactured or imported in quantities greater than 10 tonnes per year and classified as dangerous or persistent, bio-accumulative and toxic (PBT) or very persistent and very toxic (vPvT) chemicals) are to be used under conditions that are demonstrated to be safe for workers, consumers and the environment. Hazard data are used to identify benchmarks indicating acceptable levels of exposure called derived no-effect levels (DNEL) or derived minimal-effect levels (DMEL). 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) as they are considered to be sufficiently well regulated under existing EU medicine legislation (Regulation 726/2004/EC, Directive 2001/82/EC or Directive m2001/83/EC). Nonetheless many chemicals purchased and manufactured by the pharmaceutical industry are legislated for under REACH, including chemicals used in the synthesis of drug actives, ingredients in oral health care and chemicals used in packaging material (GSK, 2007). The biggest issue for the industry is intermediates which are used in the synthesis of drugs and often have a degree of pharmaceutical activity. While there are reduced requirements for these intermediates under REACH, the need to demonstrate “strictly controlled

conditions" has focused increased attention on toxicity testing and evaluation of intermediates (Pers. Comm. Steve R. Bailey).

Under REACH, manufacturers and importers of regulated materials are required to prepare a Chemical Safety Report (CSR) which must identify appropriate Operating Conditions (OC) and Risk Management Measures (RMM) to reduce or avoid chemical exposure of humans and the environment (below the previously mentioned benchmark values). Risk assessment of the chemicals and compilation of exposure scenarios for the life cycle of the chemical are essential in complying with these requirements, and must be documented in the CSR. Within REACH, the term 'exposure scenario' is defined as *"the set of conditions that describe how the substance is manufactured or used during its life-cycle and how the manufacturer or importer controls, or recommends downstream users to control, exposures of humans and the environment"*. The derivation of exposure scenarios requires information on potential exposure levels for each chemical of concern and this can be determined by available exposure measurements or by the use of exposure models. As a case-by-case assessment of exposure levels based on exposure measurement data is generally considered impracticable and expensive (Tielemans *et al.*, 2007) exposure models may be the most viable option for derivation of REACH exposure scenarios. Therefore the ART was developed by a large European collaborative group to model inhalation exposures for a defined group of workers sharing OC and RMM across different premises and locations in Europe; the ART is discussed in detail in Section 2.4.

2.2 Exposure modelling techniques

An exposure model is a mathematical, *'logical or empirical construct which allows estimation of individuals or population exposure parameters from limited input data'* (WHO, 2000). They are quantitative constructs that estimate the relationships between measurable events, which are entered into the model as input variables. The relationship between the model inputs and model outputs are described in the model using algorithms and equations (WHO, 2005). A wide variety of human exposure models are currently in use across the world and can be broadly categorised according to the following types of exposure source: environmental, dietary, consumer product and occupational (Fryer *et al.*, 2006). The following section describes a classification system for all exposure models.

2.2.1 Classification of exposure models

Exposure models may be classified as: either 1) mechanistic or 2) empirical; and both mechanistic and empirical models can be further classified as: a) deterministic or b) probabilistic models.

Mechanistic models simulate the real behaviour of an agent in the environment and in target organisms as it is transported and undergoes physical and chemical transformations; they are mathematical constructs built on laws of physics and chemistry and data on behaviours and factors influencing exposure (WHO, 2005).

Empirical models are a mathematical representation of the relationship between input and output variables based on historical measurements and they do not require or imply any causal relationships between the model variables. They are specific to the data set from which they have been calculated (WHO, 2005).

Deterministic model predictions are precisely determined through known relationships between the model input parameters and do not incorporate variation in the parameters. These models use fixed point estimates of model input variables to provide a single value 'worst-case', 'best case' or average estimate of exposure, thus they consistently produce the same exposure predictions for a given set of model input parameters.

Alternatively, **probabilistic models** incorporate the natural ranges and uncertainties in the model input parameters and they calculate a probability distribution of possible exposure outcomes. Probabilistic analysis allows presentation of information more readily and completely about prediction of exposure and related uncertainty and variability (Jayjock, 1997). Monte Carlo analysis is the statistical sampling technique most commonly employed in probabilistic exposure modelling. Monte Carlo methods involve '*a repeated random sampling from the distribution of values for each of the parameters in a generic exposure or dose equation to derive an estimate of the distribution of exposures or doses in the population'* (DiNardi *et al.,* 1998).

In the following section occupational exposure models developed for workplace exposure assessment are reviewed.

2.2.2 Review of existing occupational exposure models

As it is never going to be technically feasible for occupational hygienists to monitor every possible exposure situation in workplaces, occupational exposure models have been developed and successfully employed in the exposure assessment process. Examples of their applications include:

- Retrospective assessment of worker exposure (Friesen *et al.,* 2005; Friesen *et al.,* 2006)
- Prediction of potential hypothetical or future exposures (Meijster *et al.,* 2007).
- Strengthening exposure estimates by incorporating existing data with modelled exposure estimates (Hewitt *et al.,* 2006).
- Provision of quantitative estimation of the exposure levels in relation to REACH exposure scenarios (Tielemans *et al.,* 2007).

Existing occupational exposure models vary from screening tools to more sophisticated exposure assessment tools. The introduction of the REACH Regulations provided an impetus for the development and the classification of occupational exposure models. For the requirements of REACH a tiered approach to exposure assessment is recommended, involving tier 1 generic screening tools or models, generating conservative or 'reasonable worst case' estimates, to distinguish between exposure scenarios of concern and those which are not (Tielemans *et al.,* 2007). Screening tools such as European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) Targeted Risk Assessment (TRA) (ECETOC, 2004) and Stoffenmanager (Schinkel *et al.,* 2010) may be good candidates for tier 1 assessment. If it is not possible to demonstrate adequate control of risk using tier 1 tools, more sophisticated tier 2 exposure models may be employed to provide more confidence, sensitivity and scientifically justified exposure predictions. The lack of such a higher tier exposure assessment tool, led to the development of the Advanced REACH Tool (ART) (Tielemans *et al.,* 2007).

Table 1 presents a summary of occupational exposure models categorised according to their solution method, exposure routes, intended uses, validation studies and model developer and related scientific literature.

Table 1: Summary of currently available occupational exposure models categorised according to their solution method, exposure routes, basis of the model and intended uses, model developer and related scientific literature.

Model	Solution Method	Exposure Routes	Basis of the Model and Intended Uses	Model Developer and related scientific literature
Estimation and Assessment of Substance Exposure (EASE)	Deterministic	Dermal Inhalation	Assist both regulatory authorities and industry with the risk assessment of new and existing hazardous substances in a broad range of occupational settings. It is currently the main model used for regulatory occupational exposure assessment in the EU (Northage, 2005).	UK HSE and Health Safety Laboratory (HSL). The model was described by Tickner and colleagues (2005) and has been found to be a greatly simplified model that does not include all the important exposure determinants, and can produce estimates of exposure that are ambiguous and inaccurate (Creely *et al.*, 2004; Cherrie and Hughson, 2005)
Predictive Operator Exposure Model (POEM)	Deterministic	Dermal Inhalation	Predict exposures of operators preparing and applying agricultural pesticides in the UK. EUROPOEM, which is mainly based on POEM but incorporates elements of similar German and Dutch models, is being developed for the EU to evaluate bystanders exposure to chemicals applied to crops (Fryer *et al.*, 2004).	Scientific Subcommittee on Pesticides, UK, and the British Agrochemicals Association (Pesticide Safety Directorate, 1992). Available at http://www.pesticides.gov.uk/

Table 1 continued: Summary of currently available occupational exposure models categorised according to their solution method, exposure routes, basis of the model and intended uses, model developer and related scientific literature.

Model	Solution Method	Exposure Routes	Basis of the Model and Intended Uses	Model Developer and related scientific literature
Bayesian Exposure Assessment Tool (BEAT)	Probabilistic	Dermal	Comprises a selection of software models based around a database model to predict dermal exposures to biocides.	UK HSE in conjunction with TNO Quality of Life and HSL (Phillips and Garrod 2001; Warren, 2002)
Dermal Exposure Assessment Method (DREAM)	Deterministic	Dermal	Consists of two parts: a multiple choice questionnaire on exposure determinants and an evaluation algorithm. Semi-quantitatively predicts dermal exposures to chemical or biological agents for epidemiological research and occupational hygiene practice.	Researchers in TNO Quality of Life and Utrecht University (van Wendel de Joode, *et al.*, 2003). The method was found to result in good to excellent inter-observer agreement for ranking of total dermal exposure estimates (van Wendel de Joode, *et al.*, 2005).
Control of Substances Hazardous to Health (COSHH) Essentials	Control banding	Inhalable	Based on the control banding approach (key components are health hazard bands and exposure potential bands) and is available as a web based tool to provide assistance to small- and medium sized enterprises (SME) with respect to workplace risk assessment and control.	UK HSE and has been extensively evaluated with varying levels of accuracy reported (Maidment, 1995; Tischer, 2003; Jones and Nicas, 2006; Lee *et al.*, 2010). Available at http://www.coshh-essentials.org

Table 1 continued: Summary of currently available occupational exposure models categorised according to their solution method, exposure routes, basis of the model and intended uses, model developer and related scientific literature.

Model	Solution Method	Exposure Routes	Basis of the Model and Intended Uses	Model Developer and related scientific literature
European Centre for Ecotoxicology and Toxicology of Chemicals Targeted Risk Assessment (ECETOC TRA)	Deterministic	Inhalation Dermal	Based on a tiered approach with more hazardous substances requiring more information and a more in-depth assessment. Developed for use in regulatory risk assessment process (tier 1 for REACH) on the health (of workers and consumers) and environmental risks from the supply and use of chemicals.	ECETOC, 2004; ECETOC 2008. Spreadsheet version available at http://www.ecetoc.org/tra
Einfaches Massnahmenkonzept Gefahrstoffe (EMKG) 'Easy-to-use workplace control scheme for hazardous substances'	Probabilistic	Inhalation	Based on COSHH Essentials, this is a control banding tool which many German safety and health professionals currently use in both SME and large companies (Tischer *et al.*, 2009). Has potential as a tier 1 assessment tool for REACH.	German BaUa (Packroff *et al.*, 2005) Evaluated by Tischer and colleagues (2009) and was found to not guarantee compliance with OELs. Spreadsheet version available at http://www.reach-helpdesk.de/en/Exposure/Exposure.html.

Table 1 continued: Summary of currently available occupational exposure models categorised according to their solution method, exposure routes, basis of the model and intended uses, model developer and related scientific literature.

Model	Solution Method	Exposure Routes	Basis of the Model and Intended Uses	Model Developer and related scientific literature
Stoffenmanager	Deterministic	Inhalation	Combines hazard banding and exposure banding schemes leading to risk bands. Developed in the Netherlands to assist SMEs to prioritise and control risk of handling chemical products in their workplaces A web-based exposure database **St**offenmanager and **E**xposure **M**odelling data**BASE** (STEAMbase) is under development to enable a dynamic system of regular model calibration.	The web based tool (www.Stoffenmanager.nl) is based on the source-receptor model of Cherrie and colleagues (1996; 1999). The tool was developed by TNO Arbo Unie and Utrecht University (Marquart *et al.*, 2008; Tielemans *et al.*, 2008). Validated as a tier 1 tool for quantification of exposure levels in relation to exposure scenarios under REACH (Schinkel *et al.*, 2010).
Advanced REACH Tool (ART)	Probabilistic	Inhalation	A tier 2 advanced exposure assessment tool for quantification of exposure levels in relation to REACH exposure scenarios. The tool incorporates a mechanistic model and an exposure database, combined with Bayesian statistics.	Developed for a consortium of government and industries by TNO, Institute of Occupational Medicine (IOM), HSL, Utrecht University (Tielemans *et al.*, 2007; Tielemans *et al.*, 2008; Schinkel *et al.*, 2011, Fransman *et al.*, submitted, Tielemans *et al.*, In Prep, Marquart *et al.*, submitted). Available at www.advancedreachtool.com

While a control-banding screening tool for APIs has been employed in the pharmaceutical industry to advise the level of containment required to assure employee safety through engineering controls and safe handling procedures, this approach implicitly requires an exposure model and relies heavily on professional judgement (Nauman *et al.,* 1996). A major limitation of the currently available occupational exposure models is that they do not incorporate the specific detail such as local control measure and handling activity parameter classifications that are applicable to exposure situations encountered in the pharmaceutical industry. Also the majority of modern pharmaceuticals need to be controlled to OELs less than 100µg/m^3 (and often less than 1µg/m^3) and as existing models (such as EASE and COSHH Essentials) were developed for other industrial chemicals, they do not provide exposure categories at these low levels. Furthermore few models are capable of assessing worker behavioural effects on exposure, and this may be a significant exposure determinant across all industries (Stewart-Taylor and Cherrie, 1998). Also as discussed in Sections 2.5.2 and 2.5.3, these currently available exposure models have not been calibrated or validated with pharmaceutical datasets and their reliability and suitability for this industry has not been explicitly investigated.

At the commencement of this project a deterministic source-receptor model developed by Cherrie and co workers (Cherrie *et al.,* 1996; Cherrie and Schneider, 1999) was validated to a limited extent for predicting inhalation exposures to APIs (Cherrie *et al.,* 2009). The model algorithm incorporates a parameter to consider the potential effect of worker behaviour on exposure and also allows consideration of the percentage of API in the material being handled, which may range from <1% to 100%, and is therefore an important exposure determinant. One of the objectives of this study was to refine and validate the source-receptor model to accurately predict inhalation exposures to pharmaceutical APIs.

Parallel to the commencement of validation of the source-receptor model, a large collaborative European research group initiated the development of the ART (Tielemans *et al.,* 2007). This is a higher tier exposure assessment tool for predicting exposure levels for exposure scenarios under REACH. The mechanistic model within the ART is a development of the source-receptor

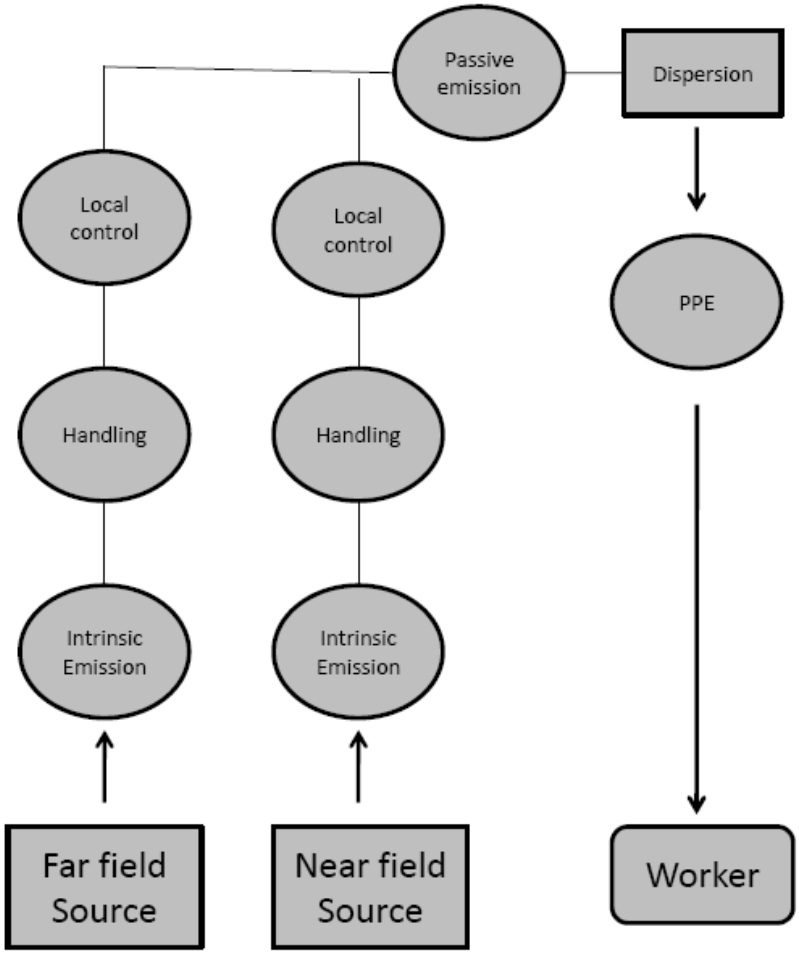
model (Cherrie and Schneider, 1999) and the tool contains a facility to allow a Bayesian update of measurement data and modelled exposures resulting in an updated exposure estimate. The advantages of the ART in comparison to the source-receptor model include: that the underlying principals of many of the modifying factors (MF) are based on scientific evidence; the logical and comprehensive classifications of MFs; the estimated exposure distribution gives an opportunity to choose more conservative exposure estimates to take into account uncertainty and variability in exposure situations; online tool with user interface; and the sustainability of the ART website and associated information technology support, during and beyond the scope of this research project. Upon commencing this research project, the ART was recognised for its potential useful applications as an exposure assessment tool for predicting inhalable dust exposures within the pharmaceutical industry. Equally in order to ensure that the ART was applicable for the pharmaceutical industry it was deemed pertinent that this industry be represented at every stage in the development of this tool. Therefore the latter part of this research project focused on refining, calibrating, validating and investigating the reliability of the inhalable dust form of the ART specifically for the pharmaceutical industry.
Sections 2.3 and 2.4 review the source-receptor model and the ART respectively.

2.3 Source-receptor model

Cherrie and colleagues developed a deterministic source-receptor model for structured subjective assessment of historic inhalation exposures (Cherrie *et al.*, 1996; Cherrie and Schneider, 1999). This model uses a mathematical algorithm relating work practices and workplace factors that have been identified as important determinants of inhalation exposures. The structure of the method is based on what is referred to as the "source-receptor" concept, and is based on: the contaminant generation at source, subsequent transmission into the work environment and the interaction with the receptor i.e. the worker. The source component represents an activity during which a hazardous substance may be emitted into the work area and it may be mobile or stationary e.g. a bag of powder material that is about to be weighed into smaller containers.

As the concentration of contaminants varies in space as well as time, the model distinguishes between sources that are in the near-field (NF) i.e. within touching distance of or close to the worker whose exposure is being investigated, and the far-field (FF) (Cherrie, 1999). For the purpose of this model, the NF is loosely defined as a volume of approximately 8 m^3 surrounding an individual's head and the FF comprises the rest of the work area. Figure 1 presents a schematic of the source-receptor concept underlying the model exposure algorithm.

Figure 1: Schematic for the source-receptor model



The exposure algorithm predicts exposure (C) based on information about the work tasks and the work environment:

$$C = ((\varepsilon_i \,.\, h \,.\, (1 - \eta_{lv})).\, t_a + \varepsilon_p) \,.\, (1 - \eta_{ppe}).\, d_{gv} \qquad \text{(eqn 1)}$$

The model considers three main parameters: the intrinsic emission (ε_i) of the material being handled; the handling or processing operations (h) involved in the tasks; and the efficiency of local controls ($1 - \eta_{lev}$), such as local ventilation (eqn 1). The parameters are divided into categories and most are scored on a logarithmic scale which leads to a dispersion of resulting exposure levels or scores over the categories, in accordance with the logarithmic distribution normally found with exposures levels.
The magnitude of these model scores for all the parameters is assigned based on subjective assessments of the occupational hygienist undertaking the assessment and the provision of guidance documents, which are based on professional judgement and research (Cherrie *et al.*, 1996).

The intrinsic emission (ε_i) refers to the tendency of a material to become airborne and subsequently deposited and is affected by its physical properties. For liquids, volatility must be considered and for powders and solid objects, dustiness must be considered. Intrinsic emission of the source is divided into six classes and scored on a logarithmic scale, ranging from 0, 0.1, 0.3, 1, 3 to 10, corresponding to no emission, very low, low, moderate, high, to very high source emission rates, respectively.

Secondly, the handling (h) of the material can influence the emissions from a source; the impact of handling relates to the amount of energy imparted to the hazardous substance (Cherrie and Schneider, 1999). For example sweeping product on the floor would produce a higher handling score than careful weighing of a powder in a weighing cabinet. Handling is categorised into six classes and scored on a logarithmic scale ranging from 0, 0.1, 0.3, 1, 3 to 10, for no energy or processing, very low, low, moderate, high and through to very high energy or impact respectively.
The third factor that determines the strength of emissions from a source is the effectiveness of local control measures ($1 - \eta_{lv}$), such as local exhaust ventilation (LEV) that reduces the emission from a source into the workroom. These are categorised into three classes ranging from 0.1 for effective controls, 0.3 for some controls, and 1 for no local controls. It is assumed that these factors are all independent and act in a multiplicative way, resulting in active emission (ε_a):

$$\varepsilon_a = \varepsilon_i \times h \times (1 - \eta_{lv}) \quad \text{(eqn 2)}$$

Passive emission (ε_p) from other sources which are not directly associated with the process, such as spills and re-suspension of settled dust in the workplace, are also taken into account. This is affected by the cleanliness of the workplace, with cleaner workplaces having a lower passive emission and may be due to uncontrolled factors such as evaporation from spills or equipment leaks. Passive emission is assigned scores based on a logarithmic scale ranging from 0 to 1 corresponding to no passive emission to significant passive emission respectively. The sum of passive emission (ε_p) and active emission (ε_a) result in total emission (ε_T).

$$\varepsilon_T = \varepsilon_a + \varepsilon_p \quad \text{(eqn 3)}$$

Two other factors are considered: the time the source is actively emitting (t_a), and the use of personal protective equipment (PPE) ($1- \eta_{ppe}$). It is assumed that these two factors will also affect exposure in a multiplicative way, with a reduction in time the source is actively emitting resulting in a linear reduction in the exposure level. The t_a parameter is scored on a scale ranging from 0 to 1 depending on the fraction of the task time the source is active e.g. a score of 1 is allocated if the source is continuously active, and a score of 0.5 is allocated if the source is only active for half the task duration. As all exposure assessments employed in the validation of the model have been monitored with the measuring device outside of any RPE this parameter was not allocated scores, therefore for all assessments, a score of 1 is entered into the exposure model for this parameter.

Taking the time the source is active and the use of RPE into account, the exposure level (C) would be:

$$C = ((\varepsilon_i \times h \times (1 - \eta_{lev}) \times t_a + \varepsilon_p) \times (1- \eta_{rpe})) \quad \text{(eqn 4)}$$

Note, that the emission parameters (ε_i and ε_p) have units of concentration ($\mu g/m^3$) that correspond to the airborne concentration generated with a certain "standardised" handling; the other parameters are dimensionless.

General ventilation in the work environment will have an impact on the contaminant concentration in both the NF and FF, and general ventilation factors for both NF and FF are taken from Cherrie (1999) who based the values on simulations. These values are influenced by the size of the room (m^3) and the number of air changes per hour (ACH). The term d_{gv}, accounts for the dilution effect of general ventilation in the work room or area. Therefore using the above notations, the contribution to exposure from FF sources would be:

$$C_{FF} = ((\varepsilon_{i,} \text{ x } h \text{ x } (1 - \eta_{lev}))_{FF} \text{ x } t_{a,FF} + \varepsilon_{p,FF}) \text{ x } (1- \eta_{rpe}) \text{ x } d_{gv,FF} \qquad \text{(eqn 5)}$$

Similarly the contribution to exposure occurring from a source in the NF is:

$$C_{NF} = ((\varepsilon_{i,} \text{ x } h \text{ x } (1 - \eta_{lev}))_{NF} \text{ x } t_{a,NF} + \varepsilon_{p,NF}) \text{ x } (1- \eta_{rpe}) \text{ x } d_{gv,NF} \qquad \text{(eqn 6)}$$

As each job the worker performs normally comprises of several tasks or operations, the model considers each task (j) separately. The tasks are then combined together as a time-weighted summation for the 'n' tasks making up the job. Thus the total exposure (C_T) is calculated as:

$$C_T = \sum_{j=1}^{n} (C_{NF,j} + C_{FF,j}) \text{ x } \Delta_j \qquad \text{(eqn 7)}$$

where Δ_j is the fraction of the overall time each task is performed.

2.4 Advanced REACH Tool (ART)

The ART was developed for the purpose of implementing the REACH Regulations, and for the compilation of exposure scenarios, to predict geometric mean (GM) exposure levels for specific groups of workers sharing OC and RMM across different workplaces and locations in Europe (Tielemans *et al.,* 2007). The ART was developed by a large European collaborative project involving research organisations and members from industries such as metals and petroleum. Data from these industries was used to calibrate the mechanistic model which 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.

The mechanistic model is based on the conceptual framework of the source-receptor model (Cherrie and Schneider, 1999), described previously in Section 2.3. The ART framework incorporates a mechanistic model to predict inhalation exposure and an exposure database containing all the required contextual information with respect to modifying factors (MFs) of the model related to the source, transmission compartments and the receptor (Tielemans *et al.,* 2008). The mechanistic model and the database are combined using Bayesian statistics to produce more precise estimates of exposure for specific exposure scenarios. The structure of the ART model is schematically depicted in Figure 2. A detailed description of the mechanistic model and its scientific underpinning is given by Fransman and colleagues (2010).

It is constructed using **three components**:

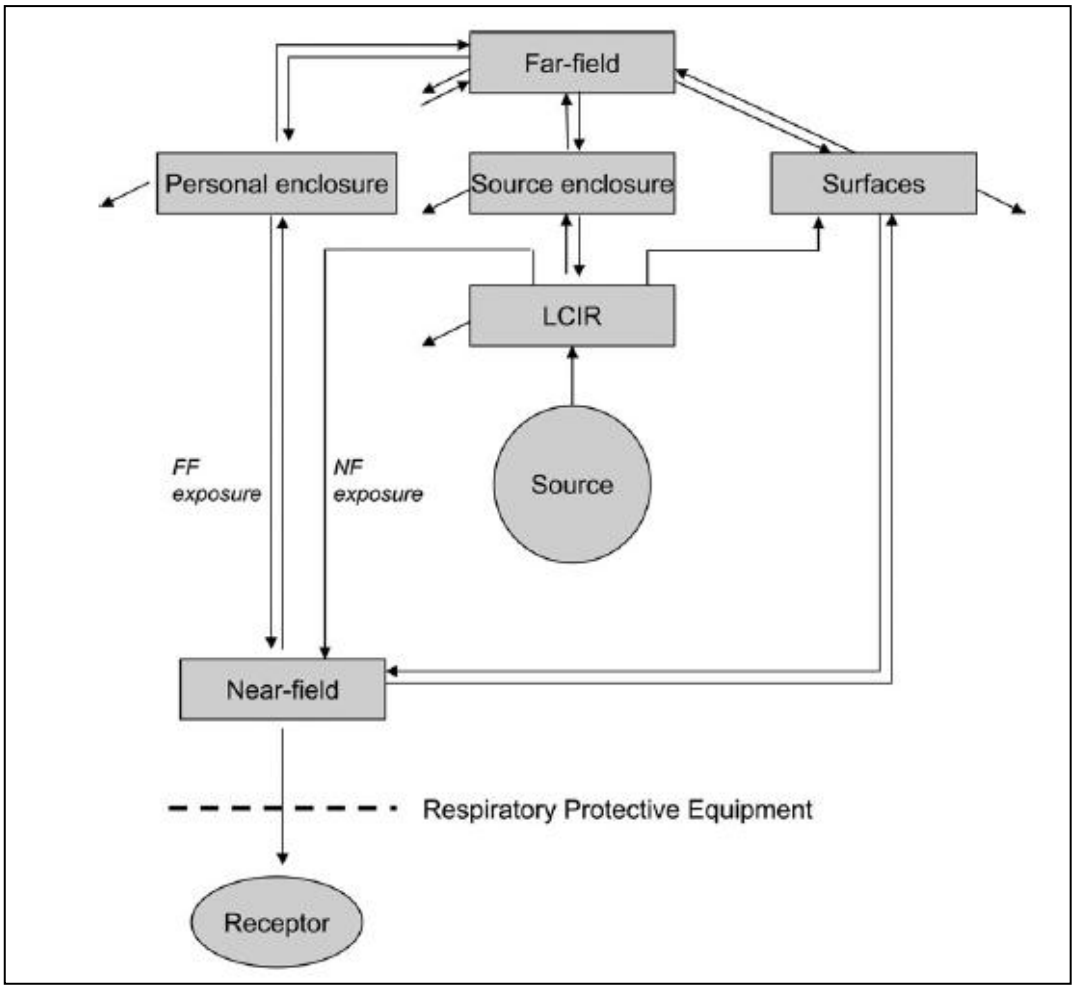
1. Sources, which represents an activity during which a hazardous substance is emitted into the air. The source can either be stationary or mobile and the strength of the source is dependent on characteristics of the activity and features of the product itself.
2. Compartments through which the contaminants may pass from the source to the receptor.
3. The receptor, which represents the respiratory tract of the worker. RPE can form a barrier for air contaminants reducing the worker’s exposure.

The following is a short description of each of the **model compartments** through which the contaminant may pass:

1. The 'local control influence region' (LCIR) compartment is a virtual boundary around the source and represents the zone of influence for a given local control.
2. The NF compartment is conceptualised as a volume of air within 1 m in any direction of the workers head. The FF compartment comprises the rest of the room. Hence the concept of NF-FF can be considered as a box inside of a box where the worker moves around in the FF zone with an enveloping NF zone. This approximates the actual concentration of contaminant which decreases with increasing distance from the source due to mixing with background air. The airflows are dependent on features like room shape and size and general ventilation.
3. A source enclosure compartment can contain a source and isolate it from the work environment (segregation).
4. A personal enclosure compartment such as an air-conditioned cabin can contain a worker (separation).
5. A surface compartment represents any surfaces that have been contaminated by the chemical of interest through general deposition in the work environment or adsorption. The deposition may result in permanent loss of contaminant due to cleaning activities. Alternatively surface contaminants may be transported to the NF or FF compartments due to re-suspension or evaporation e.g. due to moving equipment, worker movement and draughts.

Figure 2 shows the outline of the model for inhalation exposure including sources, compartments, the receptor, and transport routes between these components.

Figure 2: Schematic of the ART mechanistic model for inhalation exposure, including sources, compartments and receptor and transport routes between these compartments



(Tielemans *et al.*, 2008)

The mechanistic model includes a provision for four mechanisms of **transport of a contaminant**:

1. Separation of a vapour molecule or solid particles from the parent material.
2. Transport of the contaminants to and between compartments e.g. from contaminated surfaces to the NF compartment.
3. Loss of contaminants from compartments due to sinks (e.g. LEV, cleaning).
4. Uptake by the receptor i.e. worker.

The ART exposure algorithm incorporates nine MFs. Table 2 presents a short description of each of the principal MFs. They are defined so that they are virtually mutually independent from a physico-chemical point of view. In order to be useful for exposure modelling, these MFs have to be uniquely identifiable, observable, quantifiable and are defined at a high level of abstraction in order to be applicable across a broad range of different exposure scenarios (Fransman *et al.*, 2010).

Table 2: Components of mechanistic model and related modifying factors

Model Component	**Principal MF**	**Description**
Source	Activity emission potential (H)	Describes the potential of the activity to generate exposure and is determined by the following characteristics: type and amount of energy transfer, scale and product to air interface
	Substance emission potential (E)	Determines the intrinsic emission potential of a substance i.e. the dustiness for particulates and volatility for liquids
Local control influence region (LCIR)	Localised controls (Lc)	Local control measures in close proximity of the source intended to remove emissions
Source enclosure	Segregation (Seg)	Isolation of sources from the work environment without containment of the source itself e.g. a separate drying room segregates the source from work environment
NF and FF zone	Dilution (D)	Natural and mechanical ventilation characteristics determining the dilution of air contaminants through the room
NF zone	Personal behaviour (P)	Orientation and distance of the worker to the source in the NF determines the potential exposure
Personal enclosure	Separation (Sep)	Providing a worker with a personal enclosure within a work environment e.g. an air conditioned cabin can separate the worker from a source
Surfaces	Surface contamination (Su)	Emission related to release of deposited contaminants on surrounding surfaces due to natural means or general workplace activities
Receptor	RPE	Efficiency of RPE at preventing the inhalation of airborne substances

(Fransman *et al*, 2010)

As it was not possible to objectively quantify the effect of the MF 'personal behaviour' on worker exposure levels, this MF is currently excluded from the model algorithm; however behaviour is implicit in the activity emission potential and emission source classifications.

The model consists of one equation to estimate the contribution from NF (eqn 8) and one for estimating the contribution from FF sources (eqn 9). 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 model incorporates situations where two localised controls are present e.g. containment and LEV. The equation for a FF source (C_{ff}) also includes segregation (Seg) and separation (Sep).

$$C_{nf} = (E_{nf} \cdot H_{nf} \cdot LC_{nf1} \cdot LC_{nf2}) \cdot D_{nf} \quad \text{(eqn 8)}$$

$$C_{ff} = (E_{ff} \cdot H_{ff} \cdot LC_{ff1} \cdot LC_{ff2} \cdot Seg_{ff}) \cdot D_{ff} \cdot Sep \quad \text{(eqn 9)}$$

The level of surface contamination (Su) for each activity depends on the location of the source, i.e. whether there is i) a NF source only (eqn 10), ii) a FF source only (equation [11]), or iii) both NF and FF sources (in which case the Su in the NF is assumed to dominate that of the FF (eqn 11). Su is a function of surface contamination (Sufactor) and the NF or FF exposure level:

$$Su_{nf} = Su_{factor} \cdot (E_{nf} \cdot H_{nf} \cdot LC_{nf1} \cdot LC_{nf2} \cdot D_{nf}) \quad \text{(eqn 10)}$$

$$Su_{ff} = Su_{factor} \cdot (E_{ff} \cdot H_{ff} \cdot LC_{ff1} \cdot LC_{ff2} \cdot Seg_{ff} \cdot D_{nf} \cdot Sep_{ff}) \quad \text{(eqn 11)}$$

Subsequently, the overall exposure is estimated by equation 12:

$$C_t = \frac{1}{t_{total}} \sum_{tasks} \left\{ t_{\exp osure} \cdot (C_{nf} + C_{ff} + Su) \right\} + t_{non-\exp osure} \cdot 0 \quad \text{(eqn 12)}$$

The algorithm considers multiple activities (and exposure time ($t_{exposure}$)) within an 8 hr work shift (t_{total}) and also allows periods with assumingly zero exposure ($t_{non\text{-}exposure}$).

In order to use the equation to predict a concentration unit (mg/m^3), the dimensionless algorithm is fitted to (i.e. calibrated with) available exposure measurements using regression techniques (discussed in Section 2.5.2). The ART framework has a facility to combine the mechanistic model exposure estimates and exposure measurements combined using Bayesian probabilistic techniques in order to produce more precise estimates of exposure.

The previous sections have introduced the concept of occupational exposure modelling and reviewed the source-receptor model and the ART exposure models in further detail. Section 2.5 reviews the research needs in the area of occupational exposure modelling.

2.5 Research needs in the area of occupational exposure modelling

While much development has been made in the area of exposure modelling, all exposure models are more or less generalised (and therefore crude) representations of reality (Jayjock, 2007) and have inherent capabilities and limitations. This section addresses some of the challenges affecting the development of occupational exposure models and research needs to advance the area. Section 2.5.1 describes the uncertainty and variability affecting exposure models. Section 2.5.2 describes the calibration of occupational exposure models and Section 2.5.3 reviews the importance of evaluation of occupational exposure models, specifically their validation and reliability.

2.5.1 Uncertainty and variability affecting exposure models

Exposure predictions offered by exposure models are affected by a large degree of uncertainty and variability. Uncertainty reflects our lack of knowledge of the exposure process and how it occurs for individual scenarios while variability reflects the natural diversity over time, space or between the individuals and circumstances for which the assessment is being undertaken (Cherrie *et al,* 2004; Tielemans *et al.,* 2007). Model uncertainty and variability can be classified as: (1) model uncertainty; (2) model parameter uncertainty; (3) model parameter variability; and (4) exposure scenario uncertainty (Hertwich *et al.,* 2000; Fryer *et al.,* 2006). This section offer a short description of these four issues and

describes possible developments in the area of exposure modelling that may reduce the effect of uncertainty and variability of exposure model predictions:

- ***Model uncertainty*** arises due to differences between how the actual processes that lead to exposure are modelled and how they occur in reality. Models are simplifications of how exposure occurs and there is an assumption that the model algorithm incorporates all the significant exposure determinants. Development of our understanding of the conceptual framework explicitly describing the processes that leads to exposure should increase model transparency and reduce this uncertainty (Tielemans *et al,* 2007). While much progress has been made with ART within this area (Tielemans *et al.,* 2008), it is anticipated that further research is possible to better our understanding.

- ***Model parameter uncertainty*** represents the lack of knowledge of the true values on the input parameters e.g. efficacy of a local control measure at reducing inhalation exposure. Uncertainty in determining what is the confidence in or around these parameters and the exposure estimate, is expressed as confidence limits or error bars. This uncertainty can be reduced by acquiring further information on the values for the model input parameters. Exposure databases containing all required information on exposure determinants are an important resource for the structured storage, retrieval and sharing of exposure data. A joint ACGIH-American Industrial Hygiene Association (AIHA) Task Group on Occupational Exposure Databases (Lippmann *et al.,* 1996) and a European Working Group (Rajan *et al.,* 1997) have provided recommendations for the major categories of essential data elements to be recorded during an exposure assessment. A recent study for the purposes of REACH developed and evaluated a database on the effectiveness of RMM, known as the Exposure Control Efficacy Library (ECEL) (Fransman *et al.,* 2008). Data collected in ECEL was used to scientifically underpin the efficacy values assigned to RMM in the ART and reduce model parameter uncertainty.

- ***Model parameter variability*** represents true heterogeneity in the model input parameters such as general ventilation rates in a particular workplace or the dustiness of a material that may vary from day to day or from batch to batch respectively. This variability may be reduced by more rigid definitions of exposure scenarios, collecting contextual information on the model parameters and storage of information in exposure databases. In the pharmaceutical industry the contextual information required for investigation of parameter uncertainty and variability is not traditionally collected or stored. Exposure data is regularly stored in exposure databases e.g. Medgate database is employed by GSK; however to the best of the author's knowledge, pharmaceutical exposure databases have not been used for development of occupational exposure models.

- ***Exposure scenario uncertainty*** arises from inconsistencies between the scenario being modelled and the actual situation itself as it occurred in the workplace (Fryer *et al.*, 2006). This may be caused by uncertainty in how accurately the information was recorded at the workplace when the exposure assessment was carried out and the level of contextual information that was recorded. As regards the REACH Regulations, exposure scenario uncertainty is an issue for manufacturers who are required to predict exposure levels in user operations that they are unfamiliar with. It may be especially problematic in the pharmaceutical industry for predicting exposures in scenarios related to new chemicals or processes before the physical scenario exists (Cherrie *et al.*, 2004). Exposure scenario uncertainty, and indeed uncertainty in all model parameters, can be incorporated in the modelling process using Bayesian statistics. Bayesian Decision Analysis (BDA) allows professional judgement and modelled results, as a probability distribution ('prior' estimate of exposure), to be updated or incorporated with measured exposures ('likelihood' distribution) to obtain the 'posterior' probability distribution (Hewett *et al.*, 2006) which should be a more accurate

estimate of the average exposure level. There are several significant advantages associated with this Bayesian process, importantly it allows that prior data, professional judgement, and/or modelled information be objectively incorporated in a transparent manner into the decision-making process. Accordingly Bayesian statistics are increasingly being used in the occupational exposure assessment process (Ramachandran, 2001; Wild *et al.*, 2002; Ramachandran *et al.*, 2003; Hewitt *et al.*, 2006). Three aspects are important in determination of the likelihood function for updating model estimates with measured data and these are: the sample size, the level of similarity as assessed by the similarity module and the level of representativeness of the measurements. Further work is required on: development of data exchange modules to communicate between databases; and development of similarity modules to evaluate and incorporate the exposure scenario uncertainty in exposure modelling (Tielemans *et al.*, 2007).

2.5.2 Calibration of occupational exposure models

Likely objectives of a calibration of exposure models can include: to study whether the model scores are accurately ranked in relation to exposure measurements; to enable the model to estimate actual exposure in concentration units (e.g. mg/m^3) levels rather than relative dimensionless scores; and to provide a method to quantify model uncertainty.

Regression models can be employed to enable the dimensionless relative model estimates to be translated to quantitative exposure levels (Tielemans *et al.*, 2008; Schinkel *et al.*, 2011). For the calibration of mechanistic exposure models, mixed effects regression models with fixed (model score) and random effects (e.g. company and scenario), enable distinction between uncertainty and variability in exposure estimates. Mixed effects regression models with random between and within company components of variance were employed for the calibration of the Stoffenmanager algorithm (Tielemans *et al.*, 2008). This model was subsequently calibrated separately for four separate scenarios involving different mechanisms of handling powders and liquids (Schinkel *et al.*, 2010). Alternatively for empirical exposure models determinants of exposure may be

assigned as random effects within the regression models and a cyclical analysis performed to establish the important determinants within the dataset to be included in the model.

However, most occupational exposure models including EASE, COSHH Essential and ECETOC TRA, have not been calibrated with exposure measurements (Pers. Comm. Dr. John Cherrie). In the development of these models their outputs were 'calibrated' based on exposure judgement, possibly in combination with review of exposure measurements representative of the scenarios or determinants of concern. Their accuracy was validated by comparisons of the model estimates with exposure measurements and the validation of occupational exposure models is discussed in the following section.

In order for a model to accurately predict exposure levels for a specific scenario, industry or chemical, it is important that the model is calibrated with representative measurement data. To date pharmaceutical datasets have not largely been employed in the calibration of exposure models; approx one fifth of the data used in the calibration of the Stoffenmanager inhalable dust algorithm was derived from pharmacy shops (Tielemans *et al.*, 2008). Also as workplace scenarios and exposure levels change over time it is necessary to regularly update model calibrations with new representative and relevant exposure data (Schinkel *et al.*, 2010). The lack of calibration exercises is a big omission in the development of occupational exposure models and an important research gap which will be addressed as part of this research.

2.5.3 Evaluation of occupational exposure models

Occupational exposure models are based on the determinants of exposure and the processes leading to exposure (Burdorf, 2005). Unfortunately, as described in Section 2.5.1, occupational exposures are often affected by many factors that are difficult to describe quantitatively and simplifications are often necessary (WHO, 2005). Thus proper evaluation of a model is vital to ascertain their accuracy or validity for their intended use (WHO, 2005), with the relevant chemicals or in the relevant industry. Also the manner in which the exposure models are used or implemented by assessors should reflect the underlying

conceptual model. Thus proper evaluation of models is essential to determine their reliability among users in the relevant industries. This section reviews the importance of validation and reliability of occupational exposure models.

Validation of occupational exposure models

The process of validation of an exposure model is defined as *'a demonstration that in a specific application, the model output* (estimates) *agrees with* (exposure) *measurement data'* (WHO, 2005). However even a conceptually inaccurate model may, by chance, agree with a limited set of test data, and while it is possible to prove that a model is not valid, it is impossible to prove that a model is universally valid (WHO, 2005). Therefore while a real validation of any exposure estimation is never completely achievable, it is of utmost importance that models are at least evaluated with respect to their performance under controlled conditions and that their limitations are explicit (Delmaar *et al.,* 2006). Consequently, there is wide confusion in the scientific literature about what constitutes a thorough validation, and unfortunately one of the main weaknesses of the available models is that only a few have been properly validated (McKone, 2003; Schinkel *et al.,* 2010).

Table 1 presents the characteristics of the occupational exposure models that are currently available. Screening tools that are, at least to some extent, validated with exposure measurements include COSHH Essentials (Tischer *et al.,* 2003; Jones 2006a; Jones 2006b; Lee *et al.,* 2010), ECETOC TRA (ECETOC, 2004), EASE (Cherrie and Hughson, 2005; Hughson, 2005; Tickner *et al.,* 2005) and Stoffenmanager (Schinkel *et al.,*2010). A thorough validation study on the Stoffenmanager algorithm resulted in good correlations for handling of liquids and it was capable of discriminating among exposure levels mainly between scenarios in different companies (Schinkel *et al.,* 2010); it may have applications as a 1st tier model for REACH assessments.

There is generally a trade off between the accuracy of an exposure model and broadness of application domain (Schinkel *et al.,* 2010). Several industry and exposure 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 (Burstyn *et al.,* 2002;

Astrakianskis *et al.,* 2003; Friesen *et al.,* 2005). However there have been few studies that have validated the use of exposure models to predict exposures within the pharmaceutical industry. In a training exercise, three independent assessors of the deterministic source-receptor model reported good agreement with a small pharmaceutical dataset with spearman's correlation values of 0.88, 0.93 and 0.97 (Cherrie *et al.,* 2009). As part of this research project this source-receptor model will be validated with a larger dataset from the pharmaceutical industry. The ART is the only higher tier model currently available/under development, and a validation study of this model will also be completed as part of this research.

Reliability of occupational exposure models

Reliability is a measure of the consistency of assessments or of the ability of two or more assessors to reach the same conclusions about a specific case (Kunac, 2006). For research or a methodology to be reliable others must be able to replicate the experiment or enquiry and come up with the same results. User variation in model estimates may occur if a user has a limited understanding of the exposure scenario (OC and RMM), the exposure model and/or if the model is misused (Swartjies, 2001). The impact of user-variation could have serious consequences for workers' health, if an exposure scenario is incorrectly diagnosed as 'safe', or for the financial situation of the organisation if an exposure scenario is incorrectly diagnosed as 'unsafe', which leads to often very costly over-engineering. This might become a more widespread problem as a variety of commercial user-friendly software packages become available (Swartjies, 2001).

While studies have investigated the reliability or accuracy of subjective judgements of exposure (Kromhout *et al.,* 1987, Post *et al.,* 1991, deCock *et al.,* 1996, Ramachandaran, 2008), to date very few studies have been published on the reliability of occupational exposure models. Wendel de Joode and colleagues (2005), in their study on the reliability of the dermal exposure assessment (DREAM) method reported good to excellent inter-observer agreement for ranking of total dermal exposure estimates (intra class correlation coefficients ranged from 0.68 to 0.87). This combination of 'serious consequences' and

'limited reliability studies' is a serious problem (Swartjies, 2001) and necessitates further investigation. As models are increasingly used in the context of REACH and beyond reliability studies need more attention in the exposure science community. A study on the reliability of the ART will be completed as part of this research.

2.6 Objectives of research project

To address some of the above research gaps, this research aims to investigate the applicability of two occupational exposure models for predicting inhalable dust exposures of workers in the pharmaceutical industry. Some of this research work has been published in the peer reviewed literature and where applicable references are cited below and copies of the publications are provided in Appendix A.

Specific project objectives are to:

- Build on previous work by Cherrie and Schneider (1999) and further refine and validate the source-receptor exposure model for use within the pharmaceutical industry (Mc Donnell *et al.*, 2011).
- Refine, calibrate and validate the inhalable dust form of the ART mechanistic model for the pharmaceutical industry (Schinkel *et al.*, 2011; and Mc Donnell *et al.*, 2011).
- Investigate the reliability of the ART when used by health and safety professionals from the pharmaceutical industry (Mc Donnell *et al.*, submitted).

3.0 Overview of Chapter

The objective of this research is to investigate the applicability of two occupational exposure models for predicting inhalation exposures in the pharmaceutical industry. One of the models, referred to as the source-receptor model (Cherrie *et al.*, 1996; Cherrie *et al.*, 1999) was previously studied to a limited extend for its application in the pharmaceutical industry (Cherrie, 2009), while the ART is newly developed for use with the REACH Regulations.

This chapter presents information on the methodologies employed to meet the project objective and is presented in the following format: Revision of GSK monitoring record sheet and Medgate database (Section 3.1), the refinement and validation of the source-receptor model (Section 3.2), the refinement, calibration and validation of the ART (Section 3.3) and investigation of the reliability of the ART (Section 3.4).

3.1 Revision of GSK monitoring record sheet and Medgate database

This research project was funded by the GSK healthcare company and involved the participation of several of their manufacturing sites worldwide. Accurate information on the workplace, worker and process observations are essential for meaningful interpretation of exposure measurement results and in the development of workplace control strategies. Within GSK, occupational hygienists use monitoring record sheets (MRS) to document exposure data at the time of carrying out exposure assessments; this data is then stored in paper format and are sometimes transferred to an electronic database, called Medgate version 5.5. Within Medgate, an Industrial Hygiene Module is used to record and analyse the results of occupational exposure assessments.

As the first part of this research focused on the development of the source-receptor model, it was necessary to collate inhalation exposure assessments that contained all the information required for this exposure model. While the MRS and Medgate Industrial Hygiene Module used by GSK occupational hygienists recorded important exposure monitoring information, upon initial review of relevant literature (Rajan, 1997) and of the source-receptor exposure model

parameters, it was noted that additional information would be required to use the exposure model to assess the pharmaceutical data.

The GSK MRS and Medgate Industrial Hygiene Module were revised to require the recording of additional information on:

- % of API in the material
- Room size (m^3)
- General ventilation characteristics (air changes per hour (ACH))
- Process steps involved in the activity
- Duration (min) of each step
- Quantity of materials handled during each activity
- An assessment of the effectiveness of the local control measures
- A blank space for the occupational hygienists to enter a text description of the activity, work practice observations, unusual events and/or any employee comments as required

In February 2008 the revised MRS was distributed to several GSK occupational hygienists working in primary and secondary manufacturing sites, and Research and Development (R&D) for a trial use and to obtain feedback on its usability. Parallel to this (n=approx 12) occupational hygienists were invited to attend a presentation outlining the concept of exposure modelling and the importance of recording monitoring, task, worker and workplace information and observations was explained. The comments and suggestions from the occupational hygienists were taken into account in finalising the updated MRS (Appendix B). In April 2008 the final version of the MRS was distributed to GSK occupational hygienists, thereby facilitating the collection of complete exposure assessment data for use in the validation of the exposure model.

3.2 Refinement and validation of the source-receptor model for the pharmaceutical industry

As discussed in Section 2.2.2 and 2.5, due to the limitations of the currently available occupational exposure models one of the aims of this research was to investigate the usefulness of the source-receptor model for predicting inhalation exposures in the pharmaceutical industry.

At the commencement of this project, it was necessary to attend a training session on the source-receptor model. Details of the content of the training and the results of exposure assessments using the model are provided in Appendix C.

In order for the model to be applicable for the pharmaceutical industry, it was necessary to refine model parameters to incorporate manufacturing and control technologies relevant to exposure scenarios found in this industry. This section details the model parameter refinements (Section 3.2.1) which were necessary to include handling activities and local control measures that are used in the pharmaceutical industry. The methodologies employed in the validation of the source-receptor model (Section 3.2.2) are also described.

3.2.1 Refinement of source-receptor model input parameters

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 a thorough list of handling activities and local control measures that occur within the industry was compiled. Information on the efficacy of the local control measures at reducing inhalation exposures was collected. This was done by reviewing the literature, reviewing GSK occupational exposure assessment reports and engineering design kits (EDKs), and consulting with occupational hygienists, professional organisations and consultants working in the pharmaceutical industry (Safebridge Consultants Inc. and International Society for Pharmaceutical Engineering). Further details on the refined handling activities and local control measures parameters and assigned scores are given in this section.

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 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 3 shows the handling activity energy classes, corresponding model scores and example handling activities per class.

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Table 3: Source-receptor model handling activity energy classes, corresponding model scores and example handling activities per class

Handling activity energy classes: Model Scores	**Handling Activities**	
10	Sweeping	
3	Drying	Milling
	Material Transfers (including vacuum)	Charging
	Filling materials (>0.5m drop height)	Coating
	Blending and Mixing	Cleaning with blowing tool/hose
1	Tableting/Compression	Brushing
	De-duster	Wash objects with water or power kettle (not power hose)
	Sieving/Grating	De-lumping (>10kg)
	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 <0.5m)	Packaging (incl. Blistering & De-blistering)
	Hand sieving	Disassemble machine
	Weighing and breaking up lumps (<10kg)	Handling/Disposal of objects with limited contamination

Table 3 continued: Source-receptor model handling activity energy classes, corresponding model scores and example handling activities per class

Handling activity energy classes: Model Scores	**Handling Activities**	
0.03	Handling (opening/closing) of bags/liners/boxes	Short transfer of materials (<1kg) e.g. sampling, filling vials, probe samples
	Add liquid to powder	Seal and de-dock
0.01	Careful sampling for quality control	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	

The sub-parameter related to the quantity of material handled was categorised as tonne/hr, kg/hr, g/hr or mg/hr 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 4. 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 4; 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.

Table 4: Description of the source-receptor model worker behaviour classes and associated administration measures, model scores, and examples of handling activities per class

Worker Behaviour Class	Description	Administration Measures	Model score	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 is 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 process and involves some handling of product	Carried out as per standard operating procedures (SOPs) / training / supervised	**1**	Manipulation of wand/hose Handling (opening/closing) of bags/liners/boxes Transfers or weighing of material
Very prone Exposure greatly affected by worker behaviour	Manual process Worker very frequently intervenes/is involved in process and handling of product	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

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 were scored. An overview of the GSK control banding approach incorporating occupational hazard categories (OHC) and exposure control approaches (ECA), and a list of local controls measures and assigned model scores used in the study are presented in Table 5.

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

Table 5: GSK control banding approach detailing occupational hazard categories (OHC), performance bands and exposure control approaches (ECA) categories, with example local control measure options and model scores

OHC	Performance band ($\mu g/m^3$)		ECA	Local Control Measures	Model Score
1	> 1000 ≤ 5000	Risk Assessment	A	No special engineering containment is required General room ventilation	1
2	> 100 ≤ 1000		B	Local exhaust ventilation	0.1
				Partial enclosures	
				Downward laminar flow booths	
				Solids transfer using: standard docking station or Using Slot LEV and Transfer Sock	
3	> 10 ≤ 100		C	Downward laminar flow booths (fitted with barriers or shower curtains)	0.01
				Containment with extraction	
				Enclosed material transfer systems (e.g. split butterfly valves, flexible liners or inflatable heads)	
				Vacuum transfers	
				Shrouds	

Table 5 continued: GSK control banding approach detailing occupational hazard categories (OHC), performance bands and exposure control approaches (ECA) categories, with example local control measure options and model scores

OHC	Performance band (µg/m^3)		ECA	Local Control Measures	Model Score
4	> 1 ≤ 10	Risk Assessment	D	Slot LEV and Transfer Sock	0.001
				Enclosed processes	
				Single chamber glove boxes	
				Contained or Rapid Access Port (RAP	
5	≤1		E	Multiple compartment glove boxes	0.001
				Continuous liner systems in glove boxes	
				Isolators	
				Enclosed process plus additional containment	

3.2.2 Validation of source-receptor model

This section describes the collation of exposure assessments for validation of the source receptor model and the statistical analysis involved in the validation of this model.

Collation of exposure assessments for validation of source-receptor model

GSK has over eighty pharmaceutical and consumer healthcare manufacturing facilities worldwide, involving approximately 2,400 APIs. For this study occupational hygiene survey reports and survey monitoring record sheets were abstracted from GSK archives. Also the author spent two weeks at a GSK primary manufacturing facility carrying out occupational hygiene measurements (approx n=7 measurements). 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 influence of measurement error, measurements with a sampling duration of less than 5 min 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 validation 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 representative of exposure scenarios found in this industry. All of the exposure data was collected by experienced occupational hygienists or occupational hygiene technicians. Exposure samples were collected and 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 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) (Hornung and Reed, 1990).

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. The model estimates exposure 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 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 data set 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) (Cherrie *et al.*, 2009).

Statistical analysis involved in the validation of source-receptor model

All of the exposure information collected was summarised and model scores were assigned to the model parameters in Microsoft Excel; this exercise was carried out blind to the actual measurement data. The data was analysed using SAS statistical Software (version 9.1.3; SAS Institute, Cary, NC). Measured exposure concentration and model predictions were found to approximate a log-normal distribution and descriptive statistics are presented both as arithmetic and GM levels with geometric standard deviation (GSD) and range of the exposure distribution (Section 4.1.1, Table 10).

The model predictions of exposure were then compared to the actual measurement values. Spearman rank correlation coefficients were calculated to study the relationship between the model predictions and the actual measurement data and also the relationship between the model predictions and measurement

data when grouped to scenario level. Measurements were grouped to scenario level based on activity, local control measures and premises. Model bias i.e. the ratio of the GM of the model predictions to the GM of the measured data was determined to assess accuracy of the model exposure predictions.

As discussed in Chapter 2, due to the potential applications of the ART the remainder of the research focused on investigating the applicability of the tool for predicting inhalation exposures in the pharmaceutical industry

3.3 The Advanced REACH Tool

The following section details the methodologies employed to investigate the applicability of the inhalable dust mechanistic model of the ART for predicting exposures in the pharmaceutical industry and the analysis that was carried out with the pharmaceutical dataset: refinement of the ART modifying factors (section 3.3.1), collation of exposure data from the pharmaceutical industry and data preparation (Section 3.3.2), assignment of ART scores for calibration and validation of the ART mechanistic model (Section 3.3.3), treatment of measurement values below the limit of detection (Section 3.3.4), calibration of the ART mechanistic model (Section 3.3.5), validation of the ART mechanistic model (Section 3.3.6) and investigation of the reliability of the ART (Section 3.4.1).

3.3.1 Refinement of ART modifying factors

Prior to the calibration of the ART, 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, namely: activity emission potential, localised controls and dispersion. Proposed classifications were developed based on review of published literature (Fransman *et al.*, 2008), GSK data and exposure assessments. The classifications and assigned efficacy multipliers were reviewed by health and safety experts from GSK and the pharmaceutical industry (Astra Zeneca, members of the International Society of Pharmaceutical Engineering (ISPE) and Safebridge Consultants Inc.) 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 at GSK in London in October 2009 to

discuss the refinements of the localised control and dispersion MFs with 11 experts, including three researchers from academia and industry, seven occupational hygienists and one containment expert from GSK. The classifications and assigned efficacy values were discussed until a consensus was reached. The final proposed modifications and revisions were subsequently incorporated in ART version 1 and are outlined in this section.

Activity emission potential MF

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. 10-100g and <10g
- 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)

Localised control MF

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 6 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 (assigned efficacy multiplier=0.1) with LEV (assigned efficacy multiplier=0.1); values are treated multiplicatively to results in a local control MF weight of 0.01.

Table 6: Classification of the ART localised control modifying factor, descriptions of subclasses and assigned efficacy multipliers

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

* Classifications shown in **bold type throughout this table** were incorporated as a result of the pharmaceutical industry refinements but are applicable to other industries.

Table 6 continued: Classification of the ART localised control modifying factor, descriptions of subclasses and assigned efficacy multipliers

Local control class	Localised control subclass	Description	Assigned efficacy multiplier
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.** ***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.***	0.1
	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 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

Table 6 continued: Classification of the ART localised control modifying factor, descriptions of subclasses and assigned efficacy multipliers

Local control class	Localised control subclass	Description	Assigned efficacy Multiplier
Glove bag	**General Description**	**Large plastic bags, available in different design 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 high efficiency particulate arrestor (HEPA)** • **HEPA filtered extract air** • **Not safe change filters** • **Manual cleaning**	0.001

Table 6 continued: Classification of the ART localised control modifying factor, descriptions of subclasses and assigned efficacy multipliers

Local control class	Localised control subclass	Description	Assigned efficacy Multiplier
Glove box	**> 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** • **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** • **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 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**	0.0001

Dispersion MF

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 7 shows the classification of downward laminar flow booths and assigned multipliers.

Table 7: Classification of the ART dispersion modifying factor, description of classes and assigned multipliers

Dispersion class	Description	Assigned multipliers
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 3500-4000 m^3/h (per 1m 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 a high dust holding capacity, and performance and volume air flow need to be checked regularly. • For downward laminar flow booths the capture velocity should approximate 0.5 m/second. • 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 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

3.3.2 Collation of exposure assessments for ART and data preparation

In addition to the assessments that were collated for the validation of the source-receptor model (Section 3.2.2) further assessments were collated from across the GSK healthcare company for the calibration and validation of the ART. The same methodologies, as described in Section 3.2.2 were employed for the collation of the additional exposure assessments from GSK sites across Europe and Asia.

For the purpose of the ART mechanistic model, some further information was required for example on: substance emission potential, the activity emission potential and localised control measures MFs. For example, within the dust exposure form of the ART model, the substance emission potential MF considers: (1) the dustiness of the material, (2) the weight fraction of the substance in the material (for pharmaceutical materials this relates to the % of API in the material), and (3) the moisture content of the material. Additional information was collated for all exposure assessment from the GSK occupational hygienists.

Exposure assessments were grouped to exposure scenario level which 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 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.

In preparation for statistical analysis, as measurement error may have an impact on measurements of short duration, those measurements with sampling duration less than five minutes were excluded. 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 LOD of the analytical technique and exposure scenarios with less than three measurements were excluded.

The overall pharmaceutical dataset was divided into two separate datasets: one for the calibration and one for the validation of the ART mechanistic model. Prior to carrying out the statistical analysis the measured exposure concentrations were assessed to investigate the exposure distribution. The measured exposure concentrations were found to approximate a log-normal distribution and descriptive statistics are presented (Results Chapter) both as arithmetic and geometric mean levels with geometric standard deviation and range of the exposure distribution.

Screening of data quality for the calibration and validation of the ART

To ensure that the descriptive information was sufficient for the mechanistic model MFs, the survey reports collated from the pharmaceutical industry were analysed for data quality. While only good quality exposure data was used in the calibration of ART both good and moderate quality exposure data were included in this validation study.

Good quality data was defined by Schinkel and colleagues (2011) as data meeting the following quality standards and which:

- Has all of the required core information on companies, worker activity, product, chemical agent, exposure determinants, measurement procedure, measurement strategy and results (Rajan *et al.*, 1997; Tielmans *et al.*, 2002)
- Allows all ART MFs to be assessed for all individual activities during the measurement period
- Has information on the time registration of the different activities
- Has sampling time longer than 5 min

Moderate quality data was deemed to be broadly similar to good quality data with some missing details such as sampling durations, sampling methods or analytical methods. Nonetheless there was consensus among the assessors that this data was collected and recorded satisfactorily and it was possible to assess all ART MFs for all individual activities during the measurement period.

3.3.3 Assignment of ART scores for calibration and validation of the ART mechanistic model

Pharmaceutical exposure data and contextual information for ART MFs were recorded in Microsoft Office Excel 2007. Scores were assigned for each ART MF and were individually reviewed by and discussed with another member of the ART team (Jody Schinkel, TNO Quality of Life) until a consensus was reached. A selection (approx 25%) of the pharmaceutical data was also independently checked for assignment of scores by a third member of the ART team (Dr. Wouter Fransman, TNO Quality of Life). When multiple activities occurred during a single measurement, ART scores were calculated per activity and then combined as a time-weighted average of all of the activities that occurred during the measurement period.

3.3.4 Treatment of measurement values below the limit of detection for the calibration and validation datasets

For measurement results below the LOD, imputed values based on the maximum likelihood estimation (MLE) procedure were used (Lubin *et al.,* 2004). As only a small percentage of the measurement in the calibration dataset were below the LOD (n=2; 7% of the dataset) uniform distributions were estimated for all of the scenarios. For measurements below LOD these distributions were used to randomly impute values between zero and the LOD.

As there was a significant percentage of the validation dataset with values below the LOD (n=62; 32% of the dataset) it was also necessary to investigate the effect of the assumed exposure distribution. The following exposure distributions were investigated: global, conditional, stratified. A global exposure distribution assumes an overall exposure distribution for all the scenarios, with one mean exposure value and one standard deviation for all the scenarios; the conditional exposure distribution assumes individual exposure distributions with individual mean exposure values and the same standard deviation value for all the scenarios; and the stratified exposure distribution assumes an individual exposure distribution with individual mean exposure values and individual standard deviations per scenario. The effect of the assumed distribution was investigated by carrying out the imputations with these exposure distributions for

scenarios with greater than 50% of the measurements less than the LOD. As discussed further in Section 4.2.2 some of the exposure scenarios with measurement results below LOD had too few measurements to estimate individual stratified exposure distributions, therefore the conditional 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 preformed resulting in 30 datasets. The data were analysed using SAS Statistical Software (version 9.1.3; SAS Institute, Cary, NC, USA). Subsequently PROC MIANALYZE was used to combine the regression results from the multiple datasets.

3.3.5 Statistical analysis involved in the calibration of the ART mechanistic model

The pharmaceutical dataset (n=291) was included in the generic calibration of the inhalable dust exposure form of the ART mechanistic model. It was necessary to investigate if the generically calibrated model would be comparable to the model when calibrated with only pharmaceutical data only. This section describes the statistical analysis that was carried for the pharmaceutical specific calibration. It is important to note that this exercise was a calibration of the ART generic model, not of an industry or chemical specific version, which would comprise more specific determinant classifications specific to the pharmaceutical industry or specific chemicals.
A regression equation can be depicted as shown in equation 13:

$$y = a + b \cdot x \quad (13)$$

In the above equation y is the dependent variable, a is the constant value (i.e. intercept), b is the slope (i.e. regression coefficient) and x represents the fixed or random effects. This deterministic mechanistic model assumes that there is a perfect relationship between exposure and ART model scores. As shown in equation 14 due to the exposure weights being based on scientific data, the model has the desirable property that the calibrated model predicts zero exposure exactly when the dimensionless non-calibrated model does.

$$\text{Exposure} = \alpha \cdot \text{ARTscore} \quad (14)$$

where α=fixed slope of 1

However, in practice the mechanistic model of ART does not capture the full heterogeneity of workplace exposures and therefore an 'error' term was introduced. Although in principle this error term could be additive, this resulted in highly skewed residuals that do not conform to the assumption of normality required for fitting via least squares regression. Instead a multiplicative error was proposed that corresponds to exposure measurements being lognormally distributed (equation 15):

$$\text{Exposure} = \alpha \cdot \text{ARTscore} \cdot e^{\varepsilon} \quad (15)$$

Transforming this relationship through taking natural logarithms gives (equation 16):

$$\text{Ln (exposure)} = \text{Ln } (\alpha) + \text{Ln (ART score)} + \varepsilon \quad (16)$$

As exposure levels vary between scenarios, between companies and between workers, random scenario, company and worker components should also be included resulting in a linear mixed effect model. Unfortunately, unique codes per worker were missing for part of the dataset therefore no random component for worker was included in the model. The linear mixed effects model used for calibration of the ART mechanistic model is given in equation 17:

$$Ln(Y_{ijk}) = X_{ijk} = Ln(\alpha) + Ln(ARTscore) + \delta_i + c_{ij} + \varepsilon_{ijk} \quad (17)$$

[Dependent variable =intercept+ fixed effects + random effects + error (residual error)]

In the above equation Y_{ijk} is the exposure level for the κth measurement within the *j*th company in the *i*th scenario. X_{ijk} is the ln-transformed exposure level; Ln α is the intercept (natural logarithm of the slope on the natural scale); δ_i represents the random effect of the *i*th scenario, c_{ij} represents the random effect of the *j*th company in the *i*th scenario and ε_{ijk} is the residual error term. It was assumed that δ_i, c_{ij} and ε_{ijk} values are normally distributed with mean equal to zero and variances representing the between-scenario, between-company, and within-company components of variance.

Using this method the relative ART mechanistic model scores were still proportional to actual exposure levels and importantly the multiplicative effects

of individual MFs multipliers were preserved. For example, the efficacy of fixed local exhaust ventilation (LEV) at reducing inhalation exposures has been assessed as 90% (Fransman *et al.*, 2010); with a proportional relationship between model score and actual exposure levels this efficacy is applied over the whole range of model scores. The intercept (Ln (α)) represents the estimated exposure if the ART model score is 1.

The between-scenario component of variance (δ_i) provides an indication of the model uncertainty. The model uncertainty can be expressed as an uncertainty factor (UF) and was defined as follows:

$$UF = e^{1.6449 \cdot \sqrt{\sigma^2_{between-scenario}}} \quad (18)$$

This UF provides a 90 % probability that the true median exposure level is within that factor; e.g., an UF of 5 represents a 90% probability that the true GM of a scenario is within a factor 5 of the model estimate $\hat{Y}$.

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

1) A broad scenario was defined by the main MFs: activity emission potential, substance emission potential, and localised controls. Using this definition large scale bagging operations with and without LEV were two separate scenarios. Similarly, data from bagging operations of granules and fine powders belong to different scenarios.
2) A refined scenario was defined as above with the addition that data from different premises and industries were assigned to different scenarios. For example; comparable bagging operations of granules from two different premises were assigned to different scenarios.

3.3.6 Statistical analysis involved in the validation of the ART mechanistic model

As described previously, pharmaceutical exposure assessments for the validation of the ART mechanistic model were collated (n=192), screened for data quality and assigned model scores. This section describes the statistical analysis involved in the validation of the inhalable dust exposure form of the ART mechanistic model with the pharmaceutical dataset.

As the accuracy of the ART to estimate GM exposure levels was of interest, bias was calculated at scenario level as the difference between ART GM estimates and the GM of the measured exposure (Hornung, 1991). 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 bias divided by the GM of measured exposure, multiplied by 100% (equation 19).

$$\text{Relative bias} = (\text{bias}/\text{measured GM}) * 100\% \quad (19)$$

The mechanistic model was developed to estimate GM exposure levels of an exposure scenario. For the generic calibration, Schinkel and colleagues (2011) 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 factors difference between estimated and measured GM exposure levels were calculated (i.e. estimated GM/measured GM). If the previously reported UF of 4.4 was true for this validation dataset, 90% of these factors difference values should be between 0.23–4.4 (derived from: factor difference of 1 divided or multiplied by UF of 4.4 i.e. 1/4.4 and 1*4.4).

3.4.1 Reliability of the ART

Reliability is a measure of the consistency of assessments or of the ability of two or more assessors to reach the same conclusions about a specific case (Kunac, 2006). As reliability is an important and necessary component of validity of occupational exposure models (Siemiatycki *et al.*, 1997) it was decided to investigate the reliability of the ART. This section describes the study design and statistical analysis involved in this research.

3.4.2 Study design

Health and safety professionals and specifically occupational hygienists are normally responsible for carrying out exposure assessment in the workplace and accordingly it was anticipated that they may be qualified users of the ART as an exposure assessment tool for the purpose of REACH. As part of this research project the inhalable dust exposure form of the mechanistic model was refined and validated with a data set from the pharmaceutical industry; therefore a reliability study was conducted with professionals with experience in this industry. A list of 61 health and safety professionals was compiled with the help of the Occupational Hygiene Society of Ireland (OHSI) and from personal contacts. Potential candidates were contacted via e-mail and 18 people agreed to participate in the study (30% response rate). In advance of the workshop a questionnaire was circulated to all participants to collect details such as: current job role; academic qualifications; experience to date working as an occupational hygienist; experience conducting chemical exposure assessments; experience using exposure models; and their familiarity with the ART. The questionnaires were disseminated to participants prior to the workshop. Of the 18 participants, nine participants had greater than ten years experience in occupational hygiene. One third of the group had some previous experience with using other exposure models. Only one of the 18 participants had previously used the ART, and this was for less than one hour; the remainder of the group had no previous experience with the ART.

A one day work shop was conducted at the National University of Ireland, Galway in July 2010 during which the professionals used the ART to assess four exposure scenarios. The exposure scenarios were representative of scenarios

from the pharmaceutical industry and consisted of two activities per scenario during which a hazardous substance was handled. The scenarios were developed so as to contain similar levels of information on all the MFs as presented in Table 8. Prior to the assessment stages the participants were provided with a text copy of the exposure scenario consisting of (i) a brief text description outlining the substance, the handling activities, any localised controls, and work area size and ventilation rates, and (ii) pictures of the substance, processes and local control measures (Figure 3). For two of the scenarios the participants were provided with a container containing powder material, for which they subjectively assessed the dustiness of the materials.

Table 8 presents the MFs and classes that were included in the exposure scenarios. During the one day workshop it was only possible to assess eight activities i.e. four exposure scenarios, and those determinants considered most relevant for the pharmaceutical industry were included. In order for the workshop to be comparable to workplace use of the ART, subjective judgement was required for some of the determinants e.g. dustiness and emission source, while the information was more clearly provided for other determinants e.g. room size and ACH. Also while some MFs or determinants were not specifically referred to in the documentation e.g. segregation and separation, it was still necessary for participants to assess them all in the correct place in the tool to obtain an exposure estimate. Using the online version 1.0 of ART (www.advancedreachtool.com), the participants were asked to independently assess the four scenarios without discussions with the trainers or with each other. The participants were unaware of the gold-standard choice of determinants and exposure estimates i.e. the expert-assessment or how the developers of ART assessed the determinants and the resultant gold-standard exposure estimates. ART scores for each determinant were assigned by the author and subsequently reviewed by another member of the project team (Jody Schinkel, TNO Quality of Life) and discussed until consensus was reached.

The workshop was structured so as to consider the effect of dissemination of information on the use of the ART on the reliability of the participant's while assessing the scenarios. Each participant individually assessed four exposure

scenario at three stages throughout the day and each scenario was assessed only once: (i) one scenario was assessed *'without introduction'* to the theory of the ART or the functionalities of the tool; (ii) another scenario was assessed *'after introduction'* to the ART theory; (iii) and finally two scenarios were assessed *'after demonstration'* of the ART. To enable some comparison of participants' agreement per determinant without and after the introduction to ART, during the *'without introduction'* stage half the participants assessed Scenario 1 and the other half assessed Scenario 2, while during the *'after introduction'* stage each group assessed the opposite scenario. The participants were split into two groups so as both groups included individuals with similar years of experience in occupational hygiene.

During the introduction to ART (45 min), information was presented on the ART mechanistic model and on the model MFs. During the demonstration of using the ART (90 min) the assessment of the 'gold standard' of the previous Scenario 1 was presented. The demonstration also involved more detailed information on the use of the ART and scoring of the MFs, and discussions to clear up any uncertainties on the assessment of Scenario 1 or 2. In total only 2 hours and 15 minutes of information was presented and due to time limitations of this one day workshop, it was not possible to disseminate detailed training on the ART. After the demonstration stage all the participants assessed both Scenario 3 and Scenario 4. Upon completion of the assessments hardcopies of all of the participant's assessments were printed and were subsequently transcribed into Microsoft Excel.

Table 8: Modifying factors and determinants in scenariosand description of information provided and associated rationale

MF	Determinants in exposure scenarios	Information provided	Rationale for providing information
Substance Emission Potential	Dustiness	Physical sample or pictures of the materials	Dustiness test results are not normally available, so subjective assessment of dustiness must be used
	% of API in the material	Specify the % of API in the materials	This information is readily available in the workplace (e.g. material safety data sheets)
	Moisture	Description of material and activity e.g. wet wipe or mopping of floor	In reality this is quite subjective but the ART description text should guide participants
Activity Emission Potential	Activity class and subclass • Compression • Movement and agitation • Transfer – falling • Handling • Fracturing	Brief description of activity (e.g. scooping, disposal, tabletting) and a picture of activity taking place	Participants had to decide on activity class and subclass and further determinants
		Names of activity and corresponding duration of activities	This information is readily available in the workplace
	Quantity / use rate	Total quantities involved in the activity	Participants had to work out quantity/min
	Emission source	Description of activity e.g. at control panel located 5m away from tabletting machine or at location of manually scooping of tablets.	This information is readily available in the workplace; participants had to decide whether it is NF or FF or or a situation with NF and FF
Local Controls	Sub-classes • No Local Controls • Containment • Glove-box • LEV	Brief description and picture of the local control measure	This information is readily available in the workplace; participants had to decide on ART classification
Surface Contamination	• Questions regarding enclosure of process, housekeeping and maintenance.	Brief description referring to visible/no visible contamination on work surfaces and corresponding pictures for rest of scenario. Comment on housekeeping/maintenance	This information is readily available in the workplace e.g. if housekeeping, maintenance or other related activities are occurring
Dispersion	Indoors	Room size and ACH	This information is readily available on sites
	Down-flow room	Room size and ACH	This information is readily available on sites

Figure 3: Example of scenario provided to participants of workshop

This scenario involves the crushing of tablets for quality checks and the subsequent cleaning of the fume cupboard with dampened wipes.

The tablets, called Smartie Tablets (CAS number 110-12-3) contain 68% active pharmaceutical material (API). The tablets weigh 0.5 grams each (Fig 1).

Using a pestle and mortar, the worker crushes 10 tablets. This activity occurs within a fume cupboard and takes 7 minutes.
The worker then cleans the inside surfaces of the fume cupboard using slightly dampened wipes. This activity takes 5 minutes. For both activities the fume cupboard sash is open to the appropriate height.

The fume cupboard is located within a large room with mechanical ventilation. The fume cupboard is maintained appropriately, the work area is cleaned regularly and there is no visible contamination on any surfaces.

For the remainder of the work shift (which in total is 480 minutes shift) the worker is involved in carrying out maintenance tasks and is not in the vicinity of the API.

Fig 1: Smartie Tablets being crushed using a pestle and mortar

Fig 2: Worker crushing tablets at a fume cupboard

3.4.3 Statistical Analysis of reliability study results

Statistical analyses were performed with SAS Statistical Software (version 9.1.3; SAS Institute, Cary, NC, USA). Each MF was assessed by all of the participants (hereafter referred to as raters) (n=18) for both activities in each of the four scenarios (activities n=8). The activities related to exposure scenarios 1 and 2, which were assessed alternatively by raters during without introduction and after introduction stages, were assessed separately.

To investigate the level of agreement of raters with the gold-standard, the percentage of ratings for the determinants of each activity that were in agreement with the gold-standard were calculated. To investigate if there were any differences in the agreement levels of raters of varying years of experience in occupational hygiene, the raters were separated into two groups, which were arbitrarily categorised as: <10 years of experience and ≥10 years experience in occupational hygiene.

While the percentage agreement results indicate the agreement with the gold-standard we were also interested in the inter-rater agreement. Cohen's kappa statistic (*k*) gives the exact proportion of agreement that cannot be expected by chance alone (Steinsvag *et al.*, 2007). Kappa statistics were calculated as described by (Fleiss 2003) for multiple raters and does not assume that the raters responsible for rating one subject are the same as those rating another subject or scenario.

For the surface contamination determinants, as six out of eight activities occurred in an apparently clean work area, almost no variation in rater judgement was expected. As the MFs segregation and separation were not present in any activity, no variation in rater input was expected. For these determinants without varying rater inputs, kappa statistics were not relevant and the percentage agreement with the gold-standard results covers the conclusions about agreement. Also as the scores for the activity emission potential (AEP) MF are a result of multipliers for several determinants including for example; activity class, quantity of material, drop height and type of handling, it was not possible to calculate kappa statistics for this MF. Kappa statistics were calculated for the

following determinants: dustiness, emission source, activity class, primary local controls, room size and ventilation rate.

The strength of the inter-rater agreement was qualified using terms defined by Landis and Koch (1977) as shown in Table 9.

Table 9: Kappa statistics and corresponding strength of inter-rater agreement as defined by Landis and Koch (1977)

Kappa statistic	Agreement
≤0	None (other than would be expected by chance)
0.01–0.20	Slight
0.21–0.40	Fair
0.41–0.60	Moderate
0.61–0.80	Substantial
0.81–1.00	Almost perfect

Results are presented as the Cohen's kappa statistic and standard errors for each determinant throughout the various sessions. Where a participant did not assess a second activity in a scenario as required, all determinants were assigned to a 'blank' category that was treated as not in agreement with the 'gold standard'. Where a determinant was not applicable it was also treated as an additional category (e.g. if Dispersion='Downward laminar flow booth' was chosen then the determinants 'room size' and 'ventilation rate' were not required) and did not influence the agreement measures.

Relative weights have been assigned to the underlying categories of each of these MFs which are used as multipliers in the mechanistic model algorithm (Fransman *et al.*, 2010) to result in exposure estimates in mg/m^3 (Schinkel *et al.*, 2011). As the exposure estimate will be used in the exposure assessment process the raters eventual exposure estimates were compared to the gold-standard exposure estimate.

4.0 Overview of Chapter

This chapter contains the results of the research carried out as part of this project, presented as follows: results from the development and validation of the source-receptor model for the pharmaceutical industry (Section 4.1); results from the calibration and validation of the ART mechanistic model for the pharmaceutical industry (Section 4.2); and results from a study of the reliability of the ART for the pharmaceutical industry (Section 4.3).

4.1 Development and validation of the source-receptor model for the pharmaceutical industry

Further developments were necessary to the source-receptor model (Cherrie 1996; Cherrie and Schneider, 1999) in order for it to be applicable for the pharmaceutical industry. This section contains an overview of the measurement data that were used in the validation of the source-receptor exposure model (Section 4.1.1), and results from the statistical analysis of source-receptor model predictions and measurement data (Section 4.1.2)

4.1.1 Overview of measurement data used in the validation of source-receptor model

Data were obtained for 381 exposure measurements across primary (n=198) and secondary (n=167) pharmaceutical manufacturing and healthcare (n=16) 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 10. The dataset included a wide range of exposure measurements for pharmaceutical exposures. The lowest measured exposure level was found during a task involving dispensing an API in a negative pressure glove-box ($5x10^{-7}$ mg/m^3) while the highest exposure level was found during a sack tipping operation (200 mg/m^3), performed in a downward laminar flow booth (the worker wore RPE)[1].

[1] The measurement with the high exposure levels involved excipients and was based on a short (8 min) task based measurements for TID

Table 10: Descriptive statistics of the measured exposure data used in validation of source-receptor model

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

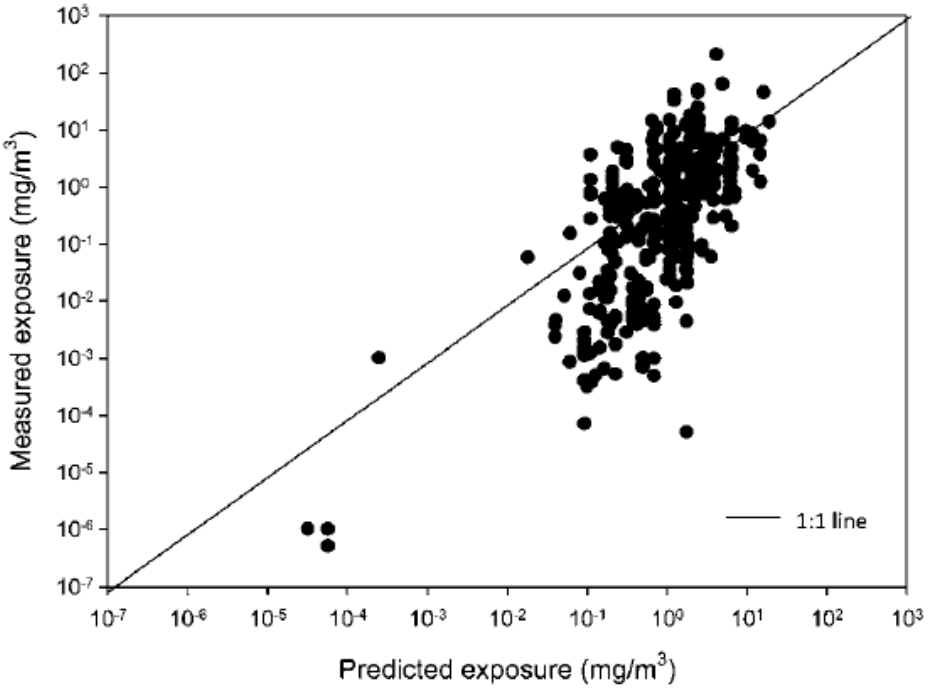
N=Number of samples; AM=Arithmetic mean; GM=Geometric mean

4.1.2 Statistical analysis of exposure model predictions and the measurement data

The following section presents comparisons of the model predictions, with the individual measurement data and measurement data grouped to scenario level.

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). Figure 4 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.

Figure 4: Relationship between the model predictions and the measured concentrations (mg/m^3) for exposure assessments



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 (range=0.003-57) indicates that the model underestimated exposure for this particular dataset.

Exposure measurements (n=381) for the same or similar tasks using the same local control measures and collected from the same site were grouped into exposure scenarios (n=48). In order to calculate a GM exposure level per exposure scenario, each scenario had a minimum of three measurements of exposure available (range 3-22). The mean exposure levels within 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 1-10 mg/m^3 and four 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). Figure 5 shows a scatter plot of the predicted exposure levels in relation to the mean measured exposure for each exposure scenario. Table 11 presents the correlation coefficients between the model predictions and the mean measured concentrations with varying number of measurements per exposure scenario

Figure 5: Relationship between the model predictions and the mean measured concentrations (mg/m^3) grouped by exposure scenarios

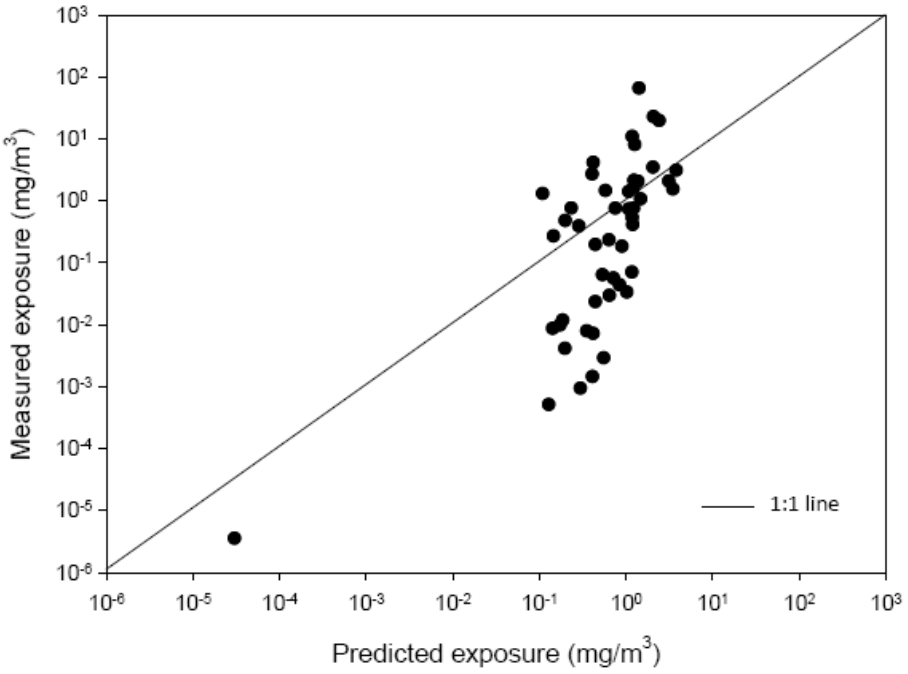


Table 11: The correlation coefficients between the model predictions and the mean measured concentrations with varying number of measurements per exposure scenario

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

As presented in Table 11 there was no clear trend of an improved correlation between the mean measured and predicted exposures with an increasing number of measurements per exposure scenario.

Statistical analysis shows that 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 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 information on the individual parameters from the algorithm and assigning the mean score for all of the other parameters, as shown in Table 12. Including information on the energy input during the handling activity, the quantity of material handled, and worker behaviour, increased the Spearmans correlation by 19%, 12% and 4% respectively. Similarly, including information on local controls 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 12: The correlation coefficients between the model predictions and the mean measured concentrations when information on 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	0.68
Full model (all parameters)	**0.69**

4.2 Calibration and validation of the Advanced REACH Tool

In order for the ART to be applicable to the pharmaceutical industry, some of the MFs of the mechanistic model were refined (Section 3.3.1) and the inhalable dust exposure form mechanistic model was calibrated and validated with data from the pharmaceutical industry (Sections 3.3.5 and 3.3.6 respectively). The following sections contain results of the calibration of the ART mechanistic model with a pharmaceutical dataset (Section 4.2.1) and the validation of the ART mechanistic model with a pharmaceutical dataset (Section 4.2.2).

4.2.1 Calibration of ART mechanistic model with a pharmaceutical dataset

The calibration of the overall ART mechanistic model for the different exposure forms, vapours, dusts, mists and fumes was described in detail elsewhere (Schinkel *et al.,* 2011). The pharmaceutical dataset (n=291) was included in that generic calibration of the inhalable dust exposure form of the ART mechanistic model (n=847; i.e. 34% of the overall dataset). This section contains an overview of the measurement data that was used in the pharmaceutical specific calibration of the inhalable dust exposure form of the ART mechanistic model and the results of the calibration of the model.

Exposure assessments collated for the calibration (n=291) were carried out over the period of 2002-2008. The assessments were collected from GSK primary (n=143), secondary (n=136) and healthcare (n=13) sites. They included a range of analytical data for various APIs (n=267) and gravimetric analysis for TID (n=24). The majority of the measurements were task-based with a median sampling time of 43 min (range 5-779 min; n=283) and 90% of measurements had sampling times <118 min in duration. In cases where sampling duration was not reported (n=8), information on the relative durations of individual tasks were obtained by consultations with the site occupational hygienists. Measured exposure levels ranged from $3.5x10^{-7}$ to 203 mg/m^3 with a GSD of 30.7 (Table 13). The lowest detectable exposure was found during a scenario which involved scooping of material from a side discharge point to a bag in a lower compartment of a glove-box ($3.5x10^{-7}$ mg/m^3); while the highest exposure level was found during a sack tipping operation (203.1 mg/m^3) which was performed in a

downward laminar flow booth [2]. 2% (n=7) of the measurements were below the LOD.

Table 13: Descriptive statistics of the measured exposure data used for the calibration of the ART mechanistic model

N	AM (mg/m^3)	GM (mg/m^3)	GSD	Minimum (mg/m^3)	Maximum (mg/m^3)
291	3.59	0.196	30.7	3.5×10^{-7}	203.1

N=Number of samples; AM=Arithmetic mean; GM=Geometric mean; GSD=Geometric standard deviation

Exposure assessments were grouped to exposure scenario level which 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); and localised controls (categories grouped to class or subclass level).

Results of the mixed effect regression models for the calibration of the ART model with GSK dust data are presented in Table 14. Model A represents the model without any fixed effects, while model B represents model A with ART model scores included as fixed effects. The results are presented for both the refined and broad scenario level definitions.

[2] This measurement with the high exposure levels involved excipients and was based on a short (8 min) task based measurement for TID

Table 14: Results of the mixed effect regression models for the calibration of ART mechanistic dust model with pharmaceutical data; with scenario and company included as random effects (Model A) and model A with ART scores added as fixed effects (Model B)

Scenario definition	Model	β_0	β_1	σ^2_{bs}	σ^2_{bc}	σ^2_{wc}	% σ^2_{bs} explained	% σ^2_{bc} explained	% σ^2_{wc} explained	Total variance explained by Model
Refined	A	-1.76	-	3.67	9.39	3.66				
	B	2.8	1	1.32	0.25	3.84	64	97.3	-4.9	67.7
Broad	A	-1.88	-	3.24	10.56	4.62				
	B	2.8	1	0.87	0.56	4.20	73.2	94.4	9.1	69.4

β_0: Intercept

β_1: Slope

σ^2_{bs}: Between-scenario component of variance

σ^2_{bc}: Between-company component of variance

σ^2_{wc}: Within-company component of variance

% σ^2_{bs} explained: Percentage of between scenario variance explained by the model

% σ^2_{bc} explained: Percentage of between company variance explained by the model

% σ^2_{wc} explained: Percentage of within company variance explained by the model

As presented in Table 14 the largest component of variance was the between-company component which indicates that exposures vary more between than within companies (94-97%). The proportion of total variance in exposure explained by the scores of the ART mechanistic model algorithm (Model B) ranged from 68-69% for the different scenario level definitions. With the refined scenario definition the model explained, 64%, 97% and none (-5%) of the between scenario, between company, and within company variance.
With the broad scenario definition the model explained, 73%, 94% and 9% of the between scenario, between company, and within company variance. This indicates that ART algorithm could mainly discriminate between exposure levels between scenarios and between companies.

Including scenario as a random component of variance in the mixed effects regression models gives insight into the model uncertainty when the model is used to estimate GM exposure levels at scenario level. Using the refined scenario level definition resulted in very limited number of companies per scenario. The broad scenario (n=34) level definition resulted in a more balanced structure but nonetheless the number of companies per scenario remained fairly small. Therefore the broad scenario level of definition was used for the calibration.

The model uncertainty was expressed as an uncertainty factor (UF) and was defined as follows: $UF = e^{1.6449 \cdot \sqrt{\sigma^2_{between-scenario}}}$

Using the pharmaceutical dataset only, the UF found for the model with broad scenario definitions was 4.6. Using the overall calibration dataset, the UF found for the model with the broad scenario definitions was 4.4 (Schinkel *et al.*, 2011). This UF can be interpreted as providing a 90 % probability that the true GM exposure level is within a factor of 4.4 of the model GM exposure estimate. The results of Model B with the broad scenario descriptions are shown in Figure 6. This figure illustrates the variation in GM exposure and GM ART scores. The 90% confidence upper limit was derived by multiplying the estimated GM by the UF, while the 90% confidence lower limit was derived by dividing the estimated GM by the UF.

Figure 6: Relationship between the ART model predictions and the measured concentrations (mg/m^3) per exposure scenario

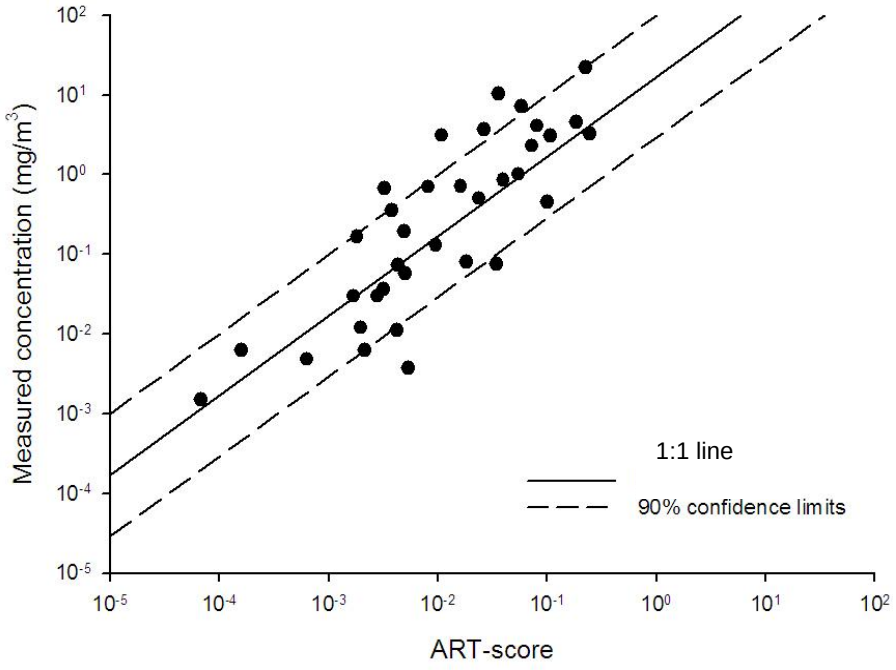


Figure 7: The residuals of the relation between measured GM exposure minus estimated GM exposure per broad scenario against the ART score

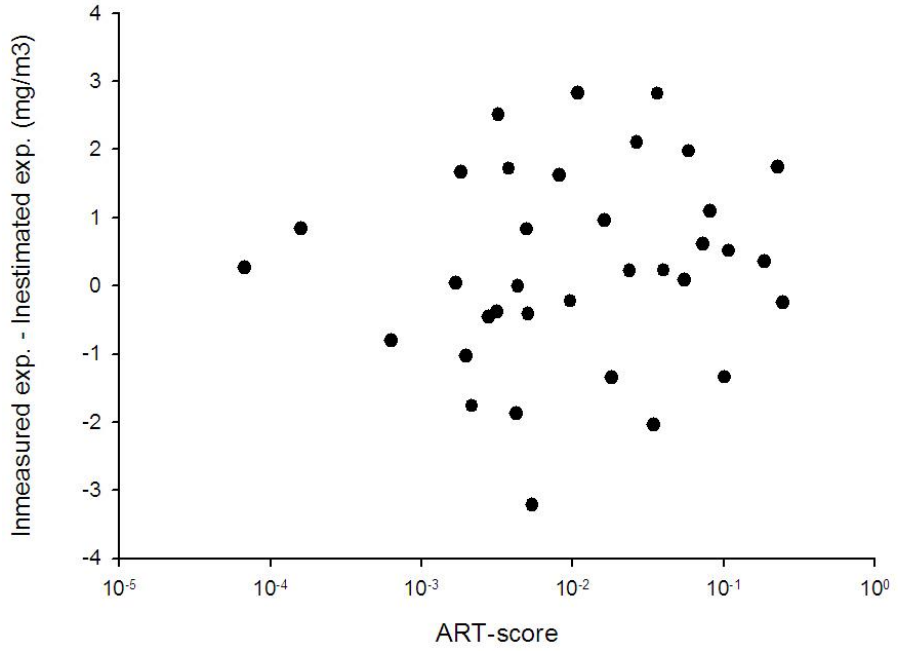


Figure 7 shows the residuals of the relation between measured GM exposure minus estimated GM exposure per broad scenario against the ART score. There is no evidence for a positive or negative correlation between residuals and ART scores, indicating that the relationship between log-transformed ART model scores and log-transformed measured concentrations was proportional.

As discussed further in Chapter 5, these results suggest that the calibration of the mechanistic model with both datasets (i.e. the pharmaceutical data only and the generic calibration reported by Schinkel *et al.,* 2011) resulted in comparable models and that the generically calibrated model would be suitable for assessing pharmaceutical scenarios. Therefore the generically calibrated inhalable dust exposure form of the ART model was validated as part of this research project with pharmaceutical data (Section 4.2.2).

4.2.2 Validation of the inhalable dust exposure form of the ART mechanistic model with a pharmaceutical dataset

This section contains an overview of the measurement data that was used in the validation of the inhalable dust exposure form of the ART mechanistic model and the results of the validation of the model.

Exposure assessments collated for the validation of the ART mechanistic model (n=192) were carried out over the period of 2002-2009; they were collected from GSK primary (n=72), secondary (n=67), healthcare (n=17) and R&D (n=36) sites. The validation dataset included activities, local controls and sampling durations etc. that are representative of scenarios in the pharmaceutical industry and were largely similar to the pharmaceutical dataset used in the calibration of the dust algorithm of the ART mechanistic model.
They included a range of analytical data for various APIs (n=130) and gravimetric analysis for TID (n=62). 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. 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 measured exposure levels ranged from $5x10^{-5}$ 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 15 presents the descriptive statistics for the exposure scenarios and the validation results of the inhalable dust form of the ART mechanistic model with the pharmaceutical data. The lowest exposure level ($5x10^{-5}$ 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)[3]. 32% of measurements used in the validation dataset (n=62 samples) were less than the LOD.

[3] This high exposure level was based on a relatively short task-based measurement (33 min) that was analysed for total inhalable dust (TID).

Table 15: Descriptive statistics of pharmaceutical data at scenario level used for the ART validation study and results of this study

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 1-10kg (dust)	7	0	1	5.03	2.3	1.83	12.33	2.42	-2.62	-51.97	0.48
Dumping 1-10kg (dust) (Downflow room)	4	2	1	1.768	2.1	0.76	4.80	1.785	0.017	0.94	1.01
Dumping 1-10kg (dust) (Glovebox)	66	6	3	0.002	5.3	1.E-04	0.10	0.001	-0.001	-50.00	0.50
Dumping 1-10kg (dust) (LEV)	5	1	3	1.87	1.6	0.84	2.50	0.46	-1.41	-75.50	0.25
Dumping 1-10kg (granules)	6	0	2	0.227	6.0	0.01	0.91	0.078	-0.149	-65.63	0.34
Dumping >10kg (dust) (Downflow room)	6	0	1	2.115	1.3	1.60	2.97	1.0875	-1.03	-48.58	0.51
Dumping >10kg (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 & LEV)	3	0	1	5.07	1.8	3.40	9.80	1.37	-3.69	-72.94	0.27
Movement & agitation >10kg (dust) (containment)	6	0	1	2.011	2.1	0.55	4.73	1.456	-0.555	-27.59	0.72
Scooping 1-10kg (dust) (Downflow room)	7	0	2	1.982	2.0	1.27	9.29	1.586	-0.396	-20.01	0.80
Scooping 1-10kg (dust) (LEV)	4	0	1	8.11	1.2	6.67	9.50	0.47	-7.64	-94.20	0.06
Scooping <1kg (dust) (enclosing hoods)	44	21	3	0.00033	3.8	5.E-05	0.02	0.0026	0.00227	687.88	7.87
Vacuum cleaning 1-10kg (dust)	4	0	1	3.072	1.2	2.47	3.67	8.4595	5.39	175.39	2.75
Vacuum cleaning <1kg (dust)	8	2	1	0.68	3.1	0.15	4.99	3.73	3.05	450.30	5.50

N = number of samples; N<LOD = number of samples below the limit of detection; K = Number of companies; GM = Geometric mean; GSD = Geometric standard deviation

This section presents the results of the validation of the ART mechanistic model including the results of: the investigation of exposure distribution for the LOD imputations; correlation analysis; and results of relative bias and uncertainty.

As the exposure distribution chosen in the imputations to deal with scenarios with measurements below the LOD could have implications on results, it was necessary to investigate the following exposure distributions: global, conditional and stratified. Table 16 presents these results. As regards the stratified analyses, it was not possible to estimate reliable exposure distributions for scenarios which had small sample sizes ($n<6$). As the exposure estimates and standard deviation results per scenario were very different for the conditional exposure distribution, compared to those of the global exposure distribution, it was decided to employ the conditional exposure distribution for the imputations of measurements less than the LOD. The conditional exposure distribution assumes individual exposure distributions with individual mean exposure values per scenario and the same standard deviation value for all the scenarios

Table 16: Investigation of exposure distributions for exposure scenarios which included measurement data less than the limit of detection

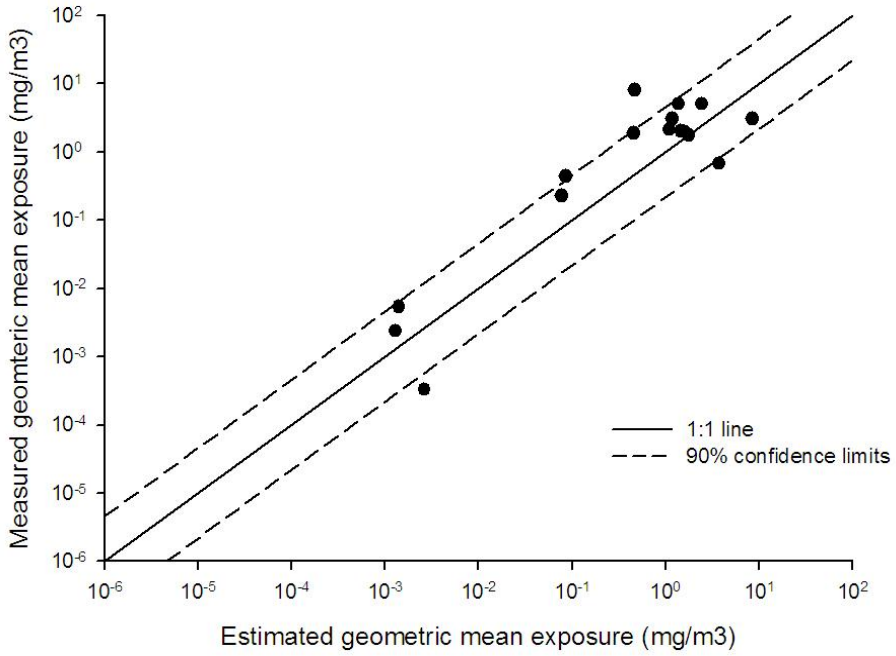
Scenario	N >LOD	N <LOD	Global		Conditional		Stratified	
			Mean exposure estimate ($\mu g/m^3$)	SD	Mean exposure estimate ($\mu g/m^3$)	SD	Mean exposure estimate ($\mu g/m^3$)	SD
Dumping 1-10kg (dust) (Glove-box)	60	6	-4.13	4.27	-6.05	1.30	-6.08	1.72
Dumping 1-10kg (dust) (LEV)	4	1	-4.13	4.27	0.60	1.30	0.81	0.09
Dumping >10kg (dust) (LEV)	8	4	-4.13	4.27	1.06	1.30	1.25	0.65
Handling of slightly/limited contaminated (dust)	1	1	-4.13	4.27	-1.57	1.30	-1.43	1.00
Handling of visible/substantial contamination (dust)	1	1	-4.13	4.27	0.22	1.30	0.57	0.58
Movement & agitation >10kg (dust) (containment)(DF room)	1	1	-4.13	4.27	0.70	1.30	-6.30	1.95
Scooping <1kg (dust) (enclosing hoods)	23	24	-4.13	4.27	-8.11	1.30	-8.27	1.66

N >LOD: number of measurements per scenario greater than the LOD
N<LOD: number of measurements per scenario less than the LOD
SD: standard deviation

Good correlation was found between the ART model scores and individual measured exposure levels (r_s=0.73 n=192, p<0.001), and at scenario level (r_s=0.58 n=16, p<0.001). Slightly better correlation values were found for exposure measurements involving a single task (r_s=0.89 n=49, p<0.001) when compared to those consisting of multiple tasks (r_s=0.78 n=143, p<0.001). Slightly lower correlations were found for exposure measurements with sampling durations greater than the median sampling time of 28 min (r_s=0.72 n=66, p<0.001) compared to those with shorter duration measurements ≤28 min (r_s=0.83 n=126, p<0.001).

Results of the validation analysis for bias, relative bias and the difference between measured and estimated GM exposure levels are presented in Table 15. Relative bias values were between -90% and 700% and the estimated GM were within a factor of 8 of the measured GM exposure; which is greater than the UF of 4.4 of the original calibration study (Schinkel et al., 2011), suggesting that there is more uncertainty in the ART estimates using the pharmaceutical data. For 75% of the scenarios the uncertainty in exposure estimates was within the UF of 4.4. 90% of the scenarios had a factor difference of less than 5.5. In general (12 out of the 16 scenarios) the ART underestimated GMs exposure levels. An overall bias value of -0.71 and an overall relative bias of -32% for estimated versus measured GM exposure levels indicated on average a one-third underestimation of GM exposure levels. Figure 8 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.

Figure 8: The relationship between GM model scores and measured GM exposures per scenario for the pharmaceutical validation dataset



4.3 Reliability of the ART for the pharmaceutical industry

The final part of this research involved holding a workshop to investigate the reliability of the ART when used by professionals from the pharmaceutical industry whom had no previous experience with the tool. Table 17 presents the percentage of ratings in agreement with the 'gold-standard' for each of the determinants at the various stages of the workshop. The average agreement values of all the determinants with the gold standard for the without introduction, after introduction, and after demonstration stages were 58, 67, and 83% respectively (values per individual determinant are presented in Table 17).

As the activity emission potential MF comprises several determinants we investigated if the raters chose the gold-standard activity class. Across all the information stages, the percentage of ratings in agreement with the gold-standard activity class was approx 80%. To obtain the activity emission potential score, raters also had to assess two or more determinants (e.g. drop height and handling type). For the without introduction and after introduction stages relatively low percentage of the ratings were in agreement with the gold standard (14 and 17%). After the demonstration stage the percentage agreement with the activity emission potential score increased to 45%. Surprisingly, some determinants (e.g. separation and segregation) which were not referred to in the scenarios were assessed by a small number of raters in some of the scenarios, resulting in a lower agreement for these MFs. While raters were provided with the information in the scenarios for ACH and room volume, there was also relatively low agreement during the without introduction stage. Also, three of the activities (denoted by * in Table 17), were not assessed by some of the raters (n=5). Although two activities were described per scenario, raters were possibly not aware of the second activity or may not have known how to assess it in the tool. After introduction and demonstration stages improvements were evident for dustiness, emission source, activity emission potential, localised controls, dispersion, surface contamination, segregation and separation. Overall no apparent differences in percentage agreement with the gold-standard were seen between the group of experienced raters (>10 years experience in occupational hygiene) and less-experienced raters (< 10 years). Also there were no apparent differences in agreement between the participants whom had previous experience with other exposure models and those with no experience (results not presented).

Table 17: Percentage of ratings in agreement with the 'gold-standard' for each determinant per activity

Activity	N	Dustiness (%)	Emission source (NF-FF) (%)	AEP		Controls		Dispersion		Surface contamination			Segregation (%)	Separation (%)	Overall (%) **
				Activity Class (%)	AEP Score (%)	1st LC (%)	2nd LC (%)	Room Size (%)	ACH (%)	1 (%)	2 (%)	3 (%)			
	Categories	**5**	**2**	**7**	**n/a**	**21**	**21**	**8**	**9**	**2**	**2**	**2**	**5**	**5**	
	Raters	**.**	**.**	**.**	**.**	**.**	**.**	**.**	**.**	**.**	**.**	**.**	**.**	**.**	
1.1	9	56	78	100	33	22	100	67	67	22	22	89	67	100	**58**
1.2	6*	33	56	11	0	22	67	33	44	67	44	56	67	67	
2.1	9	11	56	89	22	44	78	100	100	89	78	89	100	100	
2.2	9	11	44	89	0	33	67	78	78	89	89	89	100	100	
Average without introduction		**28**	**25**	**73**	**14**	**30**	**78**	**70**	**72**	**67**	**58**	**81**	**84**	**92**	
1.1	9	11	100	100	11	44	89	100	78	33	33	78	55	100	**69**
1.2	9	33	100	100	11	67	78	100	78	89	79	89	100	100	
2.1	9	33	89	89	33	11	89	78	78	100	79	78	100	100	
2.2	8*	33	78	56	11	0	89	67	61	89	89	89	89	89	
Average after introduction		**28**	**92**	**86**	**17**	**31**	**87**	**86**	**74**	**78**	**70**	**84**	**86**	**97**	
3.1	18	79	100	61	22	56	100	89	100	100	100	95	100	100	**85**
3.2	17*	79	89	83	39	72	89	83	95	95	95	95	95	95	
4.1	18	11	89	89	61	100	100	100	89	95	95	100	90	100	
4.2	18	42	100	61	56	89	78	100	83	100	100	100	90	100	
Average after demonstration		**53**	**95**	**74**	**45**	**63**	**92**	**93**	**92**	**98**	**98**	**98**	**94**	**99**	

1st LC = Primary localised controls
2nd LC = Secondary localised controls
* There were no entry/blank assessments for this activity
1= process fully enclosed
2=effective housekeeping
3=general housekeeping
**average of all columns with the exception of Activity Class (AEP score included)

Table 18: Inter-rater reliability per determinant for the various stages (kappa statistics with standard error values in brackets)

Stage	Dustiness	Emission source (NF-FF)	AEP Class	Primary Local Controls	Dispersion	
					Room size	ACH
Average without introduction	0.34 (0.04)	0.15 (0.05)	0.60 (0.04)	0.03 (0.03)	0.37 (0.05)	0.41 (0.05)
Average after introduction	0.18 (0.05)	0.67 (0.06)	0.69 (0.04)	0.13 (0.04)	0.60 (0.06)	0.31 (0.05
Average after demonstration	0.41 (0.03)	0.74 (0.03)	0.47 (0.02)	0.55 (0.03)	0.78 (0.03)	0.73 (0.03)

Level of agreement
<0: none
0.01-0.20: slight
0.21-0.4: fair
0.41-0.60: moderate
0.61-0.80: substantial
0.81-1.0: almost perfect

Table 18 presents the kappa statistics (and standard errors) at the various sessions for each of the determinants in the reliability study. Referring to the Landis and Koch agreement scale (Landis and Koch, 1977) prior to the initial introduction, there was slight to moderate agreement per determinants (k range=0.03-0.60). After introduction, there was slight to substantial agreement per determinants (range 0.13-0.69). After demonstration session, there was substantial agreement for: emission source, room size and ACH (k=0.74, 0.78, and 0.73 respectively); and moderate agreement for dustiness, activity class and primary local controls (k=0.41, 0.47 and 0.55 respectively).

Fig 9: The fold differences between rater's exposure estimates and gold-standard exposure estimates, expressed as a percentage of assessments

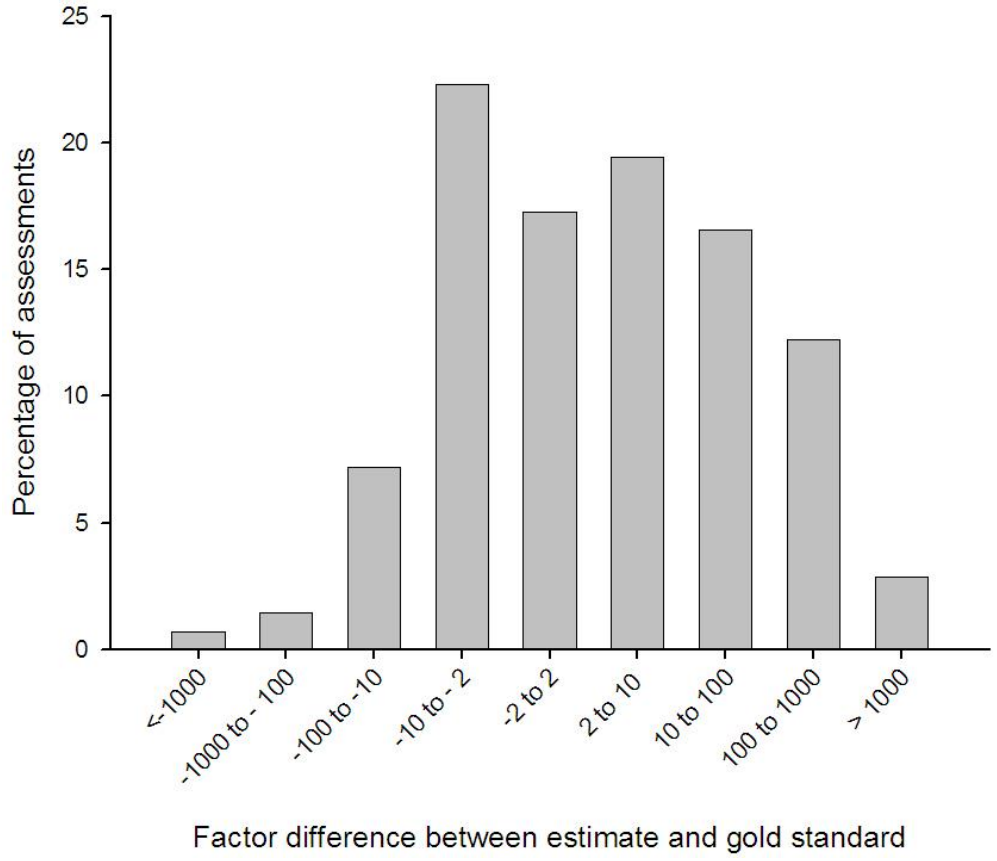


Figure 9 presents the difference between the raters' exposure estimates and the gold-standard exposure estimates. The figure shows a very broad range with approximately 60% of raters' exposure estimates within ten-fold of the gold-standard exposure estimate. Notably, the raters tended to overestimate exposure since more than 30% of the assessments were greater than ten-fold higher than the gold-standard; while only approx 10% of the assessments were more than ten-fold lower than the gold-standard. In contrast with the percentage agreement and kappa statistics results, there was no apparent effect of the information stages on the agreement of the overall exposure estimates (results not presented).

5.0 Overview of Chapter

This project aimed to investigate the applicability of two occupational exposure models to estimate inhalable dust exposures of workers in the pharmaceutical industry. Project results are discussed in the following order: refinement and validation of the source-receptor exposure model for the pharmaceutical industry (Section 5.1); refinement, calibration and validation of the ART for the pharmaceutical industry (Section 5.2); and investigating the reliability of the ART when used by health and safety professionals from the pharmaceutical industry (Section 5.3). In addition research conclusions (Section 5.4) and future research (Section 5.5) are discussed.

5.1 Discussion of results from the refinement and validation of the source-receptor model for the pharmaceutical industry

This research involved refining an existing exposure model, known as the source-receptor model (Cherrie *et al.,* 1996; Cherrie and Schneider, 1999) for use within the pharmaceutical industry. It was necessary to refine some of the model parameters, in particular, the handling activity and local control measure model parameters to reflect work tasks and control technologies common to the pharmaceutical manufacturing and healthcare industry. The refined model was then validated using a data set collected from within pharmaceutical industry. Results from the validation showed good correlations between the model predictions and the measured data, for the overall data set (r_s=0.61, n=381, p<0.001) and when grouped 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 were slightly lower than those found when using the unrefined exposure algorithm with a smaller pharmaceutical dataset (r_s=0.88-0.97, n=278) (Cherrie *et al.,* 2009). This is most likely due to the fact that in the previous study by Cherrie and colleagues, the data set included a greater number of measurements per scenario, with on average eleven compared with six measurements per scenario in this study.

The correlation coefficient for the overall data set (r_s=0.61) reported in this study is within the range of the correlation values obtained using the original unrefined exposure algorithm for non-pharmaceutical agents such as asbestos, toluene man-made mineral fibre, respirable dust and styrene (r_s=0-0.93) (Cherrie *et al.,*

1999). 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) (Friesen *et al.*, 2005), and slightly higher than those reported for cotton dust, endotoxin (r_s=0.58) and asphalt paving (r_s=0.28) (Astrakianakis *et al.,* 2006; Burstyn *et al.,* 2002). 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 (Schinkel *et al.,* 2010). 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.

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 material handled, and worker behaviour, increased the correlation coefficient by 19%, 12% and 4% respectively. Including information on local controls 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.

Results from this study show that the source receptor 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 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 reported by Cherrie and colleague (1999) for non pharmaceutical agents (bias=0.47–2.86). The tendency of the model to overestimate scenarios with low exposure levels has

also been observed (Cherrie *et al.*, 2009). Previous studies have shown that occupational hygienists tend to overestimate exposure when using exposure assessment tools (Hawkins and Evans, 1989). 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 model correlations with measurement data could be improved by providing the assessor with more information such as: photographs or video clips of the scenario; training on the identification and classification of model parameters, especially those requiring subjective assessment; reference material for the relevant industries; and also the development of a user interface for the model.

The model tended to overestimate exposure for exposure levels <0.1 mg/m^3 and this was probably related to the misclassification and scoring of the local control parameter within the model. In the pharmaceutical industry it is common practice to use dual containment systems for handling activities involving potent APIs, for example glove-boxes fitted to contained enclosures or downward laminar 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 scientific data are necessary to develop more concise parameter classifications to scientifically underpin the assigned model scores for local control measures. Work undertaken in this area includes the development of an exposure control efficacy library (ECEL) (Fransman *et al.*, 2008) for use within the ART, which will need to be continually developed as more information becomes available.

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 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 SOPs 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.

In future developments of the source-receptor model the present dataset could be used to calibrate the model to provide more accurate exposure predictions. 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. However the exposure predictions should not be used in place of measurement data which have an important role in the exposure assessment strategy. This work 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 LEV, may alter the exposure level. 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.

5.2 Discussion of results from the refinement, calibration and validation of the inhalable dust exposure form of the ART mechanistic model

The ART is a 2nd tier model that was developed for the purpose of assessing exposure scenarios as required for the REACH Regulations, to predict GM exposure levels for specific exposure scenarios from across different workplaces, companies and countries. The mechanistic model within the ART is a development of the source-receptor model algorithm (Cherrie *et al.,* 1996; Cherrie and Schneider 1999) which incorporates important exposure determinants as modifying factors (MFs) to result in a dimensionless relative model score. Mixed effects regression models were employed to enable the model scores to be translated to quantitative exposure levels in mg/m^3 using a large dataset of exposure measurements from across many companies, industries and countries (Schinkel *et al.,* 2011). The GSK pharmaceutical dataset comprised approx one third of the generic calibration dataset of the ART inhalable dust model. This chapter discusses the results of the generic calibration in comparison to the calibration using the pharmaceutical dataset.

The MFs within the ART are structured in a categorical way and for many of the MFs, especially for the activity emission potential MF, this was a first attempt to structure these options concisely and logically within an occupational exposure model (Tielemans *et al.,* 2008). As part of this research significant refinements of some of the ART MFs were incorporated in the tool in order to allow the model assess exposure scenarios from the pharmaceutical industry e.g. to include activities involving small quantities of materials, and activities within glove-bags, glove-boxes and downward laminar flow rooms.

Section 4.2.1 presents the results of the calibration of the dust exposure form of the ART mechanistic model. In addition to enabling the mechanistic model to estimate exposure levels (in mg/m^3), the calibration provided insight into the uncertainty of the estimated GM exposure levels for specific scenarios. This uncertainty was expressed as an uncertainty factor (UF) which was used to calculate confidence limits around the estimated GM exposure levels. The same methods were used to calibrate the mechanistic model of ART using the pharmaceutical dataset only. The analysis with the pharmaceutical data indicated that the model could estimate (with 90% confidence) the GM exposure levels

within a factor of 4.6 of the measured GM exposure. This is comparable to the UF of 4.4, found when the model was calibrated with the generic dust dataset derived from many industries (Schinkel *et al.*, 2011). The comparable UFs indicate that the models were similar regarding their precision in exposure estimates.

Using the pharmaceutical data only, the influence of different scenario level definitions on the calibration results was investigated by running linear mixed effect models separately with two different scenario definitions included as random effects. The broader scenario definition resulted in slightly less between-scenario variance and more between company variance. A detailed scenario definition resulted in an unbalanced dataset due to limited numbers of measurements from different companies, when compared with the broader scenario definition. Similar trends were observed with the generic calibration (Schinkel *et al.*, 2011). For the purpose of REACH, the ART is intended to estimate exposures at this broad scenario level, and so the results of the broad scenario definition were used to quantify the relative scores from the mechanistic model of ART.

ART scores were assigned per measurement and subsequently measurements with similar exposure determinants were grouped to scenario level. Therefore, differences in model scores were found mainly between scenario and to a smaller extent within scenarios. Consequently, the generic calibrated ART mostly explained between-scenario variability (87%), less between company variability (72%), and only 4% of the within company variance. When calibrated with only pharmaceutical data, the model explained 73% of the between-scenario variability, 94% of the between-company variability and only 9% of the within company variance. The total percentage of explained variance in exposure levels was 64% for the generic model (Schinkel *et al.*, 2011) and was slightly higher (69%) when calibrated with the pharmaceutical dataset only. Also the intercepts of the generic and pharmaceutical specific model were quite similar (3.0 and 2.8 respectively) which indicates that the generic model would estimate slightly higher exposure levels compared to the pharmaceutical specific model. This indicates that in addition to resulting in similar intercepts and UFs, the calibration of the mechanistic model with both datasets resulted in similar models that explained comparable levels of exposure variance.

Several exposure studies found time trends in a range of exposures, with decreasing exposure levels over time (van Tongeren *et al.*, 2000; Kromhout and Vermeulen, 2000). Vermeulen and colleagues (2000) reported that modelling the effectiveness of localised control measures explained almost entirely the observed drop in inhalable exposure levels over time. While a generic exposure assessment tool like the ART does not take into account these trends in exposure it is assumed that many of the determinants causing these reductions are described in the MFs of the model (Schinkel *et al.*, 2011). However, it will be necessary to update the calibration in the future in order to account for these time trends. The overall calibration of the ART was performed on a comprehensive set of exposure measurements. Although the collated exposure data cover a broad range of exposures situations across many industries and companies not all the possible ART MF combinations were included in the dataset. Ideally more exposure data from more companies and industries including more MF combinations would have been available for calibration. Different exposure levels between countries were reported by de Vocht and colleagues (2006). They reported that a two- to three fold difference in exposure levels over a time period was likely attributable to advancements in technology such as improved localised control measures. The generic mechanistic model of the ART is not able to entirely account for technology driven variation in exposures and therefore these differences are expressed in the UF. The resulting technology driven variability is accounted for in the Bayesian model (McNally *et al.*, 2010). Measurements from companies located in Western-Europe were mainly used in the calibration dataset and it is reasonable to assume that technology driven differences in exposure levels could be seen between companies in this region. Technical differences are likely to be larger between different regions of Europe (e.g. Western and Eastern Europe) and therefore the influence of this effect is possibly underestimated by the current UF.

The above comparisons indicate that both calibrations resulted in comparable models with similar UFs, which were able to explain comparable levels of exposure variance. Therefore the next section of this research focused on the validation of the generically calibrated inhalable dust exposure form of the ART mechanistic model, using a pharmaceutical dataset. This gave an insight into the

applicability of the generically calibrated model for assessing pharmaceutical scenarios and the model uncertainty in exposure estimates. Results indicate that 75% of the exposure 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 (Schinkel *et al.*, 2011). 90% of the scenarios had a factor difference of less than 5.5. An overall relative bias of -32% indicated that on average, the model resulted in a one-third underestimation of GM exposure levels for exposure scenarios from the pharmaceutical industry. To date no other validation studies of the dust exposure form of the mechanistic model have been published so comparisons are not possible. Few comparably detailed validation studies of generic occupational exposure models have been published and where possible, they will be compared with results from this study.

While this 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. A limitation of the pharmaceutical dataset used in this validation study was the small sample size per exposure scenario and that most of the exposure scenarios were derived from one company. As exposure levels vary between scenarios, between companies and between and within workers (Kromhout *et al.*, 1993, Symanski *et al.*, 2006) a more 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, and with repeat measurements on a number of workers. Hence, the somewhat larger uncertainty observed in the validation study compared to the calibration study might, in part, be due to the limited number of measurements and companies included per scenario. The UF of 4.4 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 the pharmaceutical validation dataset, it was not possible to validate the mechanistic model estimates of the different percentiles of the exposure

distribution; therefore the following discussion will focus only on the uncertainty of the model estimates.

The overall uncertainty of the model exposure estimates is a consequence of: a combination of model and model parameter uncertainty; user or input error; and exposure scenario uncertainty. User error and exposure scenario uncertainty were potentially relevant to the results of this study and are discussed here. As all pharmaceutical assessments were individually reviewed by another member of the ART team (Jody Schinkel, TNO Quality of Life), and a selection reviewed by a third member (Dr. Wouter Fransman, TNO Quality of Life), user or input error is not considered to significantly affect the results of this validation study. However it may be significant when the tool is used for the purposes of REACH assessments etc. For users of the ART, it was anticipated that the provision of training and better guidance would ensure that the model was used more reliably which would likely improve the accuracy of exposure predictions (Therefore the final part of this research, involved a study of the reliability of the ART when used by occupational health and safety professionals (Section 5.3)). Exposure scenario uncertainty arises from inconsistencies between the scenario being modelled and the actual situation itself as it occurred in the workplace (Fryer *et al.*, 2006). While the level of contextual information in the original pharmaceutical survey reports was screened to ensure only good and moderate quality data was used, 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 have been used for testing the validity of the exposure models, and may be the most direct measure of validity and reducing exposure scenario uncertainty (Hornung and Reed, 1991). This would involve comparing the exposure model estimates to exposure data collected in an occupational hygiene survey specifically designed for the validation study, and would most likely result in less subjective judgement and decreased exposure scenario uncertainty.

The validation study of the ART mechanistic model with a pharmaceutical dataset was an important investigation of the applicability of the tool for assessing exposure scenarios typical of this industry. 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 mechanistic model (Schinkel *et al.*,

2011), with some important 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. Also as both datasets excluded all exposure scenarios with greater than 50% of measurements less than the LOD, this largely resulted in exclusion of scenarios with high specification localised controls. 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 such scenarios.

To the author's knowledge there have been no other comparably detailed validation studies of generic models specifically with data 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 (Astrakianakis *et al.*, 2006; Friesen *et al.*, 2005). No other higher tier models are currently available for comparison of our studies results. Stoffenmanager is the only generic 1st tier deterministic model with which the results of this study can be compared to. The validation study of Stoffenmanager showed a relative bias of -77% for dust exposure scenarios (Schinkel *et al.*, 2010) which is greater than that found in this validation study of ART (overall bias -32%). However the relative bias value reported for Stoffenmanager was calculated at an individual measurement level while the relative bias found in this study was calculated on at a scenario level.

5.3 Discussion of results from the investigation of the reliability of the dust exposure form of the ART mechanistic model

The results of a pilot study to assess the reliability of the ART when used by health and safety professionals from the pharmaceutical industry will be discussed here. The study considered the effect of disseminating information on the ART on study participant's reliability to assess eight activities included in four exposure scenarios from the pharmaceutical industry. The results indicate that the ART cannot be used with sufficient reliability by health and safety professionals without the provision of further information on the tool.

The results of this study give an indication of the effect of provision of information on the reliability of untrained users of the ART. However it is possible that the level of information provided or complexity of the MFs in the exposure scenarios differed per stage of the workshop. Also, the assessments of the exposure scenarios before and after delivery of the introduction were made by different groups of randomly chosen health and safety professionals. Nonetheless we believe that the results indicate that provision of information will improve user reliability. For all model determinants (n=12), the average percentage of ratings in agreement with the gold-standard increased with the provision of information. When assessing room size and ACH determinants, the raters had the option to choose the exact room size and ventilation rates or choose from categories (e.g. 100m^3 or small work room); while these choices are linked to the same model score, only the exact information specified in the scenario documentation was assessed as being in agreement with the gold-standard. Therefore for room size and ACH determinants, the percentage agreement was indeed slightly higher for some of the activities than the results presented. There were no apparent differences in percentage of ratings in agreement with the gold-standard with regard to years of experience in occupational hygiene practice. For five of the six model determinants, there was an increased inter-rater agreement with the provision of information, with substantial to moderate agreement for all determinants after the workshop facilitators delivered a demonstration of the ART. There was a very broad range between the raters' exposure estimates and the gold-standard exposure estimate; approximately 60% of rater's exposure estimates were within ten-fold of the gold-standard exposure estimate. Notably, raters tended to overestimate exposure

and previous studies have also shown that occupational hygienists tend to overestimate exposure when using exposure assessment tools (Hawkins and Evans, 1989). As some MFs i.e. separation and segregation were not varied in the exposure scenarios it is possible that the reliability results are underestimated as a result, however as shown in Table 2, some raters still assessed these as being applicable, resulting in a broad variation in exposure estimates.

It is likely that the raters made errors in their assessments due to two broad issues: technical errors when using the ART website; and exposure assessment judgement errors. Firstly, it is likely that the participants did not receive enough adequately detailed information on how to use the website, and so even if they did understand the given scenarios, they did not know how to use the tool properly or how to input the required information in the correct places. Also while a lot of guidance text and photographs are provided on the ART website to assist users choose the correct categories, it is possible that due to time constraints, the participants did not locate or consider them adequately. Secondly, it is likely that the participants made mistakes in their exposure assessment judgements or with the theoretical use of the tool. Results of this study indicate that some of the model determinants were more problematic for participants to assess e.g. dustiness is acknowledged as being subjective. Also a limited amount of the information and photographs were provided in the exposure scenario documentation. Therefore it is possible that the raters encountered difficulties with assessing e.g. the level of contamination on objects, or the containment levels of the localised controls and so choose the conservative options during their assessments. Such choices could have a big influence on the exposure estimate and the reliability results. Consider the following example of a scenario where the gold-standard involves scooping coarse dust in a high specification glove-box. Referring to the available pictures and text in the scenario and the guidance within the tool, a rater assessed the scenario as involving fine dust in a low specification glove-box as opposed to coarse dust in a high specification glove-box, with all other determinants assessed correctly. The conservative rationale behind the choices of this rater is logical, but following the mechanistic model of the ART (Fransman *et al.,* 2011), the choices results in a factor of 30 differences with the gold standard exposure estimate. Due to the multiplicative nature of the algorithm, wherein determinants result in

multipliers possibly ranging from 0.0001 to 100, differences in assessment of each determinant can potentially have a large effect on the eventual ART exposure estimate. Users of the ART should be cognisant of the multiplicative algorithm, and that even if they assess all other determinants correctly, choosing one incorrect category can drastically affect the resulting ART exposure estimates. Also in some cases, even when the information was explicitly provided in the documentation e.g. room size and ACH, the participants inputted the wrong information. This observation highlights a more generic problem of user error, i.e. misinterpreting the assessment process, which may not be directly related to the ART.

In the future, more detailed training sessions for users of the ART should be provided. They should focus on: technical aspects of using the website and availing of the substantial guidance available on the tool; the multiplicative algorithm of the ART mechanistic model; improving exposure assessment judgement including, assessment of determinants, particularly those highlighted as problematic to assess (e.g. dustiness and localised controls); demonstration use of the tool and of assessments; and feedback on assessments. Also the results of this study could be used to improve the user guidance for specific MFs, which may reduce the sources of variation between users of the ART.

Due to time limitations of a one day workshop it was not possible to do the following: investigate intra-rater reliability (i.e. reliability over time for individual raters) as it was believed that this would have reflected a learning effect rather than reflect reproducibility of assessments; or investigate the effect of provision of more comprehensive training on the rater's reliability.

Considering the above limitations, a more extensive reliability study is necessary to: assess a more advanced training program; vary and assess all determinants and MFs e.g. secondary localised controls, separation and segregation; address the aforementioned limitations of this study; investigate the reliability of the other exposure forms of ART, with exposure scenarios from other industries, and when used by experts or non-experts from other industries.

This study investigated the reliability of the ART when workplace conditions were described in paper documents with limited text and photos and as a result it was necessary for raters to interpret information which would influence reliability. It is possible that the reliability of the ART may be better when used

for the purposes of assessing REACH exposure scenarios, where users have access to relevant information in the REACH dossier documentation and so user interpretation of ART determinants should be minimal. Reliability is an important and a necessary component of the validity of occupational exposure models (Siemiatycki *et al.,* 1997). Nonetheless, there are few published reliability studies for occupational exposure models. The results of this study are not directly comparable to a study on the reliability of the dermal exposure assessment (DREAM) method, in which occupational hygienists used DREAM while performing side by side observations of different workplace tasks (Van Wendel de Joode *et al.,* 2005). This observational approach would likely involve less of a need to interpret workplace conditions than was required in this study.

While the pharmaceutical industry is largely exempt from the requirements of REACH (as per Article 2 (5) (a) of the Regulations), it was anticipated that the ART could have useful applications for exposure assessment and risk management within this industry. The validation study of the ART using a dataset for the pharmaceutical industry reported that for 90% of the scenarios, the exposure estimates were within the 90% uncertainty factor of 5.5. Results of this reliability study indicate that while approximately 60% of rater's exposure estimates were within a factor ten of the gold-standard exposure estimate, the remainder varied widely. This variability is unacceptable, particularly for assessment of exposures to harmful chemicals, such as those in use in the pharmaceutical industry. Results from this study signifies that it is not reasonable to assume that health and safety professionals, regardless of their years experience in occupational hygiene practice, will know how to use the ART without any prior training on the tool.

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5.4 Research Conclusions

- This objective of this study was to investigate the applicability of occupational exposure models to predict inhalable dust exposures of workers in the pharmaceutical industry. Although there are many models available, to the author's knowledge, none have been extensively calibrated or validated with a pharmaceutical dataset. While this research project was completed in conjunction with GSK, as many processes and controls are commonly used across the broader pharmaceutical industry, it is likely that the results are applicable across this industry.

- The results of this research have shown that the refined source-receptor exposure model provides a useful basis for an exposure assessment tool for the pharmaceutical industry enabling improved targeting of exposure monitoring strategies.

- The calibration of the ART inhalable dust mechanistic model, with the generic dataset and with the pharmaceutical dataset only, resulted in comparable models with similar UFs, which were able to explain comparable levels of exposure variance. This analysis indicates that the generically calibrated model would be applicable for assessing pharmaceutical scenarios.

- The validation of the generically calibrated ART inhalable dust mechanistic model with a pharmaceutical dataset resulted in a one third underestimation of exposure levels. The uncertainty found for estimating GM exposure levels was slightly higher than the factor of 4.4 found in the generic calibration study. When interpreting these results one should take into account the relatively small dataset with scenarios largely derived from single premises.

- These results, combined with the previously discussed benefits of the tier 2 ART, suggest that the tool will have more useful applications than the source-receptor model for the pharmaceutical industry as part of their exposure assessment strategy under the Chemical Agents Directive; for

example, deciding on risk management measures and predicting hypothetical exposures before the work process has been commissioned.

- The ART will also have useful applications for risk evaluations for example within the scope of REACH, as it was able to estimate GM exposure levels for exposure scenarios collated across premises and countries.

- It is not recommended to replace traditional occupational hygiene exposure measurements with the use of the ART as it is not a suitably accurate tool 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.

- Results from the reliability study indicate that the ART is an expert tool and use without training is not recommended. Occupational hygienists need to be carefully trained on the use of the ART, and more extensively than the information and demonstration sessions that were provided in the workshop during this study. Results highlight the model determinants and aspects associated with the tool that require particular attention during training, and indicate that with focused extended training it may be possible to improve user reliability.

- As exposure models are increasingly used in the context of REACH and beyond, this study emphasises that proper validation of models and evaluation of reliability needs much more attention in the exposure science community

5.5 Future Research

- Uncertainty in model estimates can be reduced in the future by collecting more exposure data with all the relevant contextual information or with better underpinning of the scaling of the ART MFs. Therefore more experimental exposure studies providing insight into specific processes (e.g. dustiness and efficacy of localised controls) are welcomed.

- It will be necessary to update the calibration of the ART to take into account time trends in exposure levels e.g. to reflect changes in effectiveness of localised control measures. Ideally more exposure data from more countries and industries, including more MF combinations, would be available for future calibrations of the tool.

- The current modelling framework of lower and higher tier models is useful and necessary to assess large amounts of exposure scenarios as required within the scope of the REACH Regulations. However all exposure models clearly need further development and await the necessary validation research. The exposure modelling science will only evolve when more of such comparisons with good quality data become available and thus this field would benefit substantially from the development of databases and sharing of exposure data.

- Validity studies focused on the exposure estimates and variability of the other exposure forms of the ART mechanistic model, and of the Bayesian facility, should follow in the near future which will provide additional insight into the validity domain of ART.

- A more extensive reliability study is necessary to assess all combinations of determinants and MFs and other exposure forms of the ART. It is also necessary to investigate the effect of training on reliability and when the tool is used by experts or non-experts to assess scenarios from other industries.

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Websties

Advanced REACH Tool: http://www.advancedreachtool.com

1. Control of Substances Hazardous to Health: http://www.coshh-essentials.org
2. European Centre for Ecotoxicology and Toxicology of Chemicals: (ECETOC TRA) http://www.ecetoc.org/tra
3. REACH CLP Helpdesk: http://www.reach-helpdesk.de/en/Exposure/Exposure.html

5. Stoffenmanager: http://www.stoffenmanager.nl

Legislation

1. Directive 98/24/EC on the protection of the health and safety of workers from the risks related to chemical agents at work.
2. Directive 2001/82/EC on the Community code relating to veterinary medicinal products,
3. Directive m2001/83/EC on the Community code for medicinal products for human use
4. Regulation 726/2004/EC on Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency
5. UK Regulation on Control of Substances Hazardous to Health (COSHH), 2002 (No 2677)
6. Regulation 1907/2006/EC on the Registration Evaluation Authorisation and restriction of Chemicals
7. Safety, Health and Welfare at Work (Chemical Agents) Regulations 2001 (S.I. No 619 of 2001)
8. 2010 Code of Practice for the Chemical Agents Regulation (S.I. No 619 of 2001)

Appendix A: Peer Reviewed Published Papers

1. **Mc Donnell, P., Cherrie, J., Sleeuwenhoek, A., Gilles, A. And Coggins, M. (2011).** Refinement and validation of an exposure model for the pharmaceutical industry,*J. Env. Monit*. **13:** 641-648.

2. **Schinkel, J., Warren, N., Fransman, W., van Tongeren, M., Mc Donnell, P., Voogd, E., Cherrie, J., Tischer, M., Kromhout, H. and Tielemans, E. (2011).** Advanced REACH Tool (ART): Calibration of the mechanistic model. *J of Env Monitoring,* **13,** 1374-1382

3. **Mc Donnell, P., Schinkel, J., Coggins, M., Fransman, W., Kromhout, H., Cherrie, J. and Tielemans, E. (2011).** Validation of the inhalable dust algorithm of the Advanced REACH Tool using a dataset from the Pharmaceutical Industry. *J of Env Monit,***13:**1597-1606

4. **Mc Donnell, P., Schinkel, J., Coggins, M., Fransman, W., Kromhout, H. and Tielemans, E.** Reliability of the Advanced REACH Tool when used by health and safety professionals with no previous experience, *J of Env Monit.* (**submitted**)

Appendix B: Updated GSK Monitoring Record Sheet

Appendix C: Exposure Assessment Training Exercise