Guide on
Inhalation Safety Assessment for Spray Products

In collaboration and agreement with:

International Association for Soaps, Detergents and Maintenance Products

European Personal Care Association

Research Institute for Fragrance Materials

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Foreword

It is a real pleasure, as President of the European Aerosol Federation, to introduce this new and useful *Guide on Inhalation Safety Assessment for Spray Products*. It has been jointly developed by FEA and industry experts from A.I.S.E., Cosmetics Europe and RIFM to get the full and most up-to-date competence in such a complex task gathered.

FEA, being fully committed to highest safety standards in aerosol products, has taken the responsibility and lead to develop a guide that provides clear directions in assessing the safety of aerosols.
I would like to express my particular thanks to the group of experts in this cross industry collaboration. The highly motivated team has been very effective resulting in an absolutely valuable document that experts and non-experts can use in their daily work environment.

The particular value of this document is achieved through the fact, that for a first time in one comprehensive document practical and scientifically sound information are captured. Across the entire aerosol industry the safe use of aerosol products is a basic but key requirement.
I am confident the readers of that document will benefit from its information as it provides a solid guidance to all persons in the entire chain of the product development.

This document aims to become an industry-wide standard, but to ensure legal compliance you have to check relevant legislation too.
For an aerosol industry that is committed to provide save products to our consumers, I highly recommend the following document as several approaches for the inhalation safety assessment of spray products are introduced. Practical information and examples are provided to give a maximum guidance. The approach one would use will depend on the product-type, the formulation and the specified conditions of application.

I am convinced this excellent guide will be of great help for you when- and wherever aerosol and spray products will be developed.

Dr. Rolf Bayersdörfer

FEA President

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Diagrams were either supplied as acknowledged or are FEA interpretation of diagrams appearing in the original references texts.

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1. Acronyms and Abbreviations

ACGIH	American Conference of Governmental Industrial Hygienists
ADD	Aerosol Dispensers Directive 75/324/EEC
ADI	Acceptable Daily Intake
AF	Assessment Factor
BAMA	British Aerosol Manufacturers' Association
BMD	Bench Mark Dose
BMDL	Bench Mark Dose (Lower confidence limit)
bw	body weight
CFD	Computational Fluid Dynamics
CHRIP	Chemical Risk Information Platform
CICADs	Concise International Chemical Assessment Documents
CLP	Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006
CMR	Carcinogenic, Mutagenic or Reprotoxic substance
CSA	Chemical Safety Assessment
DfE	Design for the Environment (US EPA)
DMEL	Derived Minimal Effect Level
DNEL	Derived No Effect Level
EBW	Exposure Based Waiving
ECETOC	European Centre for Ecotoxicology and Toxicology of Chemicals
EC	European Community
ECHA	European Chemicals Agency
EFSA	European Food Standards Agency
EPA	Environment Protection Agency (USA)
ES	Exposure Scenario
e-SDS	extended Safety Data Sheet
ESIS	European Chemical Substance Information System
EU	European Union

EU-OSHA	European Agency for Safety and Health at Work
FAO	Food and Agriculture Organization (UN)
GHS	Globally Harmonized System of classification and labelling of chemicals (UN)
GLP	Good Laboratory Practice
HPV	High Production Volume
IAQ	Indoor Air Quality
IARC	International Agency for Research on Cancer
ICCA	International Council of Chemical Associations
IR/CSA	Information Requirements and Chemical Safety Assessment
IFCS	Intergovernmental Forum on Chemical Safety
IPCS	International Programme on Chemical Safety
JECFA	Joint FAO/WHO Expert Committee on Food Additives
LC_{50}	median Lethal Concentration
LD_{50}	median Lethal Dose
LOAEL	Lowest Observed Adverse Effect Level
MAK	Maximale Arbeitsplatzkonzentration
MoE	Margin of Exposure
MoS	Margin of Safety
MPPD	Multiple Path Particle Deposition
NEL	No Effect Level
NITE	National Institute of Technology and Evaluation (Japan)
NOAEC	No Observed Adverse Effect Concentration
NOAEL	No Observed Adverse Effect Level
NOEC	No Observed Effect Concentration
NOEL	No Observed Effect Level
OECD	Organisation for Economic Co-operation and Development
OEL	European Occupational Exposure Limits
ORATS	Online European Risk Assessment Tracking System
RCR	Risk Characterisation Ratio
REACH	Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC

RDis	Respirable Discharge
RDose	Respirable Dose
RfD	Reference Dose (US EPA)
RIFM	Research Institute for Fragrance Materials
RIVM	Rijksinstituut voor Volksgezondheid en Milieu, National Institute for Public Health and the Environment (The Netherlands)
RMM	Risk Management Measure
SCCS	Scientific Committee on Consumer Safety (European Commission)
SDS	Safety Data Sheet
SED	Systemic Exposure Dose
TDI	Tolerable Daily Intake
TTC	Threshold of Toxicological Concern
TWA	Time-Weighted Average concentration
UN	United Nations
WHO	World Health Organization

2. Introduction

2.1. Legislative Provisions

In recent years legislation controlling the manufacture and supply of chemicals, chemical mixtures (formerly called preparations) and end-user products has undergone major changes. In the case of spray products a consistent theme has been the introduction of enhanced requirements to assess potential risk to the user from any toxicological hazards resulting from inhaling the spray.

The two key pieces of legislation covered by this guide are:

- The Aerosol Dispensers Directive (ADD) 75/324/EEC places an explicit obligation on the person responsible for marketing the aerosol dispenser to analyse and identify the hazards which could arise from the use of the aerosol dispenser. This analysis must include consideration of the *'risks from inhalation of the spray under normal and reasonably foreseeable conditions of use, taking into account droplet size distribution as well as the chemical and physical properties of the contents'*. It is important to note that it is the person responsible for marketing the aerosol dispenser, not the filler, who bears the legal responsibility for ensuring that all the necessary testing has been carried out and labelling is correct.
- The Cosmetic Products Regulation (EC) No 1223/2009 obliges the responsible person to ensure that the safety assessment required prior to placing a cosmetic product on the EU market contains data on exposure via *'the normal and reasonably foreseeable exposure route(s)'*. Clearly for spray products this would include exposure by inhalation. It is possible for the marketer to designate a suitably qualified supplier as the 'responsible person' for conducting the safety assessment.

Common to both the Aerosol Dispensers Directive and the Cosmetic Products Regulation is that both regulatory texts are lacking in details on relevant aspects and guidance for hazard analysis/safety assessment of spray products. However, in many ways both regulations reflect the REACH Regulation (EC) No 1907/2006 which requires suppliers, and in certain circumstances downstream users of chemicals to carry out a Chemical Safety Assessment (CSA). From the CSA, appropriate Risk Management Measures (RMM) may be identified to adequately control the risk from using these substances to human health and the environment from using these substances. The RMM must be communicated to downstream users and distributors in exposure scenarios (ES) as part of an extended safety data sheet (e-SDS).

2.2. Scope of the Guidance Document

This document aims only to provide guidance for inhalation safety assessment of these spray products; to ensure legal compliance you should check the relevant legislation and not rely solely on this guide.

Several approaches for inhalation safety assessment for spray products will be introduced. The approach used will depend on the product-type, the formulation and the specified conditions of use.

This guidance recommends a tiered (step-wise) approach for a robust safety assessment for chemicals used in spray products.

Different levels of information are needed depending on the hazard potential of individual ingredients, the characteristics of the spray and the nature of the exposure.

When using this guidance it is important to note that:

- Only toxic effects relevant to humans exposed to inhalable spray products are discussed (physical and environmental safety aspects are not considered here).
- Local effects to the respiratory tract and systemic inhalation effects must be taken into account for both acute and repeated exposure.
- Relevant use in industrial and professional (occupational) environments must be considered as well as typical consumer use.
- The exposure assessment described in this guidance is limited to the inhalation route but other possible routes (such as dermal, oral and/or environmental background exposure) may also contribute to the total systemic exposure body burden.

The scope is summarised in Table 1.

Safety Assessment		Target Groups	Route of Exposure	Types of Effect
Human Health		Workers	Inhalation	Acute and chronic; Local and systemic
		Professional users		
		Consumers		

Table 1: Scope of the inhalation safety assessment guidance document

2.3. Respiratory Tract

The respiratory tract is a dynamic system responsible for gas exchange, fluid, electrolyte and acid-base balance, and acts as a filter for airborne pathogens and foreign material.

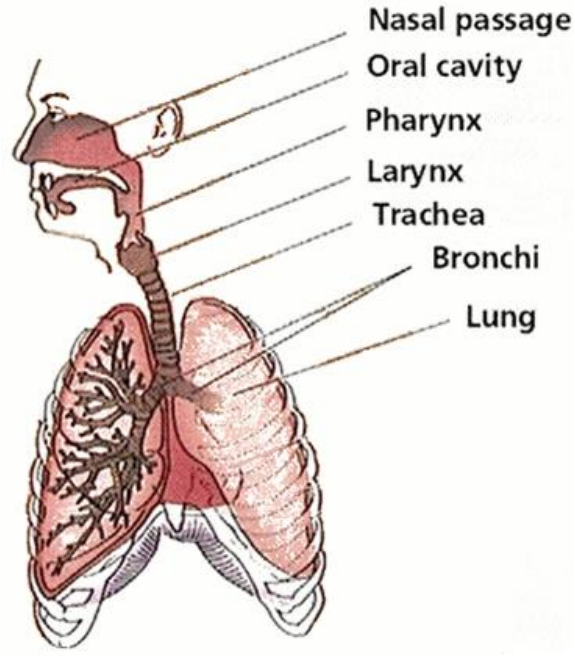
For the purposes of this guidance, however, the focus will remain on deposition of inhaled material and its toxicological potential in the context of spray products.

Propellants (gases) and solvents (vapours) can exert local effects, e.g. irritant effects on different parts of the respiratory tract as well as possible systemic effects.

Different defence mechanisms exist in different anatomical areas. In order to describe the role of each component of normal respiratory defence, it is important to understand the basics of the anatomy of the respiratory tract in the context of particle/droplet exposure. Respiratory defences are comprised of the vestibular hairs in the nose, mucociliary clearance, high-velocity clearance and reflex mechanisms (sneezing and coughing). Additional, non-ciliated airway secretions, blood, lymph clearance, immunological responses as well as other protective mechanisms that include responses to respiratory injury contribute to this protective function.

2.4. Particle/Droplet Deposition in Airways

Particle/droplet deposition throughout the respiratory tract (i.e. nose, mouth, pharynx, larynx, trachea bronchi, lungs) occurs by different mechanisms and is highly dependent upon the nature of the flow of air breathed in, particles/droplets size and the physicochemical characteristics of the particles/droplets inhaled (see Figure 1).



Nasopharyngeal region

Deposition:	impaction, diffusion
Clearance:	mucociliary, sneezing/blowing
Pathology:	inflammation, cancer, ulceration
Targeted by:	>30 µm particles highly reactive, water soluble gas, "inhalable fraction"

Tracheobronchial region

Deposition:	impaction, sedimentation, diffusion
Clearance:	mucociliary, coughing
Pathology:	obstruction, irritation, cancer, ulceration
Targeted by:	10-30 µm particles, 200 µm fibres, "thoracic fraction"

Pulmonary region (parenchyma)

Deposition:	sedimentation, diffusion
Clearance:	phagocytosis, solubilisation, interstitial
Pathology:	inflammation, fibrosis, cancer, oedema, emphysema
Targeted by:	<10 µm particles, 10-12 µm fibres less reactive/water soluble gas, "respirable fraction"

Figure 1: The human respiratory tract

Particle/droplet deposition in the airway is determined by the size and density of the particles/droplets breathed in (known as gravitational settling). Particles/droplets, larger than 30 µm in diameter, encounter inertial impaction in the nasal passages. Particles/droplets smaller than 30 µm in diameter, interface with the movement of gas molecules and may reach the lower airways. Particle/droplet size can be the primary determinant of entry into the lower airways. The mucosal lining of the upper respiratory tract can serve as a preventative barrier to smaller particles/droplets. The mucociliary escalator which facilitates the fluid upward movement of trapped material contributes to the clearance process.

The German MAK states that particles/droplets with an aerodynamic diameter of >15 µm are deposited almost exclusively extrathoracic (nose, mouth, throat) (MAK-Commission, 2012), and healthy humans will clear particles >7 µm within 24 hours from the tracheo-bronchial compartment (Phalen and Oldham, 2006; MAK-Commission, 2012; Heyder *et al.*, 1986; Swiss Federal Office of Public Health, 2009). The threshold of particles/droplets diameter small enough to reach the alveoli is often set to be 5 µm (MAK-Commission, 2012). However, in this guidance as a conservative assumption for risk assessment, particles/droplets with an aerodynamic diameter of less than 10 µm are considered to be respirable (Heyder *et al.*, 1986), (i.e. reaching the deeper lung).

2.5. Safety Assessment

A staged approach based on the CSA (as outlined in Annex 1 of REACH) is recommended. The same approach is also recommended for assessing cosmetic spray products under Annex 1 of the Cosmetic Products Regulation.

The four key stages for human health safety assessment are:

Stage 1: Data collection (§ 3)

- Collecting Data on all ingredients e.g. safety data sheets, restriction, authorisations published data etc.

Stage 2: Hazard Assessment (§ 4)

This is composed of several steps:

- Hazard identification: Review available data to identify ingredients giving cause for concern relevant to spray products and inhalation exposure (for example substances which may cause local irritation).
- Hazard characterisation: Derive a level of exposure to the substance above which humans should not be exposed.
- Amount in spray product: Assess the quantity of ingredient in the formulation and if an exposure assessment is needed.

If no hazardous chemicals are present in the spray product, or are only present at negligible concentrations, then there is no need to carry out an exposure assessment but to proceed directly to the Risk Characterisation.

Stage 3: Exposure Assessment (§ 5)

This stage is to assess human exposure via inhalation to any ingredient identified that has potentially hazardous local and/or systemic effects. The first step is to determine the spray conditions of use, e.g. how and where the spray is used, how often, for how long. Understanding how a spray product is used is important in deciding how to assess the exposure, for which there are a number of options:

- Screening Assessment: determining the absolute worst case exposure.
- Exposure Modelling: using a range of progressively more complex models to predict exposure.
- Exposure Measurement: measuring the actual amount of spray inhaled.

It is important to note that the exposure assessment of a specific ingredient in a spray product depends on individual product-specific parameters. The final particle size (and particle size distribution) of a spray product under conditions of use is determined by the composition of the formula, the concentration of individual ingredients and the packaging (e.g. spray nozzle, can size, propellant type). Any change to these parameters may affect the spray pattern, or particle/droplet size distribution, and consequently the exposure via the inhalation route.

Stage 4: Risk Characterisation (§ 6)

- Compare modelled or measured human inhalation exposure to suitable thresholds derived for toxic effects (acute / chronic; local / systemic).

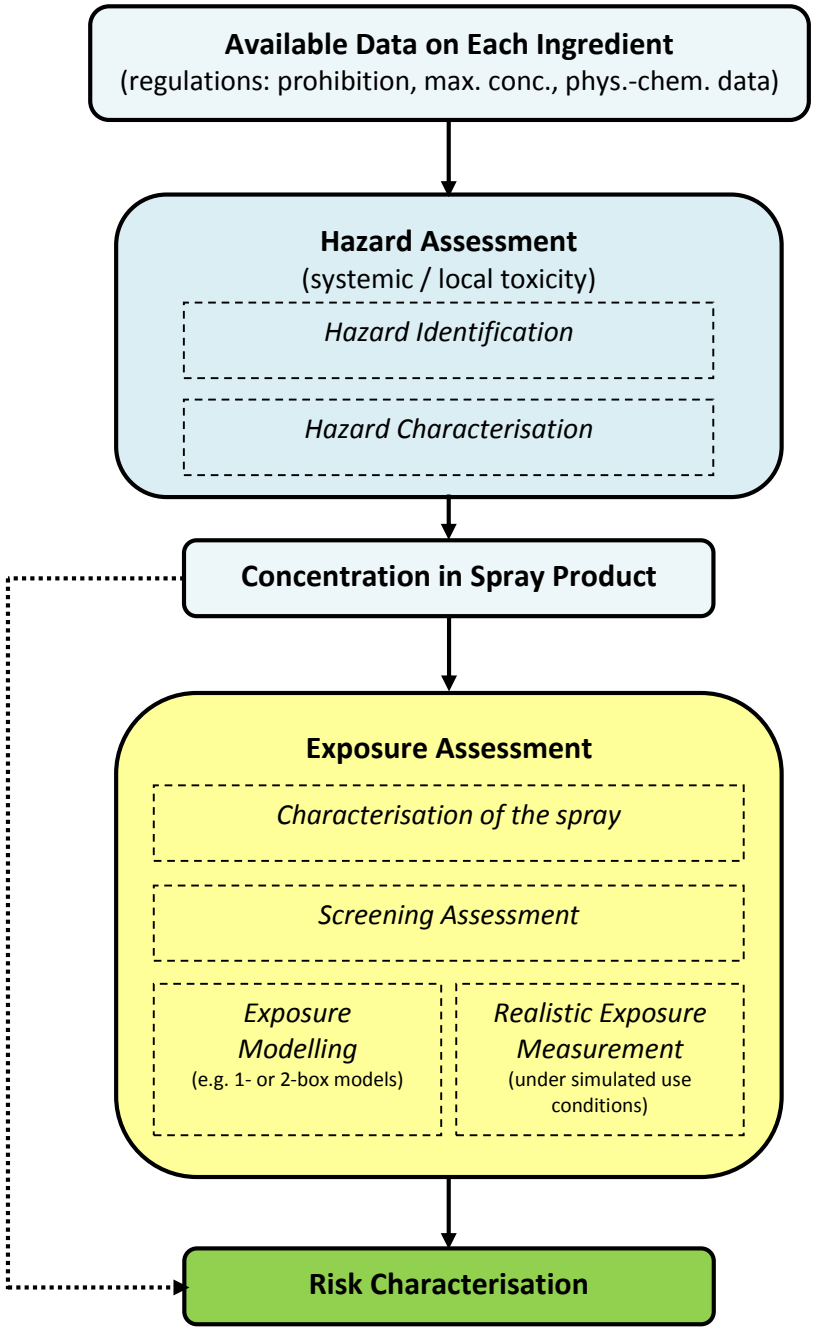
If the risk characterisation is unfavourable, there is a need to refine the exposure assessment, modify the spray characteristics or reformulate.

In all cases, clear use instructions must also be provided via the pack label.

In this approach the first stage is to identify and characterise any hazardous ingredient present in the spray product (Hazard Assessment). The Second Stage is to determine if there is a risk

of exposure to the hazardous ingredients due to spray use (Exposure Assessment). The final stage is to quantify the safety of the spray product (Risk Characterisation).

Figure 2 illustrates the basic principles of a robust tiered safety assessment of a spray product.



Colour code in boxes: Blue related to ingredients. Yellow related to product exposure.

Figure 2: Inhalation Safety Assessment

It is important to keep in mind that the actual techniques and terminology used for this Safety Assessment process must comply with relevant legislation and official guidance.

3. Data Collection (Stage 1)

The first step of a safety assessment is to check whether any of the ingredients in the spray products have hazardous properties. The hazardous nature of the spray product can then be assessed by considering the amounts of these ingredients present.

A SDS may be a first source to get such basic toxicological information. However, in order to carry out an inhalation safety assessment, it may also be necessary to access primary sources of data such as toxicological reports, official data files, safety studies, peer-reviewed articles, evaluations by regulatory bodies, etc. (see Appendix I).

4. Hazard assessment (Stage 2)

4.1. Hazard identification

The hazard classification according to UN Globally Harmonized System of Classification and Labelling of Chemicals (GHS) / EU Classification, Labelling and Packaging Regulation (EC) No 1272/2008 (CLP) and toxicological profiles of individual ingredients of the spray product have to be reviewed and assessed in the context of their individual physicochemical data.

As required under REACH, Manufacturers/Importers have to determine the Derived No-Effect Levels (DNELs) for those chemicals identified as hazardous. REACH (Annex I, § 1.0.1) defines the DNEL as the level of exposure to the substance above which humans should not be exposed. DNELs are established for threshold effects, reflecting the likely route(s), duration and frequency of exposure (see Appendix F).

The data collected in Stage 1 provides a useful understanding of the toxicological properties of an individual chemical:

- Acute toxicity
    - Systemic toxicity after oral, dermal or inhalation exposure (median lethal dose LD_{50}-, median lethal concentration LC_{50}- values)
- Irritation/Corrosion (local effects)
    - Sensory (mucosal, dermal and/or inhalation)
    - Pulmonary (deposition of inert materials)
- Sensitisation (skin and respiratory sensitiser)
- Mutagenicity / Carcinogenicity
- Repeated dose toxicity (oral, dermal, inhalation)
    - Reproductive or developmental toxicity (maternal / foetal no observed adverse effect level (NOAEL) / no observed effect level (NOEL) or no observed adverse effect concentration (NOAEC) / no observed effect concentration (NOEC))
    - Systemic toxicity after repeated dose (e.g. 28-day/90-day studies to derive NOAEL/NOEL or NOAEC/NOEC)

The reliability and robustness of the safety assessment is dependent upon the quality of information used in the process (Schneider *et al.*, 2009), so the most robust studies should be used, ideally those directly related to inhalation.

4.2. Hazard characterisation for inhalation exposure

4.2.1. Available data for hazard characterisation

Hazard characterisation must cover all possible systemic effects and local (respiratory tract) effects. In toxicological studies investigating the hazards of an individual substance when inhaled, the dose descriptors [mg/kg bw/day] for systemic and [mg/cm² lung surface area] or

[mg/g lung weight] for local effects have to be determined. Usually they are expressed as a NOAEC (for local and systemic effects), LC_{50} (for acute lethal concentration), BMD (bench mark dose, with rate specified e.g. 10 percent effect), etc.

However, for many chemicals, at least for the foreseeable future, there may be gaps in the available data. In the absence of data from inhalation studies, NOAEL and LD_{50} may be used with appropriate extrapolation.

If some toxicity data is not available for a certain chemical, but it is known that the exposure is very low, then in some cases the Exposure Based Waiving (EBW) approach could be considered (Carthew, *et al.,* 2009) as a justification for concluding that there is no hazard.

EBW is the principle that a level of exposure to a chemical can be established, where it would be possible to consider waiving the conducting of animal studies, by a particular route, or for a specific endpoint, as the likelihood of adverse effects is so low as to be negligible.

It can be appropriate for the evaluation of toxicological effects in the respiratory tract, in particular, leading to the waiving of an inhalation study to address the specific potential for localized effects in the respiratory tract.

The key point with EBW is that the level of exposure of the user respiratory tract under the intended and foreseeable conditions of use should be low enough to fall below an established toxicological threshold derived from a database of chemicals used in aerosols and sprays (e.g. Carthew *et al.,* 2009). However applications of such approaches require expert judgment and an understanding of the restrictions and limitations of the specific methodology.

4.2.2. Determining and estimating systemic effects

Significant deposition of ingredients is likely due to the large surface area of the lung. Water and lipid soluble compounds, as well as gases, and vapours may then be absorbed across the respiratory mucosa and epithelia upon contact. The total systemic dose of a spray ingredient (body burden) is calculated from all routes of exposure (dermal + inhalation + oral). Guidance for estimation of the systemic exposure from the swallowed (non respirable) fraction is found at the European Chemicals Agency (ECHA, 2012b).

The potential for systemic toxicity is best evaluated in standardised toxicity tests in which test animals are repeatedly exposed via the inhalation route. Instead of specific inhalation toxicity data, appropriate sufficiently detailed oral toxicity data could function as an adequate surrogate as detailed in the ECHA guidance on route to route extrapolation (ECHA, 2012a).

Other toxicity data such as Acceptable Daily Intake (ADI), Reference Doses and occupational exposure limit values may also be useful in this evaluation process.

Standard data required for characterisation of inhalation effects for high production volume (HPV) chemicals, where daily exposure is likely up to life span, are subacute (28-day) or subchronic (90-day) repeat dose toxicity tests, preferably performed in line with the corresponding OECD guidelines. For chemicals of less concern inhalation toxicity testing may be limited to short term single exposure studies with typically 4 hours exposure. For materials known or suspected to have systemic toxic potential, a repeat dose study (even if only by the oral route) would be most appropriate for a proper hazard characterisation.

4.2.3. Determining and estimating local (respiratory tract) effects.

Whether the potential for local effects to the respiratory tract needs to be specifically tested can be decided from a weight of evidence approach if there is no repeat dose inhalation route toxicity study. Local effects cannot be assessed by route to route extrapolation from oral

studies, but skin sensitisation and eye irritation data may be useful as adequate surrogates (Abraham *et al.*, 1998a, Abraham *et al.*, 1998b, Elberling *et al.*, 2006, Emmen *et al.*, 2003, Kleno and Wolkoff, 2004, Leonardi *et al.*, 2008, Millqvist *et al.*, 1999, Takezawa *et al.*, 2011, Walker *et al.*, 2001, Wolkoff *et al.*, 2003). Therefore, mucous membrane irritation data may be used as part of a weight of evidence approach to predict respiratory irritation.

4.3. Considerations of the concentration in the spray product.

Once the hazardous nature of the ingredients have been determined the hazardous nature of the spray product can be assessed. It will save a lot of work if at this stage it can be shown that the hazardous ingredients are not present in sufficient concentrations to present a risk through inhalation. In this case the assessment can proceed to risk characterisation without the need to determine the exposure.

As well as the assessing the concentration of ingredients added, other aspects of the formulation need to be considered. For example several ingredients can interact either intentionally or non-intentionally in the container, so it is important to consider ingredient interactions because the apparent presence of hazardous ingredients may not be the case in reality. Other points to consider include:

- A formulation may contain a strong acid, and a strong base in parallel. Such mixture could be either acidic or alkaline and be an irritant or compatible. In this case the pH of the mixture could be a key indicator of the likelihood of an irritation hazard.
- Some ingredients (e.g. solvents) might make other ingredients more readily available for inhalation than others.
- Hazardous by-products might be formed during processing or storage. For example, bis-chloromethyl ether may be formed if dimethyl ether is used as the propellant in a formulation which also includes an ingredient containing chlorine. Conditions by which a hazardous substance is formed as a by-product during manufacture or storage should be prevented or closely controlled and levels of possible reaction products monitored.

5. Exposure assessment (Stage 3)

Spray products have a wide variety of applications and the risk of an adverse effect to human health is dependent on the hazards present and the exposure of the user to the chemical ingredient under specified conditions of use (workers, professional users, consumers, etc.). Therefore, the exposure assessment should be based on knowledge of the conditions of use as based on habits and practices data.

The exposure pattern is affected by a combination of elements:

Spray can:	Size Pressurizing system (propellant driven spray, pump spray) Geometry (volume) Nozzle construction
Spray formulation:	Qualitative/quantitative composition Propellant and solvents used Application format e.g. foam, mousse, gel, jet, fine spray, coarse spray Particle/droplet size distribution at spraying and its maturation
Spray usage:	Frequency Duration Product release per application/time Surface spray or space spray Spray direction (towards or away from the body)
Exposure situation:	Application environment (consumer, professional) Duration of stay in spray environment Room volume (e.g. box 1) Ventilation rate (air exchange) Room temperature Activity of exposed individuals (working, inactive)

For practical reasons, only data which are relevant for the required safety assessment of the spray product should be taken into account.

ECHA has published guidance on the exposure assessment of spray products as part of their IR/CSA guidance Chapter 15 that provides a useful starting point:

> *'Some consumer products are used as sprays in the form of aerosols. In this case the exposure to the substance is related to the characteristics of the droplets (e.g. particle size) which need to be considered specifically in a higher tier exposure model.*
>
> *Inhalation exposure is expressed in terms of external exposure, as a concentration, usually as mg/m^3'.*

5.1. Screening assessment

For screening purposes, a rough estimate of the exposure to a certain sprayed product/chemical could be appropriate or even sufficient as suggested by the ECHA IR/CSA guidance Chapter R.15 (ECHA, 2012b):

> *'For inhalation exposure, the concentration of the substance in the room air (e.g. mg/m³) must be estimated. The event duration is assumed to be 24 hours in the worst case. For a Tier 1 evaluation, it is assumed that 100% of the substance in the consumer product will be released at once into the room and there is no ventilation. The two essential parameters used are:*
>
> - *Amount of product used*
> - *Fraction of substance in the product (concentration)'*

In other words, for a screening assessment, often referred as Tier 1 evaluation, it is assumed that exposure is to the whole content of the dispenser released instantaneously.

Thus for an ingredient to be studied:

$$\text{Tier 1 Exposure} = \frac{\text{Weight of Ingredient in the Spray Formulation}}{\text{Room Volume}} \left[\frac{\text{mg}}{\text{m}^3}\right]$$

Equation 1

This conservative approach will provide overestimated exposure for volatile substances (fixed room volume without air exchange). However for particles/droplets this approach will underestimate short term local exposure (inhomogeneous distribution of product in the room shortly after spraying). Standard values for room volumes that can be used for such an assessment are given in Appendix B (see Table 9).

For Tier 1 assessment for short-term local exposure, the value for room volume could be reduced (e.g. to 2 m^3) to represent the volume of air immediately surrounding the user ('personal zone').

This conservative approach is also suitable for non-volatile materials. One may adjust the cloud volume to represent individual product-types.

The application of the product under specified conditions of use should be taken into consideration when selecting an appropriate exposure volume. For example products typically sprayed into confined spaces (such as oven cleaners and shower cleaners) should use a volume representative of the dispersible volume rather than the complete room.

Also, cosmetic and personal care products are known to exhibit higher local exposure at the point of application because they are generally sprayed towards the body of the user rather than away. Therefore, for these product categories it should be assumed that the total amount of the sprayed product (including the non-volatile ingredients) enters immediately and homogenously the volume of air surrounding the user (e.g. 2 m^3).

The results of the screening (exposure) assessment are then used for risk characterisation (see § 6).

For some sprays further exposure assessment is not necessary, however a screening assessment is a simple but very conservative approach. A more accurate determination of exposure could be necessary for a robust and reliable risk characterisation.

5.2. Exposure Modelling

5.2.1. Guidance for selecting an appropriate exposure model

Based on the diversity of spray products and their applications, a number of models for quantitative exposure assessment, varying in complexity, have been developed (see § 5.2.3). All the models have individual strengths and weaknesses to estimate the robust exposure to a certain spray product/chemical. Assumptions and boundary conditions vary between models. Therefore it is important to understand the principles of a specific model before using it as this will avoid accidental misuse.

As stated in the ECHA IR/CSA guidance Chapter R.15:

> *'The concentration of a chemical in the room air will depend on the amount of chemical present in the room, the room size, ventilation of the room, vapour pressure of the compound and the rate at which the compound is released into the air. A refined estimation should consider time.'*

More sophisticated exposure assessment should take into account the amount of sprayed product/chemical in a given time and room, the initial air concentration, dilution by ventilation and sedimentation. As exposure is expressed as a time weighted average concentration (TWA), it is necessary to either measure airborne concentrations or to calculate them on a theoretical level.

Such exposure data will be used in risk characterisation (see § 6).

5.2.2. Data to establish exposure scenarios

For a robust risk characterization, the exposure scenario has to display the conditions found under 'real use' of aerosol products.

In order to help building such exposure scenarios, several typical parameter and definitions are tabulated in the following.

Table 2 gives the World Health Organization (WHO, 1998) classification of spray characteristics with regard to the median diameter of droplets. Each spray product has its own particle size distribution with smaller and larger particles.

Droplet volume median diameter [a] [µm]	Description
<15	fog
<25	fine aerosol
25 - 50	coarse aerosol
51 - 100	mist
101 - 200	fine spray
201 - 400	medium spray
>400	coarse spray

[a] Volume median diameter: the diameter at which half the volume of the spray contains droplets larger or smaller than the volume median diameter.

Table 2: Description of aerosol droplets by volume median diameter (WHO, 1998)

Typical discharge rates for some aerosol dispenser applications are given in Table 3, but where possible the actually measured discharge rate of the aerosol product should be used.

Table 3 also presents typical spray time for certain aerosol applications. The spray time is key in determining the 'dose' delivered when applied. However, it is an individual habit and any two people may use a product differently (Steiling *et al.*, 2012). To build realistic exposure scenarios it is therefore important to understand how spray products are realistically used.

Aerosol dispenser product type	Discharge rate [g/s]	Spray time [s]
Hairspray [a]	0.7	3 - 4
Antiperspirant/Deodorant Spray (90th percentile)	0.8[c]	1.4[d]
Air freshener [a]	1.5 - 1.8	4 - 5
Furniture Polish [a]	1.8	2 - 3
All-purpose Cleaning Spray	1.2[e]	24[e]
Starch [a]	2.0	2 - 3
Carpet Cleaner [a]	2.0	20 - 30
Oven Cleaner [a]	2.0	10 - 15
Flying Insect Killer [b]	1.5	10
Crawling Insect Killer [b]	1.5	60- 90
De-icer [a]	2.5	15 - 20
Paints [a]	0.8	30 - 40

Table 3: Discharge rates (including propellants and solvents) and spray times for aerosol applications ([a]) BAMA, 2008; [b]) Bremmer *et al.*,, 2006c; [c]) Bremmer *et al.*,, 2006a; [d]) Steiling *et al.*, 2012; [e]) Weerdesteijn *et al.*, 1999)

Table 4 gives amounts of product sprayed and frequency of application for deodorants (aerosol) and hairsprays (aerosol and pump spray). These values can be considered as default values for these product categories. The amount per application represents the total amount of product expelled from the spray product, i.e. including propellant and solvent (can weight loss), but not the quantity of product remaining on the skin or hair, which is much lower e.g. for deodorants/antiperspirants (Steiling *et al.*, 2012).

Product application	Amount/day [g]	Frequency of application/day	Reference
Deodorant (aerosol)	6.1 (90th percentile)	2	McNamara *et al.*, 2007 Hall *et al.*, 2007
Hairspray (aerosol)	6.8 (75th percentile)	1	Bremmer *et al.*, 2006a
Hairspray (pump spray)	3.6	1	Loretz *et al.*, 2006

Table 4: Daily amounts (including propellants and solvents) applied and frequency of use for certain cosmetic spray products

Table 5 gives some typical data on the exposure time for the use of some household aerosol products from the Exposure Factors Handbook (US EPA, 2011).

Products	Mean per use [min]	90th Percentile
Spray shoe polish	7.49	18.00
Aerosol spray paint	39.54	60.00
Aerosol rust remover	18.57	60.00
Aerosol spray paints for cars	42.77	120.00
Spray lubricant for cars	9.90	15.00

Table 5: Typical data on the exposure time for the use of household solvent aerosol products (US EPA, 2011).

5.2.3. Brief introduction of major exposure models available

Modelling of inhalation exposure varies from relatively simple to very sophisticated models by taking into account various factors to determine how much of a spray/chemical is actually inhaled, exhaled/unabsorbed or is bio-available or deposited in the lung.

The following exposure models are described in detail in Appendix C:

a) BAMA/FEA Indoor Air model (one-box)

b) RIVM ConsExpo 4.1 models (one-box)

c) BAuA SprayExpo 2.0 model (one-box)

d) RIFM 2-Box Indoor Air Dispersion model (two-box)

e) RIFM Computational Fluid Dynamics (CFD) and Multiple Path Particle Deposition (MPPD) model

<u>One Box Models</u>

The one-box model is based on the assumption of a homogeneous distribution of particles/droplets in a room (volume). Concentrations are computed as a function of sprayed product quantity, room volume and ventilation rates as well as the time elapsed from the start of the emission. This model is inappropriate for cases where poor mixing conditions exist.

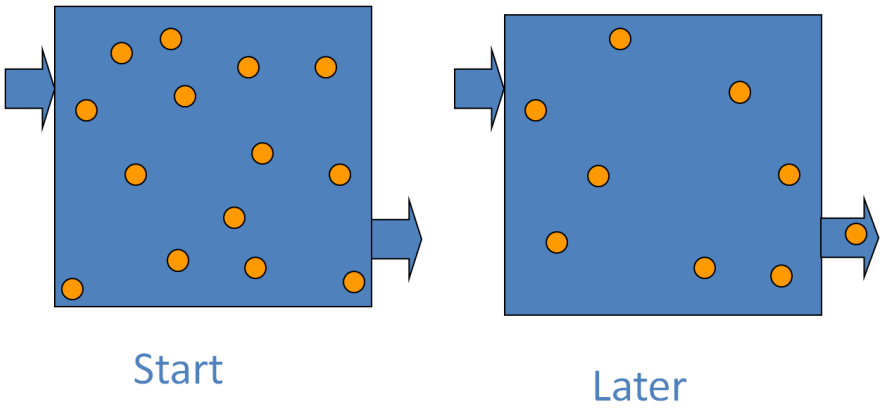


Figure 3: Theoretical behaviour of vapour in a room

A worked example of a safety assessment with a one-box model is provided in Appendix D.

Two Box Models

A more sophisticated approach is the two box model which assumes 2 different zones, e.g. rooms (Box A and Box B) into which the emitted material will disperse. The model assumes perfect mixing in Box A where the emission occurred and dispersion into Box B, which can be e.g. the rest of the house or just an annexed room/volume (see Figure 4).

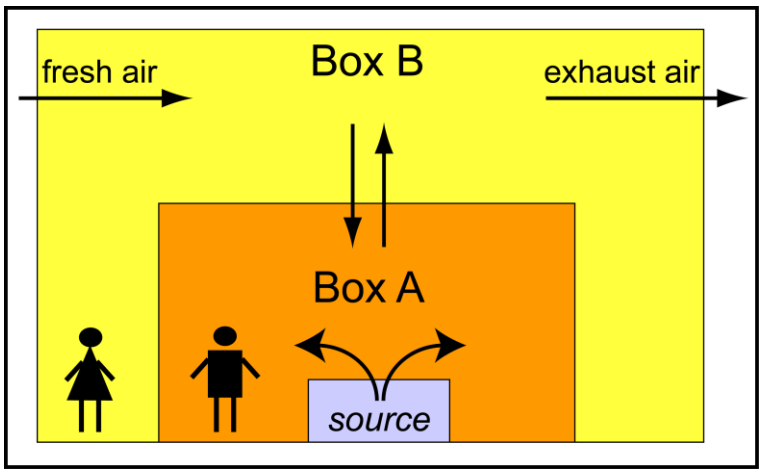


Figure 4: Assumption of a homogeneous distribution of whole quantity of sprayed product in Box A and Box B for a far field scenario

Although the air concentration will be higher in Box A, systemic exposure will depend on the time spent in each box. The amount of a material that can potentially be inhaled is given by its concentration in each box, the time spent in these individual boxes (e.g. rooms) and the physiological minute ventilation (product of breathing frequency and depth of ventilation) of the exposed individual.

Exposure can be assessed using this model in an alternative way, where Box A is the breathing zone and Box B as the rest of the room (see Figure 5).

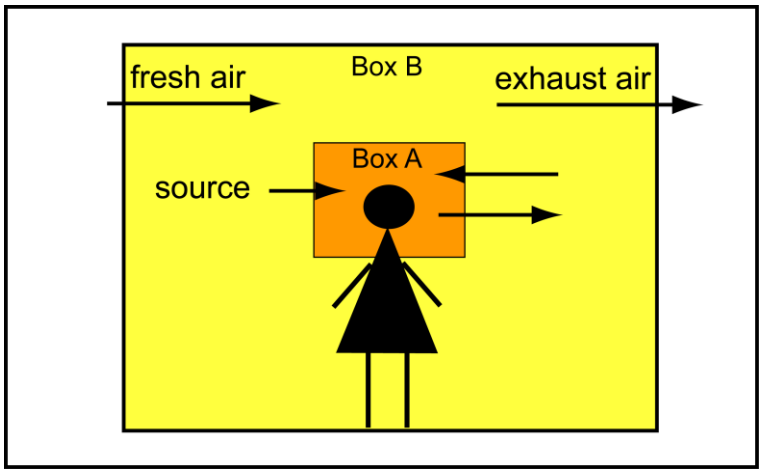


Figure 5: Assumption of a homogeneous distribution of whole quantity of sprayed product in Box A and Box B for a near field scenario

A worked example of a safety assessment with a two-box model is provided in Appendix E.

Multiple Path Particle Deposition Model

The Multiple Path Particle Deposition (MPPD) model is a higher tier exposure assessment model developed to study the uptake of vapours and deposition of aerosol particulate/droplet components using a computational model of the nasal and lung airways of humans and rats. Such coupled human-rat deposition modelling allows the extrapolation of laboratory measurements data for the human health risk. Specifically, the model is capable of informing tissue reaction kinetics and dose metrics for materials chemicals (Schroeter *et al.*, 2006a, Schroeter *et al.*, 2006b, Martonen *et al.*, 2003, Garcia *et al.*, 2009, Schroeter, 2009). Such data may be useful for toxicological risk assessment in addition to its primary function for exposure assessment. In particular, with the MPPD model, one can determine the dose deposited locally at various sites of contact in the respiratory tract, as well as establish the concentration that can be up taken across the tissue surface into the systemic circulation, thus becoming available to other organs. This evaluation and quantification of the deposited/absorbed amount with the MPPD model requires using respiratory (preferred, if known) or dermal absorption coefficients and is dependent on knowledge of the specific physicochemical characteristics of each chemical that is evaluated in the model.

Other higher tier models, such as the US EPA Multi- Chamber Concentration and Exposure Model (MCCEM) (Koontz *et al.*, 1991. US EPA, 1995), exist but are not covered in this document.

Use of publically available models

Models using publicly available software packages such as the BAMA/FEA Indoor Air, Model, RIVM ConsExpo, SprayExpo (Koch *et al.*, 2004), and BG-Spray (Eickmann, 2007a) models are particularly useful for assessing for systemic effects.

The application of these models to assess exposure to different types of spray products is summarised in Table 6 below.

Exposure model	Products for which the model can be used
BAMA/FEA Indoor Air model (one-box)	Products sprayed into the air Products sprayed onto a horizontal surface
RIVM ConsExpo 4.1 models (one-box)	Products sprayed into the air Products sprayed at the body Products sprayed at a vertical surface Products sprayed on to a horizontal surface (see RIVM Factsheets for specific product types)
BAuA SprayExpo 2.0 model (one-box)	Products sprayed into the air Products sprayed towards a surface
RIFM 2-Box Indoor Air Dispersion model (two-box)	Products sprayed into the air Products sprayed at the body Products that are combustible (candles) Products that are passive or heated diffusers (See 2-Box guidance for specific product types)
RIFM Computational Fluid Dynamics (CFD) and Multiple Path Particle Deposition (MPPD) model	Products sprayed into the air Products sprayed at the body Products sprayed at a vertical surface Products sprayed on to a horizontal surface

Table 6: Consumer exposure models for spray products

A fuller discussion of the advantages and drawbacks of different types of models has been published by Eickmann, *et al*. (2007b).

5.3. Exposure Measurement

For some applications and/or ingredients modelling may not give a sufficiently realistic estimation of exposure to the respirable fraction of the spray. In such circumstances the relevant fraction of respirable material from the sprayed product should be measured close to the breathing zone of the user and/or applicant. This fraction may be different to that emitted from the spray dispenser as it is actuated (i.e. near the spray nozzle).

ECHA has published guidance on the exposure assessment of spray products as part of their IR/CSA guidance Chapter.15:

> *'Some consumer products are used as sprays in the form of aerosols. In this case the exposure to the substance is related to the characteristics of the droplets (e.g. particle size) which need to be considered specifically in a higher tier exposure model.*
>
> *Inhalation exposure is expressed in terms of external exposure, as a concentration, usually as. mg/m^3'.*

A spray is a dynamic population as larger particles/droplets become smaller as the propellant and/or solvent, contained evaporates. As discussed in the FEA Guide on particle size measurement (FEA, 2009), the sprayed particles/droplets change after the initial spraying event over time (maturation). Therefore, for health assessments of many spray applications, it is not simply the particles/droplets produced at the time of spraying that need to be assessed but also their development during the time of exposure. Thus, for a realistic exposure assessment the concentration of spray that is actually inhaled and which could become bio-available should be taken into account. Unfortunately, at present, it is not possible to easily use modelling to assess the behaviour of particles/droplets produced by an aerosol spray and therefore it is necessary to resort to measurement.

Bigger particles/droplets will quickly deposit on intended or unintended surfaces outside the respiratory tract. The exception is, of course, short term exposure during spraying when larger particles/droplets could be breathed in, but most of these, depending on particle/droplet size, will deposit in the nose or throat rather than being inhaled into the lung. Therefore, if the particle/droplet size distribution of the spray during use is measured, the exposure estimate can take account of the fraction of the spray breathed in and the Risk Characterisation Ratio (RCR) adjusted. For some assessments, the understanding of the exposure to the spray may mean that modelling of exposure should be bypassed in favour of measuring particle size distribution.

5.3.1. Measurement of doses from particulates in consumer aerosols and spray products.

Spray clouds of products are always complex time-dependent mixtures of particles/droplets of various sizes determined by their chemical composition as well as by the geometry of the spray container including its release nozzle.

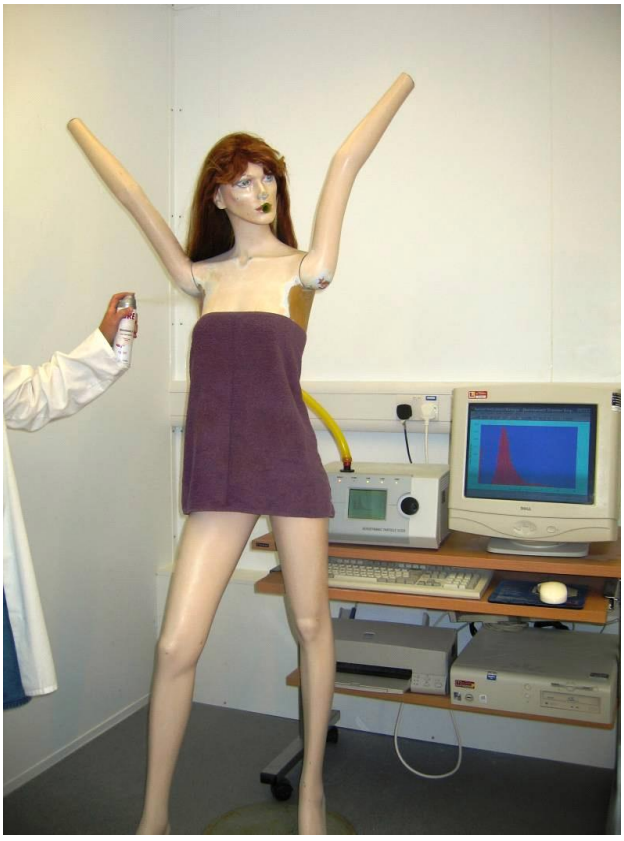


Figure 6: Mannequin with particle sizer spectrometer

With the help of a mannequin equipped with an aerosol sampler in the mimicked upper respiratory tract and connected to a particle size spectrometer (Figure 6), measurements are possible to get most realistic data on inhaled particle/droplet fractions. Dose results can be recorded under realistic in-use conditions simulating physiological breathing frequency and respiratory volume of a person (see Table 8 in Appendix A).

Respirable dose (RDose) method (Carthew *et al*., 2002)

The respirable dose (RDose) is defined as a fraction of the inhaled dose which contains particles/droplets small enough to reach the deeper respiratory tract. To measure such fraction, specifically designed mannequins could assist, equipped with technical features to simulate both the anatomically correct situation in men e.g. hair wig for testing hair sprays and axillary region if deodorants have to be tested. Such a mannequin should be appropriate to be exposed under individual use conditions, e.g. habits and practices of spraying (frequency and duration). The air in the 'breathing zone' is sampled and analysed for a period of e.g. 10 minutes. Therefore, the aerodynamic diameter of individual airborne particles/droplets and the number of individual particles/droplets in a defined volume of air are measured per minute using a particle size spectrometer. These data are used to give a particle size distribution plot over the measured aerodynamic diameter and to extrapolate the respirable dose [g/s spray] for that given formulation under the test conditions.

Respirable discharge (RDis) method (Carthew *et al*., 2002)

Respirable discharge (RDis) is the estimation of the mass of any individual ingredient that has the potential to reach the bronchial, bronchiolar and alveolar regions of the human lung if inhaled.

The respirable discharge method is used to collect the respirable fraction that remains airborne after spraying a product into a chamber of standardised dimensions. The aerosol product is sprayed into the chamber directly at a vertical positioned plate intended to simulate the surface on to which the sample is being applied. Any material remaining airborne that is not deposited onto the vertical plate or settling on to the surfaces of the chamber is sampled through a single-stage impactor inlet. The impactor inlet samples the airborne fraction and collects the respirable fraction on to a filter. The respirable discharge [g/s spray] is gravimetrically measured and could be chemically analysed. This method is considered to simulate a realistic exposure to a spray formulation.

A worked example of a risk assessment for consumer use of hair spray products based on data generation is provided in Appendix G.

6. Risk characterisation (Stage 4)

6.1. Approaches to the risk assessment of chemicals in spray products.

Once the exposure to the spray has been estimated or measured, the next step is to assess the risk to human health of that level of exposure. Although the different regulatory regimes use broadly similar methodologies, unfortunately they use different terminologies, often requiring specific calculations for their safety assessment. The most commonly used values to be used for safety assessment for chemicals are the margin of safety (MoS) and the RCR.

The commonly used quantitative methods of risk assessment are split into consideration of whether the hazard effects identified for a chemical or substance are thresholded or non-thresholded.

For thresholded effects there is a NOAEL/NOAEC (see § 4.2.1) that can be identified from an adequately designed toxicology study defined as the dose below which there is no statistically significant increase in adverse effects on the exposed organism.

Non-thresholded effects are those for which there is no such threshold due to the dose response for effects extending to zero exposure. Such chemicals could be genotoxic carcinogens, which are prohibited to be used as ingredients in consumer products but may occur as contaminants. There is also a method developed by Joint FAO/WHO Expert Committee on Food Additives (JECFA) for assessing non-thresholded effects from genotoxic carcinogens (Barlow *et al.*, 2006).

6.2. Risk characterisation for spray products falling under the scope of REACH.

6.2.1. Risk Characterisation Ratio (RCR)

Under REACH the assessment of chemicals, in relation to human health is part of a process which entails a sequence of actions that together are known as a Chemical Safety Assessment (CSA). How this is to be achieved is outlined in Annex 1 of REACH Regulation and set out in detail in the ECHA *guidance on information requirements and chemical safety assessment*[1]. The ECHA IR/CSA guidance, Chapter R.15 (ECHA, 2012b) describes how to estimate exposure:

> *'Consumer exposure estimation can be performed by a tiered assessment, beginning with a screening estimation (Tier 1). If the result of the screening for that exposure is below the accepted thresholds (DNEL = Derived No Effect Level, or other thresholds), then there is "no concern" and the risks of the product can be considered to be controlled. If this is not the case, the exposure estimation has to be refined in the iterations of the chemical safety assessment until the risk characterization shows that risks are sufficiently controlled. This can be done e.g. by improving the Tier 1 assumptions, using measured data, going to higher tier exposure estimation models or by introducing risk management measures.'*

[1] Available at: http://echa.europa.eu/web/guest/support/guidance-on-reach-and-clp-implementation

For a spray product this means knowing the percentage composition of each ingredient in the formulation and how much product is discharged with each application. Thus for a given exposure to each ingredient, the Risk Characterisation Ratio, RCR is:

$$\text{RCR} = \frac{\text{Exposure}}{\text{DNEL}}$$

Equation 2

According to ECHA IR/CSA guidance Chapter R.8 (ECHA, 2012a):

- RCR <1, there is no cause for concern or risk reduction measures are not necessary.
- RCR >1, a refinement of exposure information is required or risk reduction measures are necessary e.g. to modify the spray character or to reformulate.

A DNEL is a derived no effect level (for man) and is the level of which exposure above which humans should not be exposed. More information on DNEL is provided in Appendix F.

A DNEL is analogous to ADI (acceptable daily intake for food ingredients) or TDI (tolerable daily intake for food contaminants) or RfD (reference dose, US EPA pesticides) and defined as:

$$\mathbf{DNEL} = \frac{\mathbf{NOAEL\ (for\ endpoint)}}{\mathbf{AF1xAF2x\ \ldots xAFn}}$$

Equation 3

AF stands for assessment factor.

In the case of contaminants having non-threshold effects the concept of the derived minimum effect level (DMEL) should be used, for more information see Appendix H.

6.2.2. Derivation of a DNEL

In order to derive a DNEL one may select the relevant dose-descriptor(s) for the endpoint concerned e.g. (L)NOAEL, BMD, LD_{50}, LC_{50}, T25, BMD(L)10.

The dose-descriptor(s) may need to be modified to the correct exposure unit by dividing by appropriate AFs (see Appendix F).

6.2.3. Assessment Factors for Inhalation

Assessment factors are applied for uncertainty in interspecies extrapolation, (2.5 for differences in toxicodynamics) and intraspecies variation (10 for man). Additional assessment factors may also be applied for the relevant exposure pattern such as issues related to dose-response such as the use of a LOAEL because no NOAEL was established.

The ECHA IR/CSA guidance Chapter R.8 (ECHA, 2012a) contains a number of AFs for the extrapolation of animal data to man, which should be used in the absence of substance-specific information. The AFs are based on experience and convention, and are thus proposed as default values for determining DNELs under REACH.

6.3. Risk characterisation for spray products falling under the scope of the Cosmetics Regulation, using the Margin of Safety (MoS)

In many toxicological text books the *Margin of Safety* (MoS) is defined as a dimensionless number that establishes the relationship between the dose of a certain chemical necessary for a

desired effect and the dose of the same chemical resulting in an undesired effect. Such calculation is regularly used in the safety assessment for e.g. drugs where a clear beneficial or effective dose can be distinguished from those which are toxic or ineffective.

For other areas like cosmetics, the term MoS is used quite differently to represent the relationship of an estimated or measured systemic exposure dose (SED) for the applicant and the NOAEL determined in appropriate animal tests. Usually, the NOAEC (*no observed adverse effect concentration*) represents the highest systemic concentration for which a test chemical does not induce an adverse effect in the test animal when exposed repeatedly to that concentration (typically daily for a period of 90 days).

In this form, the MoS, sometimes more accurately known as a *Margin of Exposure* (MoE), is regularly used in risk-assessment procedures, for example, the EU Scientific Committee on Consumer Safety (SCCS, 2012b) applies this MoS approach to define the expected level of safety in the assessment of cosmetic products.

Beside the estimated or measured exposure dose, the NOAEL/NOAEC has to be measured in animal tests using the most relevant exposure route (oral, dermal, inhalation). In case of dermal or oral exposure both the SED and the NOAEL have the unit [mg/kg bw/d]. For inhalation the NOAEC are typically given with the unit [mg/m³] or [ppm].

$$\text{MoS (for systemic effects)} = \frac{\text{NOAEL (derived from NOAEC)}}{\text{SED}}$$

Equation 4

The MoS is not necessarily limited to systemic effects, but can also be applied to local effects, e.g.:

$$\text{MoS (for local effects)} = \frac{\text{NOAEC}}{\text{Respiratory Tract Exposure}}$$

Equation 5

However, for cosmetic ingredients the MoS is more often applied to the assessment of systemic effects, mainly because of the limited availability of quantitative dose-response data [mg/cm² of exposed tissue] from standard toxicity tests for local irritancy/corrosivity.

The general assumption is that a MoS value of at least 100 ensures an appropriate level of safety for systemic exposure from consumer products like cosmetics. This minimum requirement is built on the assumption of a factor 10 for the interspecies diversity between test animals and men to react on systemic exposure and a second factor of 10 for the intraspecies diversity between human beings. It is important to note that for this MoS-approach the NOAEL/NOAEC used is based on an exposure scenario with a repeated application on a daily matter (typically for a period of 90 days).

If explicit information on systemic exposure is available from test animals and men (e.g. plasma level of the chemical after realistic exposure), then regulators will accept for MoS values ≥25 as safe (SCCS, 2012a; SCCS, 2012b).

In contrast, for local lung effects the MoS should be at least 25-fold, based on a default of 2.5 for interspecies and 10 for intra-species differences (ECHA, 2012a).

For the safety assessment of spray products, the MoS calculation is much more complex because not only the chemical dose, but also the physical nature of particles i.e. is it solid or liquid, as well as their dimension will have a serious impact on the exposure. As discussed

above, the physical characteristics and particle/droplet size is determined by the solvent used, the vehicle formulation and by technical aspects of the spray applicator (pressure, spray can and nozzle etc.). Such technical details define where exposure occurs in the respiratory tract and lung region (see Figure 1). As both, the area of exposure and the particle/droplet size influence the local exposure [mg/cm² lung tissue], a risk assessment just based on a "simple" MoS calculation becomes inadequate.

However, if reliable area specific exposure data and appropriate information (dose-response relationship) on both systemic and local effects from standard toxicity tests are available, a combination of "systemic MoS" and "local MoS" calculations may be an acceptable data package for a proper risk assessment of sprayed consumer products.

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8. Glossary of terms

Acceptable daily intake (ADI) Estimated maximum amount of an agent, expressed on a body mass basis, to which individuals in a (sub)population may be exposed daily over their lifetimes without appreciable health risk. Related terms: *Reference dose, Tolerable daily intake*

Activity pattern data Information on human activities used in exposure assessments. These may include a description of the activity, frequency of activity, duration spent performing the activity, and the microenvironment in which the activity occurs.

Acute exposure A contact between an agent and a target occurring over a short time, generally less than a day. (Other terms, such as "short-term exposure" and "single dose," are also used.)

Adverse effect Change in the morphology, physiology, growth, development, reproduction, or life span of an organism, system, or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress, or an increase in susceptibility to other influences.

Agent A chemical, biological, or physical entity that contacts a target.

Assessment Evaluation or appraisal of an analysis of facts and the inference of possible consequences concerning a particular object or process.

Assessment end-point Quantitative/qualitative expression of a specific factor with which a risk may be associated as determined through an appropriate risk assessment.

Assessment factor Numerical adjustment used to extrapolate from experimentally determined (dose–response) relationships to estimate the agent exposure below which an adverse effect is not likely to occur. Related terms: *Safety factor, Uncertainty factor*

Bio-availability The rate and extent to which an agent can be absorbed by an organism and is available for metabolism or interaction with biologically significant receptors. Bio-availability involves both release from a medium (if present) and absorption by an organism.

Chronic exposure A continuous or intermittent long-term contact between an agent and a target. (Other terms, such as "long-term exposure," are also used.)

Concentration Amount of a material or agent dissolved or contained in unit quantity in a given medium or system.

Dose Total amount of an agent administered to, taken up by, or absorbed by an organism, system, or (sub)population. The amount of agent that enters a target after crossing an exposure surface. If the exposure surface is an absorption barrier, the dose is an absorbed dose/uptake dose (see uptake); otherwise, it is an intake dose (see intake).

Dose–response Relationship between the amount of an agent administered to, taken up by, or absorbed by an organism, system, or (sub)population and the change developed in that organism, system, or (sub)population in reaction to the agent. Synonymous with *Dose–response relationship*. Related terms: *Dose–effect relationship, Effect assessment, Concentration–effect relationship*

Effect Change in the state or dynamics of an organism, system, or (sub)population caused by the exposure to an agent.

Exposure Contact between an agent and a target. Contact takes place at an exposure surface over an exposure period. Concentration or amount of a particular agent that reaches a target organism, system, or (sub) population in a specific frequency for a defined duration.

Exposure assessment Evaluation of the exposure of an organism, system, or (sub)population to an agent (and its derivatives). Exposure assessment is the third step in the process of risk assessment.

Exposure model A conceptual or mathematical representation of the exposure process.

Exposure route The way in which an agent enters a target after contact (e.g., by ingestion, inhalation, or dermal absorption).

Exposure scenario A set of conditions or assumptions about sources, exposure pathways, amounts or concentrations of agent(s)involved, and exposed organism, system, or (sub)population (i.e., numbers, characteristics, habits) used to aid in the evaluation and quantification of exposure(s) in a given situation. However, under REACH, exposure scenario means the set of conditions, including operational conditions and risk management measures, 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.

Hazard Inherent property of an agent or situation having the potential to cause adverse effects when an organism, system, or (sub)population is exposed to that agent.

Hazard assessment A process designed to determine the possible adverse effects of an agent or situation to which an organism, system, or (sub)population could be exposed. The process includes hazard identification and hazard characterization. The process focuses on the hazard, in contrast to risk assessment, where exposure assessment is a distinct additional step.

Hazard characterization The qualitative and, wherever possible, quantitative description of the inherent property of an agent or situation having the potential to cause adverse effects. This should, where possible, include a dose–response assessment and its attendant uncertainties. Hazard characterization is the second stage in the process of hazard assessment and the second of four steps in risk assessment. Related terms: *Dose–effect relationship, Effect assessment, Dose–response relationship, Concentration–effect relationship*

Hazard identification The identification of the type and nature of adverse effects that an agent has an inherent capacity to cause in an organism, system, or (sub)population. Hazard identification is the first stage in hazard assessment and the first of four steps in risk assessment.

Inhalable fraction Mass fraction of total airborne particles/droplets which is inhaled through the nose and mouth. The inhalable fraction depends on the speed and direction of the air movement, on the rate of breathing and other factors.

Intake The process by which an agent crosses an outer exposure surface of a target without passing an absorption barrier, i.e., through ingestion or inhalation (see *Dose*).

Local Effect A local effect refers to an adverse health effect that takes place at the point or area of contact. The site may be skin, mucous membranes, the respiratory tract, gastrointestinal system, eyes, etc. Absorption does not necessarily occur.

Oropharyngeal breathing Breathing pertaining to the mouth and pharynx

Pulmonary Pertaining to the lungs

Respirable fraction Mass fraction of inhaled particles/droplets which penetrate to the non-ciliated airways. The term 'respirable' has been used in English since at least 1952 for the fraction penetrating to the non-ciliated airways.

Risk The probability of an adverse effect in an organism, system, or (sub)population caused under specified circumstances by exposure to an agent.

Risk assessment A process intended to calculate or estimate the risk to a given target organism, system, or (sub)population, including the identification of attendant uncertainties, following exposure to a particular agent, taking into account the inherent characteristics of the agent of concern as well as the characteristics of the specific target system. The risk assessment process includes four steps: hazard identification, hazard characterization (related term: *Dose–response assessment*), exposure assessment, and risk characterization. It is the first component in a risk analysis process.

Risk characterisation The qualitative and, wherever possible, quantitative determination, including attendant uncertainties, of the probability of occurrence of known and potential adverse effects of an agent in a given organism, system, or (sub)population, under defined exposure conditions. Risk characterization is the fourth step in the risk assessment process.

Risk estimation Quantification of the probability, including attendant uncertainties, that specific adverse effects will occur in an organism, system, or (sub)population due to actual or predicted exposure.

Safety Practical certainty that adverse effects will not result from exposure to an agent under defined circumstances. It is the reciprocal of risk.

Safety factor Composite (reductive) factor by which an observed or estimated no-observed-adverse-effect level (NOAEL) is divided to arrive at a criterion or standard that is considered safe or without appreciable risk. Related terms: *Assessment factor, Uncertainty factor*

Sensory Pertaining to peripheral nerves.

Source The origin of an agent for the purposes of an exposure assessment.

Systemic effect A systemic effect refers to an adverse health effect that takes place at a location distant from the body's initial point of contact and presupposes absorption has taken place.

Target Any biological entity that receives an exposure or a dose (e.g., a human, a human population, or a human organ).

Threshold Dose or exposure concentration of an agent below which a stated effect is not observed or expected to occur.

Time-averaged exposure The time-integrated exposure divided by the exposure duration. An example is the daily average exposure of an individual to carbon monoxide.

Time-weighted–average Exposure When the concentration of a substance in an atmosphere is measured in a number of consecutive sampling period t_1, t_2, t_3, …t_n (not necessarily of the same duration) giving concentrations of c_1, c_2, c_3, ….c_n respectively, the time weighted average exposure concentration is given by:

$$TWA = (t_1c_1, +t_2c_2 + t_3c_3 \ldots + t_nc_n)/ (t_1 + t_2 + t_3 \ldots . + t_n)$$

Total Systemic Exposure Sum of dermal, oral and inhalation exposures.

Toxicity Inherent property of an agent to cause an adverse biological effect.

Uncertainty Imperfect knowledge concerning the present or future state of an organism, system, or (sub)population under consideration.

Uncertainty factor Reductive factor by which an observed or estimated no-observed-adverse effect level (NOAEL) is divided to arrive at a criterion or standard that is considered safe or without appreciable risk. Related terms: *Assessment factor, Safety factor*

Appendix A – Exposure factors – Inhalation rates

Table 7 presents some animal minute volumes and body weights.

	Subchronic						Chronic					
	MV [L/min]			BW [kg]			MV [L/min]			BW [kg]		
Species and Strain	♂	♀	♂/♀	♂	♀	♂/♀	♂	♀	♂/♀	♂	♀	♂/♀
Rats			+			+			+			+
Fisher 344	0.14	0.10	0.12	0.180	0.124	0.152	0.25	0.17	0.21	0.380	0.229	0.305
Sprague-Dawley	0.19	0.15	0.17	0.267	0.204	0.236	0.33	0.23	0.28	0.523	0.338	0.431
Long-Evans	0.18	0.14	0.16	0.248	0.179	0.124	0.30	0.23	0.27	0.472	0.344	0.408
Osborne-Mendel	0.19	0.15	0.17	0.263	0.201	0.232	0.32	0.26	0.29	0.514	0.389	0.452
Wistar	0.16	0.12	0.14	0.217	0.156	0.187	0.30	0.21	0.25	0.462	0.297	0.380
Mice												
B6C3F1	0.037	0.028	0.033	0.032	0.025	0.028	0.044	0.041	0.043	0.037	0.035	0.036
BAF1	0.026	0.023	0.024	0.022	0.020	0.021	0.030	0.026	0.028	0.026	0.022	0.024
Hamsters												
Syrian	0.043	0.042	0.042	0.097	0.095	0.096	0.057	0.061	0.059	0.134	0.145	0.140
Chinese	0.015	0.013	0.014	0.030	0.025	0.028	0.020	0.018	0.019	0.041	0.038	0.040
Guinea pigs												
[Not specified]	0.21	0.19	0.20	0.48	0.39	0.44	0.29	0.28	0.28	0.89	0.86	0.88
Rabbits												
New Zealand	1.09	1.17	1.13	2.86	3.10	2.98	1.37	1.43	1.40	3.76	3.93	3.85

MV = minute volume, the total volume of new air moved into the respiratory passages each minute (mean tidal volume × respiratory rate).

BW = body weight, mean body weight.

Table 7: Animal minute volumes and body weights (Inhalation Toxicology, Salem and Katz, 2006)

Other inhalation rate data are available in the literature.

It should be noted that subchronic and chronic refer to the length of time of each study type as it relates to the age of the animal (and consequently its size) during the length of such a study. With an OECD-based protocol, for example, when a study is started, a Sprague-Dawley rat should be 6-9 weeks of age. A subchronic study is less than 90 days in length and a chronic study is 90 days or longer in duration. The average body weights and minute ventilation corresponds to the change in body over the course of the length of those study types.

Table 8 presents typical human minute volumes.

	Short-Term Exposures				
	Rest [L/min]	**Sedentary Activity** [L/min]	**Light Activity** [L/min]	**Moderate Activity** [L/min]	**Heavy Activity** [L/min]
Children	5.0	6.7	16.7	20.0	31.7
Adults	6.7	8.3	16.7	26.7	53.3

	Long-Term Exposures (24-h means)							
Age	**< 1 y**	**1-2 y**	**3-5 y**	**6-8 y**	**9-11 y**	**12-14 y**	**15-18 y**	**19-65 +**
Litre/minute	3.1	4.7	5.8	6.9	9.7 ♂ 9.0 ♀	10.4 ♂ 8.3 ♀	11.8 ♂ 8.3 ♀	10.6 ♂ 7.8 ♀

Rest: lying down.

Sedentary: sitting, pilot, driving a tractor.

Light: flagger, mixer/loader (containers <50lb), pneumatic reel sprayer, lawn treatment, most harvesters.

Moderate: mixer/loader (containers >50lb), backpack sprayer (greenhouse applicator, hilly conditions, heavy brush), harvesters using ladders.

Heavy: generally not applicable to occupational exposure to pesticides.

Minute volume: total volume of new air moved into the respiratory passages each minute (mean tidal volume × respiratory rate).

Table 8: Human minute volumes (Inhalation Toxicology, Salem and Katz, 2006)

Other relevant sources exist such as the Handbook of Toxicology (Derelanko *et al*., 2002) or the Exposure Factors Handbook (US EPA, 2011).

Appendix B – Room volumes and air flow rates

Table 9 presents different room volumes in the residential/living environment. The given data are intended to be applied for exposure modelling in combination with values given can be used with the data presented in Table 3, Table 4 and Table 5 to model exposure.

Title of Data Set	Value/Unit Data Type	Source Document
Default values of rooms in Dutch homes	**20** [m^3] for unspecified room **58** [m^3] for living room **15** [m^3] for kitchen (incl. open kitchen) **16-22 or 27** [m^3] for bedroom **10** [m^3] for bathroom **2.5** [m^3] for toilet **10** [m^3] for shed **34** [m^3] for garage	General Fact Sheet, *Limiting conditions and reliability, ventilation, room size, body surface area* Updated version for ConsExpo 4 RIVM report 320104002/2006
Minimal estimated room sizes	**2** [m^3] for lavatory **10** [m^3] for small bathroom **18** [m^3] for dress room **20** [m^3] for small bedroom **50** [m^3] for living room **100** [m^3] for apartment	*Exposure estimation for selected aerosol ingredients*, FEA briefing paper, 21 March 2007 (Correction: 4 February 2009)
Immediate volume of air surrounding head	**1.5** [m^3] (*single point default*)	EC. Technical Guidance Document. *1996; Part I*
Room Volume, Living Room in Germany	**64** [m^3] (*50th percentile*)	EC JRC - IHCP – ECB. Technical Guidance Document. *2003; Part I* • *TGD: Data available pp. 238, Table 7 of the source document* • *TGD refers to Original Source /Document:* ○ Statistisches Bundesamt (Wiesbaden), Germany

Title of Data Set	Value/Unit Data Type	Source Document
Room Volume, Sleeping Room1 (children's room) in Germany	**43** [m^3] (*50th percentile*)	EC JRC - IHCP – ECB. Technical Guidance Document. *2003; Part I* • *TGD: Data available pp. 238, Table 7 of the source document* • *TGD refers to Original Source /Document:* ○ *Statistisches Bundesamt (Wiesbaden), Germany*
Toilet/bathroom (typical EU dimension)	**3.3** [m^3] (*single point default*)	Hartop, P.J., Cook, T.L., and Adams, M.G. Simulated consumer exposure to dimethyl ether and propane-butane in hairsprays *1991 - Int J Cosmet Sci; 13 (4):161-168*
Room volume when using spray paint for hobby use	**20** [m^3] (*single point default*)	Bremmer HJ, Veen van MP Factsheet Algemeen, randvoorwaarden en betrouwbaarheid, ventilatie, kamergrootte, lichaamsoppervlak *1999 - Bilthoven*
Indoor room volume when gluing with a glue for hobby use	**20** [m^3] (*single point default*)	
Room volume of garage at home where car polisher is used	**20** [m^3] (*single point default*)	
Room	**18** [m^3] (*single point default*)	EC – ECB. EU Risk Assessment Report on naphthalene *2003; Vol. 33*
Room height, Toilet/bathroom (typical EU dimension)	**2.3** [m] (*single point default*)	EC – ECB. EU Risk Assessment Report on n-pentane *2003; Vol. 40*
Residence volume of a standard room	**20** [m^3] (*single point default*)	Danish Environmental Protection Agency (Authors: S.E. Laursen, J. Hansen, A. Drøjdahl, O.C. Hansen, K. Pommer, E. Pedersen, and N. Bernth of the Danish Technological Institute) Survey of chemical compounds in textile fabrics *2003 - Survey of Chemical Substances in Consumer Products no. 23*
Volume of hair salon	**40-200** [m3] (*range*)	EC – ECB. EU Risk Assessment Report on Hydrogen peroxide *2003; Vol. 38*
Volume of hair salon	**50-60** [m3] (*range*)	

Title of Data Set	Value/Unit Data Type	Source Document
Volume of hair salon (as a surrogate for modelling exposure to all-purpose cleaners)	**50-60** [m3] (*range*)	EC – ECB. EU Risk Assessment Report on Hydrogen peroxide *2003; Vol. 38*
Room volume when using textile bleach to bleach cloth	**20** [m^3] (*single point default*)	
Residence Volume of the whole house	**292** [m^3] (*single point default*)	EC – ECB. EU Risk Assessment Report on methyl acetate *2003; Vol. 34*
Room with floor area 25 m2	**60** [m^3] (*single point default*)	
Whole house	**292** [m^3] (*single point default*)	
Zone of release/room	**60** [m^3] (*single point default*)	
Zone of release/room from the use of a nail varnish remover	**15** [m^3] (*single point default*)	
Volume in immediate vicinity of user during single usage of a hairspray	**2** [m^3] (*single point default*)	EC – ECB. EU Risk Assessment Report on 1-vinyl-2-pyrrolidone *2003; Vol. 39*
Volume of air around a person using a nail polish product	**5** [m^3] (*single point default*)	EC – ECB. EU Risk Assessment Report on dibutyl phthalate *2004; Vol. 29*
Volume of room where Nail Polish is used	**25** [m^3] (*single point default*)	
Volume in room where carpets are glued	**5** [m^3] (*single point default*)	

Title of Data Set	Value/Unit Data Type	Source Document
Volume of the residence where the ironing by a consumer takes place	**244** [m^3] (*single point default*)	Washburn, S.T., Bingman, T.S., Braithwaite, S.K., Buck, R.C., Buxton, L.W., Clewell, H.J., Haroun, L.A., Kester, J.E., Rickard, R.W., and Shipp, A.M. "Supporting Information" for Exposure assessment and risk characterization for perfluorooctanoate in selected consumer articles *2005 Environmental Science and Technology*
Volume of the room where the ironing by a professional takes place	**50** [m^3] (*single point default*)	
Short term respiration volume	**1** [m^3] (*single point default*)	Danish Environmental Protection Agency (Authors: Nanna Svendsen, Søren F. Pedersen, Ole Chr. Hansen, Eva Pedersen and Nils Bernth) Survey and release of chemical substances in "slimy" toys *2006 - Survey of Chemical Substances in Consumer Products, No. 67*
Average room volume for subjects using hair spray	**30** [m^3] (*single point default*)	Weegels M.F. , *Exposure to chemicals in consumer products*, TU Delft report (April 1997)

Table 9: Room volumes

In addition, specific room volumes and air flow rates have been assigned as default parameters in the RIFM 2-Box Indoor Air Dispersion model (see Appendix C.4. RIFM 2-Box Indoor Air Dispersion model (two-box)). Default parameters for farfield and nearfield exposure estimation are shown in Table 10 below.

Farfield exposure estimation **Rooms**	**Volume of Room** **(Zone 1)** **[m³][a]**	**Volume of Rest of Residence (Zone 2)** **[m³][b]**	**Flow: Room to Outdoor (Zone 1 to Outdoors)** **[m³/min][c]**	**Flow: Rest of Residence to Outdoor (Zone 2 to Outdoors)** **[m³/min][c]**	**Flow: Room to Rest of Residence (Zone 1 to Zone 2)** **[m³/min)[c]**
House (total)	198.5[b]				
Living room	58.0	140.5	0.58	1.41	0.93
Kitchen	15.0	183.5	0.15	1.84	0.93
Bedroom 1	27.0	171.5	n/a	n/a	n/a
Bedroom 2	22.0	176.5	n/a	n/a	n/a
Bathroom	10.0	188.5	0.10	1.89	0.87
Toilet	2.5	196.0	n/a	n/a	n/a
Shed	10.0	188.5	n/a	n/a	n/a
Garage	34.0	164.5	n/a	n/a	n/a
Unspecified	20.0	178.5	n/a	n/a	n/a

[a] RIVM report 320104002/2006, General Fact Sheet, Limiting conditions and reliability, ventilation, room size, body surface area, Updated version for ConsExpo 4, Table 4, Page 14/31.

[b] (Volume of Rest of Residence) = (Volume of House = 198.5 m3) - (Volume of Room).

Volume of house (assumption) = Living room + Kitchen + Bedroom 1+ Bedroom 2 + Bathroom + Toilet + Shed + Garage + Unspecified room = 58 + 15 + 27 + 22 + 10 + 2.5 + 10 + 34 + 20 = 198.5m^3

[c] Calculated air flow rates (confidential industry report). Only values in RIFM 2-Box Indoor Air Dispersion model are shown.

Nearfield exposure estimation **Products**	**Volume of Cloud** **(Zone 1)** **[m³]**	**Volume of Bathroom** **(Zone 2)** **[m³]**	**Flow: Cloud to Outdoor (Zone 1 to Outdoors)** **[m³/min]**	**Flow: Bathroom to Outdoor (Zone 2 to Outdoors)** **[m³/min]**	**Flow: Cloud to Rest of Bathroom (Zone 1 to Zone 2)** **[m³/min)**
Hairspray Fine Fragrance AP Deodorant	1	10	0	1.89	7.24

Justifications for the values in the Nearfield table can be found in Appendix E.1. Consumer exposure to hairspray using the nearfield model

Table 10: Default room volumes and air flow rates for the RIFM 2-Box Indoor Air Dispersion model.

Appendix C – Description of Models

C.1. BAMA/FEA Indoor Air model (one-box)

C.1.1. Description

The BAMA/FEA Indoor Air model is a simple deterministic model for predicting the change of concentration with time of airborne chemicals in a room (see Figure 7).

It assumes that:

i) All emitted material rapidly transforms into vapour or very small particles/droplets that approximate to the behaviour of vapour.

ii) All non-volatile material present in the formulation is contained within the small particles/droplets.

iii) Concentrations are homogeneously distributed throughout the room at all times.

iv) Loss of airborne material occurs only as a result of ventilation in the room.

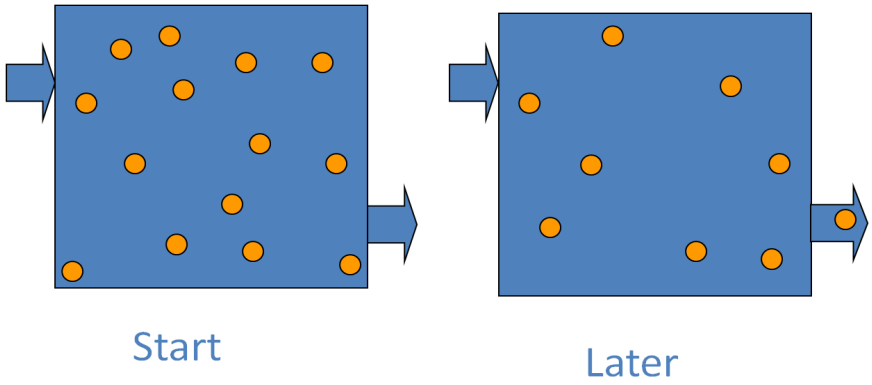

Figure 7: Theoretical behaviour of vapour in a room

This simple approach gives a concentration where all sprayed material is available to be inhaled.

A simple mathematical decay model, applicable to calculate concentration at a given time, triggers the actual concentration by changing the ventilation rate. Thus the concentration at any time after emission is a function of the initial concentration and the ventilation rate and the time elapsed since the emission occurred.

The initial concentration is defined by the amount emitted and the volume of the cloud formed (usually but not necessarily set as the room volume for simplicity).

To calculate the TWA in this model, typical time periods like 15 minutes, 4 hours, 8 hours, 16 hours and 24 hours are taken to reflect short term exposure, workplace exposure and the longer term exposure of people at home (see Table 11).

Input parameters:	
Room volume	[m^3]
Ventilation rate	[1/h]
Weight fraction compound	[%]
Spray duration	[s]
Mass generation (spray) rate	[g/s]
Output parameters:	
Single use Repeat use Continual use Continuous release	Concentration in [mg/m^3] 15-min TWA 4-hour TWA 8-hour TWA 16-hour TWA 24-hour TWA

Table 11: Input-output parameters for the BAMA/FEA Indoor Air model

C.1.2. Using this model for exposure estimation

The key advantages of using the BAMA/FEA Indoor Air model to estimate indoor air concentration of spray products is that it requires minimal input and is fairly easy to generate data on a range of use scenarios. The model is particularly useful for generating time-weighted values for longer term exposures. It was shown that a period of about 2 hours after spraying is necessary to get a homogeneous distribution of volatile ingredients and aerodynamically stable particles (i.e. less than about 10µm) within a room (Lu and Howarth, 1995). Larger particles of non-volatile ingredients are likely to have 'dropped' out of the air either by settling due to gravity or impaction on surfaces in the room. Therefore the model can be confidently used to generate 'conservative' estimates for exposures lasting more than about 2 hours.

However, the BAMA/FEA Indoor Air model has an important limitation when applied to assessment of short-term exposure to spray products/chemicals as an immediate, homogeneous distribution of spray particles/droplets is unrealistically assumed. Experimental evidence (Rowley and Crump, 2005) suggests that a period of up to 2 hours is needed for such situation, affected by a number of parameters such as, the room size; the ventilation rate and the spray jet dynamics. Consequently, the model may not reflect real exposure which will be influenced by the position of the particle receiver (not necessarily the position of the user).

For products sprayed away from the body or on to a horizontal surface, the BAMA/FEA Indoor Air model is likely to over-predict short-term exposure because the 'breathing zone' will be outside of the spray cloud and 'breathed-in' concentrations will be lower than those modelled for the room volume as a whole. The model will therefore give rise to conservative short-term exposure estimates that may indicate a problem when in reality none exists.

On the other hand for products sprayed at the body or a vertical surface directly in front of the user where the spray can bounce back towards the user, the BAMA/FEA Indoor Air model is likely to lead to an under-prediction of short term exposure. In this case the 'breathing zone' will be in the spray cloud and so 'breathed-in' concentrations could be higher than those

modelled for the room volume as a whole. In this case modelling could give false reassurance about the use of an ingredient.

ECHA has suggested that 'under-prediction' could be eliminated by using an initial volume of 2 m^3 for the modelling. For many sprays, the spray cloud will expand quickly beyond 2 m^3 and as a result the estimated exposure might be extremely conservative, but can be used for screening purposes.

However, some cosmetic spray products e.g. hairsprays are intended to be directed to the part of the body which is the breathing zone. For these spray products an initial volume of 2 m^3 is considered to be too large. An alternative is to use an initial volume of 1 m^3 for short-term exposure. To use this model to estimate exposure for using this type a product a two-step process of using a small initial volume of 1 or 2 m^3 for short-term exposure in conjunction with the room volume for longer-term exposures could be used. However, as the BAMA/FEA Indoor Air model is a one-box model and was not developed to reflect this specific use scenarios, used this way it is likely to significantly overestimate exposure. Therefore for these applications measurement or more complex exposure models that take account of particle size distribution, or that model the expansion of the spray cloud more accurately should be considered (Rothe *et al*., 2011).

Exposure Time	Volume to be used in Modelling	
	Sprayed Away from Body	Sprayed towards the Body
Long term >2 hours	Room volume†	Room volume†
Short term <2 hours	Room volume†	2 m^3 - at body but not head or upper torso 2 m^3 - at vertical surface directly in front of user
During use <5 min	Room volume†	2 m^3 - at body but not head or upper torso 2 m^3 - at vertical surface directly in front of user 1 m^3 - at the head or upper torso

† The room volume will vary depending upon where the spray product is used, i.e. bathroom, living room etc.

Table 12: Recommended volume for use with the BAMA/FEA Indoor Air Model

C.2. RIVM ConsExpo 4.1 models (one-box)

ConsExpo is a consumer exposure model developed by RIVM for the estimation of internal or external exposure to chemicals via the dermal, oral and inhalation route. Each product scenario is pre-populated with default values for specific product types. These are referenced in a series of product factsheets (available via the RIVM website). All default values can be overwritten by actual ones, specific for the product to be evaluated.

The current version, ConsExpo 4.1, contains 2 models for estimating inhalation exposure: 'Exposure to Spray' and 'Exposure to Vapour'. The Spray model describes inhalation of aerosolised particles/droplets with non-volatile or slowly evaporating compounds whereas the Vapour model describes the inhalation of volatile compounds evaporating from a surface into the air. Both permit the calculation of an air concentration or a systemic dose and the key features are outlined below. It is advisable to also explore the RIVM product factsheets and

program manual in more detail prior to utilising the model (RIVM website, Delmaar *et al.*, 2004).

C.2.1. RIVM ConsExpo 4.1 'exposure to spray' model

The 'Exposure to Spray' model describes inhalation exposure to non-volatile or slowly evaporating compounds present in droplets that are released from an aerosol or trigger spray. It assumes that larger particles/droplets either settle quickly from the air (so are not available to the respiratory tract) or are deposited in the upper airways. The latter will result in a clearance by mucociliary transport or coughing with a certain possibility to swallow. Only particles/droplets small enough to reach the alveolar region will result in relevant exposure.

The general parameters that need to be defined for this model are the dimensions of the room and its ventilation rate, the person's exposure duration and the spray duration. Notably, the exposure duration includes time spent in the room after spraying. The spray duration is defined as the duration of the spraying process from start to finish, which may differ from the period of active spraying. The model assumes that products are sprayed away from the body (e.g. bathroom trigger spray) unless the user specifies that spraying is directed towards the exposed person (for example in the case of cosmetic products). For products sprayed towards the consumer, it is assumed that the exposed individual is situated within the spray cloud, the volume of which can be defined. After 1 second, the volume of the cloud is assumed to increase linearly until spraying ends or the volume reaches that of the room of interest. The exposed individual is assumed to remain within the cloud during the spray duration, after which the spray is evenly distributed in the specified room.

The air concentration is based on the fraction of airborne particles/droplets composed of non-volatile material. The particles/droplets are assumed to be homogeneously distributed within the volume of the room or cloud and loss of particles/droplets from the air occurs by ventilation and gravitational precipitation.

The input parameters for the spray model will vary slightly depending on the product type selected. The input and output parameters are shown in Table 13.

Input parameters:	
Frequency	[per year]
Body weight	[kg]
Room volume	[m^3]
Ventilation rate	[per hour]
Exposure duration	[min]
Spray duration	[min]
Cloud volume	[m^3]
Room height	[m]
Mass generation rate	[g/s]
Airborne fraction	Fraction
Weight fraction non-volatile	Fraction
Weight fraction compound	Fraction
Density non-volatile	[g/cm^3]

Input parameters:	
Initial droplet distribution	Normal (mean & standard deviation) or lognormal (median & coefficient of variation (fraction) Maximum diameter in [µm]
Inhalation cut-off diameter	[µm]
Spray direction	(towards a person or from a person)
Uptake fraction	Fraction
Inhalation rate	[L/min]
Output parameters:	
Mean event concentration	[mg/m^3]
Mean concentration on day of exposure	[mg/m^3]
Mean concentration yearly	[mg/m^3]
Acute (internal) dose	[mg/kg bw]
Chronic (internal) dose	[mg/kg bw/day]

Table 13: Input-output parameters for the ConsExpo 4.1 'spray' model

Note: A beta version of ConsExpo (v.5) has been released on the RIVM website recently. Improvements include a first tier mode for the 'exposure to spray' model. This simplified mode assumes the sprayed material is released immediately and is removed by ventilation only. In addition, new values for the mass generation rate and the particle size distribution, based on spray data, have been added. The particle size distribution has also been adjusted to describe the distribution of the smaller particles/droplets in a more conservative manner. A release date for the final version has not yet been confirmed.

C.2.2. RIVM ConsExpo 4.1 'exposure to vapour' model

The 'Exposure to Vapour' model describes a scenario where a compound evaporates from a surface into the air of a room. This could be, for example, evaporation from a surface that has been cleaned by a bathroom trigger spray. The subsequent air concentration is dependent on the room size and ventilation rate, the amount of compound, its vapour pressure and its release rate into the air. The model offers three modes options developed to adequately calculate the release of the compound into the room: "Instantaneous release", "Constant rate" and "Evaporation". The key input parameters for this model and the output parameters are shown in Table 14.

Input parameters:	
Frequency	[per year]
Body weight	[kg]
Room volume	[m^3]
Ventilation rate	[per hour]
Exposure duration	[min]
Weight fraction compound	fraction

Output parameters:	
Inhalation mean event concentration	[mg/m³]
Inhalation mean concentration on day of exposure	[mg/m³]
Inhalation air concentration year average	[mg/m³/day]
Inhalation acute (internal) dose	[mg/kg]
Inhalation chronic (internal) dose	[mg/kg/day]

Table 14: General input-output parameters common to the Instantaneous release, Constant rate and Evaporation modes in the ConsExpo 4.1 'vapour' model

The "Instantaneous release mode", which can be used as a first tier approach, describes a compound that is instantly released into a room. The clearance of this room is maintained by an increased ventilation and a reduction of emission in to this room. It is recommended that this mode should be selected for volatile compounds with high diffusion rates or if no information is available on the emission duration.

The "Constant rate mode" assumes that the compound is released at a constant rate and removal from the air is by ventilation. This mode can be used if the evaporation properties of the chemical are unknown but an estimation of the emission duration cannot be made.

The "Evaporation mode" has the greatest number of data requirements, describing the surface area from which the compound evaporates, the duration of application and the rate of release of the chemical. The user can specify whether the surface area is constant (e.g. a treated floor) or is increasing over time (e.g. a wall being painted). The release rate requires information on the temperature of the room, physicochemical properties of the compound (such as vapour pressure), and the mass transfer rate. The mass transfer rate describes how quickly the evaporated substance is removed from the product surface. It can be defined using Langmuir's method (which assumes rapid diffusion and is likely to overestimate the evaporation rate) or Thibodeaux's method (which results in a lower rate but is suited to evaporation of a substance from water). Both methods are described in more details in the introduction to apply this model. Finally, the user must also calculate the molecular weight of the matrix using equation provided, unless the product is composed entirely of the compound of interest.

The RIVM ConsExpo 4.1 models for exposure estimation have the following limitations:

1. The Spray model is based on relatively complicated mathematical modelling. Exposure takes into account particle size distribution, expansion of the spray cloud over time (for products aimed towards the body) and particle loss from the atmosphere via gravitational settling. These require a good understanding of the use characteristics of the product, the formula and the model itself, although default values are available. Some of the sub-models within the Vapour model also require understanding of how the compound is released (release area and duration) and the mass transfer rate (to describe the speed at which the substance evaporates from the product surface). The relative complexity of these models means the user really needs to take time to familiarise themselves with the input parameters, product characteristics and limitations of the models prior to exposure estimation.
2. The Spray model makes the simplified assumption that following release of particles, immediate homogeneous mixing occurs within a specified cloud or room volume. However, in reality, a spray cloud takes time to evenly distribute in a room and therefore

an individual's exposure will depend on their position in the room as the cloud disperses. For products sprayed away from the body, this model does not consider dispersion of the cloud over time and therefore may overestimate short term inhalation exposure if the exposed individual is actually positioned outside the spray cloud. However for products aimed towards the body, expansion of the spray cloud over time is taken into account using simplified modelling. Similarly, the vapour model assumes homogeneous mixing within a specified room volume, although the rate of release can be specified by 1 of 3 evaporation models.

3. Another limitation of the Spray model is that it assumes propellants and solvents evaporate rapidly from airborne droplets after spraying, and consequently these particles are composed of only non-volatile components. The user is therefore advised by RIVM that the Vapour model is more appropriate for volatile substances. Additionally, the Spray model does not describe bounce back of particles or deposition of particles in specific areas of the respiratory tract. Also, whilst particle loss occurs via gravitational settling and air exchange, deposition on walls is not accounted for.

4. The Spray and Vapour models are likely to produce relatively high exposure estimates due to the conservative assumptions and percentiles used for the default parameters. This is not necessarily a limitation in itself as it is appropriate to determine a 'reasonable worst-case' exposure estimate to cover certain exposed people. However, over prediction of exposure may incorrectly indicate a safety issue and exposure will have to be refined using product specific data, higher tier modelling or measurement. It is not possible to determine if the Spray model significantly overestimates consumer exposure to chemicals as there are no published comparisons of model estimates with measured data for spray products under typical use conditions.

C.3. BAuA SprayExpo 2.0 model (one-box)

(Baughman *et al.*, 1994; CEN, 1992; Drescher *et al.*, 1995; Hinds, 1999; Koch *et al.*, 2012; US EPA, 2011)

The model calculates the airborne concentration of the respirable, the thoracic and the inhalable (Figure 1), or any other meaningful size fraction of aerosols generated during working processes. Special attention is directed to aerosols containing biocidal substances in indoor environments originating from the release of liquid biocidal sprays. From the calculated concentration the inhalation as well as the dermal exposure is determined. Long term emissions of vapours from walls and other surfaces are not included.

It is assumed that the sprayed product is composed of a non-volatile substance dissolved in a solvent with known volatility. The model is based on a simulation of the motion of released droplets taking into account gravitational settling, turbulent mixing with the surrounding air, and droplet evaporation. In the model, continuous spatial release patterns can be simulated. No artificial distribution volumes need to be defined. In the calculation of the inhaled dose and the dermal dose the spatial distribution of the concentration is explicitly taken into account.

The main input parameters are: the released droplet spectrum, the release rate, the concentration of the non-volatile substance, the spatial and temporal pattern of the release process (surface spraying against floor, ceiling, wall; room spraying), the vapour pressure of the liquid, the size of the room and the ventilation rate. The path of the sprayer can be explicitly included into the model. The user can select standard scenarios with predefined default values or can select these input parameters freely.

For surface treatment by spraying, a droplet deposition module is incorporated in the program package. This module calculates the fraction of non-impacting droplets which are relevant for human exposure. The improved version takes into account the entrainment of air into the spray jet according to Bernoulli's principle. This leads to a decrease in the droplet deceleration that is due to air friction, resulting in an increased operating distance of the spray compared to injection of the droplets into still air.

The first level is an input form for the definition of general data such as room size, room ventilation rate, turbulent intensity, nozzle and spray parameters as well as relevant parameters of the spray liquid. The second level allows for the definition of the spray path and the release rate. It also provides an adjustable 3D image of the room including the spray pattern. The third level is the report level that contains the calculated values listed in an EXCEL spreadsheet, a concentration vs. time diagram and the time integrated inhaled and deposited dose of non-volatile substance.

Input parameters:	
Released droplet spectrum	[µm] (% fraction of each size range)
Release rate	[ml/s]
Concentration of the non-volatile substance	This is assumed to be 100% as the model only quantifies the non-volatile fraction of a spray product
Spatial and temporal pattern of the release process	Surface spraying against floor, ceiling, wall; room spraying
Vapour pressure of the liquid	[mmHg]
Room size (volume)	[m^3]
Room ventilation rate (air exchange rate)	[per hour]
Human minute ventilation	[L/min]
Output parameters:	
Inhaled dose	[mg]
Average concentration	[mg/m^3]

Table 15: Input-output parameters for the BAuA SprayExpo 2.0 model

The main limitation of this model is that the spray process of the non-volatile substance will be either liquid droplets or remain as dry aerosol particles after complete evaporation of the solvent. The exposure to the volatile solvent is not calculated in this program.

C.4. RIFM 2-Box Indoor Air Dispersion model (two-box)

The RIFM 2-Box Air Dispersion model is an indoor environment air model that characterizes the dispersion of a single chemical inside two connected enclosed "zones" or "boxes" (both terms are used interchangeably in the context of this model), and determines air exposure concentrations. Inputs to this model include chemical source parameters, zone volumes, and air flow parameters. Model outputs include a temporal profile of chemical concentrations in the two zones.

Chemical source exposures can occur from two mechanisms:

i) Release of chemical in one or both zones (e.g., the use of a consumer product that contains the chemical of interest) and

ii) Infiltration of chemical present in outdoor air into the indoor zones.

Chemical source exposures can be instantaneous, constant over a period of time, or intermittent with specified frequencies.

When human activity pattern information (time spent in the two zones, product use characteristics) and human factors such as inhalation rate (volume per unit time), body weight and inhalation fraction absorbed into body are provided, inhalation exposure can be defined and the exposure dose can be calculated for the exposed time period.

The model incorporates the following basic assumptions:

i) The concentration in Zone 1/Box A (source room/room of interest or the immediate breathing zone of an individual) and Zone 2/Box B (rest of the residence or, in the case of evaluating the immediate breathing zone, the room in which the individual is standing) are homogeneous.

ii) All chemical losses are treated through a single degradation term. This term, which is assumed to be a first-order loss term, is represented by a degradation half life.

iii) 100% of what is inhaled is absorbed.

iv) One day is defined as a 24-hour time period and is not limited to a specific time period of a day.

The RIFM 2-Box Indoor Air Dispersion model is inappropriate to represent indoor environments that are large enough to contain stratified levels of a chemical.

The key input parameters for aerosols and the output parameters are shown in Table 16.

Input parameters:	
Spray rate	[g/s]
Spray duration per use	[s]
Uses per day	
Room volume	[m^3]
Room air exchange with outdoors	[m^3/min]
Residency time in room per day	[h]
Room air exchange between room and the rest of the house	[m^3/min]
Room air exchange between outdoors and the rest of the house	[m^3/min]
Residency time in the rest of the house per day	[h]
Inhalation rate	[L/min]

Output parameters:	
Zone 1/Box A Peak Concentration	[mg/m^3]
Zone 2/Box B Peak Concentration	[mg/m^3]
Peak Exposure Rate	[mg/min]
Total Cumulative Exposure	[mg]
Total Exposure/Body Weight	[mg/kg]

Table 16: General input-output parameters for aerosols

Currently, for RIFM members only, the tool can be downloaded at: http://rifmdatabase.rifm.org/nd/Login.cfm

For non-RIFM subscriber access, please visit www.rifm.org

C.5. RIFM Computational Fluid Dynamics (CFD) and Multiple Path Particle Deposition (MPPD) Model

(Asgharian, Price *et al.*, 2011; Asgharian *et al.*, 2012; Conolly *et al.*, 2004; Garcia and Kimbell, 2009; Garcia, Schroeter *et al.*, 2009; Kimbell, Subramaniam, *et al.*, 2001; Overton, Kimbell *et al.*, 2001; Schroeter, Kimbell *et al.*, 2006a; Schroeter *et al.*, 2006b; Schroeter, Kimbell *et al.*, 2012; Schroeter, Kimbell *et al.*, 2006b; Asgharian, Price *et al.*, 2012).

The uptake of vapour and deposition of particulate components can be studied by computational models of the nasal and lung airways of humans and rats. Detailed computational fluid dynamics simulations for the upper airways of the respiratory tract allow for the computation of losses of inhaled materials, while a whole-lung dosimetry modelling approach models material losses in lung airways.

Exposure information obtained from the literature, or provided by the end user, can be fed into the models e.g. to calculate losses in the nasal airways and lungs of humans and rats. Coupled human-rat deposition modelling allows for interspecies data extrapolation using laboratory measurements to assess human health risk from exposure to inhaled materials.

Two different approaches are adopted in calculating losses in the respiratory tract depending on available information on airway geometry and the desired level of predictions.

The first approach is site-specific modelling for which the precise geometry of the region of interest as well as information on airflow and compound transport at the boundaries (inlet and outlets) of the geometry are known. This approach is most useful at the entry port to the respiratory tract (i.e., nasal and oral airways) for which airway passages are reconstructed from scanned images of airway coronal sections and combined with breathing information to form anatomically- and physiologically-realistic geometric models. Since the full transport equations with the full account of dominant physical mechanisms are solved, detailed information regarding the airflow and compound losses to the airway walls is obtained, however, at the expense of a heavy computational cost.

The second approach is whole-lung modelling in which airways are described dimensionally but precise detail configuration (e.g. curvature and other artifacts) is neglected. By simple description of the geometry, the entire respiratory tract can be studied. In addition, the transport equations are made manageable by making simplifying assumptions as to include major mechanisms influencing transport but neglecting higher order effects such as local variation in airflow and particle transport due to unsmooth geometry. The whole-lung modelling approach is ideal when considering deposition in the entire lung for which site-specific modelling is

handicapped by enormity of the lung airways and lack of information on ventilation distribution in the lung. As a result of making simplifying assumptions, computations can be carried out in a relatively short time, however, detailed, site-specific deposition information are either unavailable or unreliable.

C.5.1. Site-specific modelling: nasal uptake and deposition calculations

Deposition of inhaled materials in the nasal passages is needed not only to determine the amount entering the lung, but also to assess nasal tissue dose since many inhaled compounds have been shown to elicit effects in rodent nasal passages (Kimbell *et al.*, 2007). Anatomically accurate three-dimensional reconstructions of the rat and human nasal passages have been constructed for use in airflow and mass transfer studies (Subramaniam *et al*., 1998). Steady-state inspiratory and expiratory airflow is simulated by numerically solving the Navier-Stokes equations to obtain velocity and pressure at every nodal point in the computational mesh.

Methods are currently in place to compute mass transfer of inhaled material in the nasal passages of rats and humans. Vapour uptake is governed by molecular diffusion onto airway walls and is a function of the chemical solubility, diffusivity, and metabolic/clearance processes in nasal mucosa. Boundary conditions for vapour absorption at the air-mucus interface of the nasal models incorporate these physical constants and will use available reactivity/metabolism information that can be obtained from the literature. Deposition of inhaled particles assumes a perfect particle absorption condition on nasal airway walls where deposition is a function of diffusion and inertial impaction for ultrafine and coarse particles, respectively.

C.5.2. Whole lung modelling: regional and total lung uptake and deposition calculations

Lung airway dimensions span over multiple scales ranging from centimetres to micrometres. Lung reconstruction from scanned images can be made only for the first few airway generations of the lung conducting airways. Outlet boundary conditions, that incorporate lung compliance, are constructed based on pressure information in the pleural cavity. Pressure in the pleural cavity is gravity dependent and varies vertically. In addition, pleural pressure varies with the time into the breathing cycle and breathing frequency adding complications to detailed computations of lung ventilation. Hence, fluid dynamics analysis (site-specific modelling) in the deep lung is severely limited by the lack of detailed information on lung geometry and pressure information.

To facilitate particle deposition computations in the lung, lung geometry is assumed to be a collection of cylindrically-shaped tubes arranged as a dichotomous branching network. Airway dimensions and orientations are calculated from available measurements. Additional volumes are added to respiratory bronchial airways in the acinar region to account for the alveolar space. Mathematical models of airflow and particle transport in the model geometry are developed and solved to calculate vapour uptake and particle deposition.

The most popular lung geometry for humans is the typical-path lung structure obtained from limited airway measurements in the lung (Weibel, 1973). The lung geometry is assumed to consist of 23 airway generations, of which the first 16 generations comprise the tracheobronchial region (conducting airways), and the last 7 generations form the alveolar region. Using measurements of Raabe *et al*. (1976), Yeh and Schum (1980) constructed a similar typical path, but additionally developed a 5-lobe lung model with each lobe being symmetric but different in dimensions. Koblinger and Hofmann (1985) further expanded the human geometric model by using measurements of Raabe *et al*. (1976) to create stochastic lung

geometries that were asymmetric and closely resembled the anatomical structure of the lung. However, airway shapes were still cylindrical and deviated from reality. In rats, Anjilvel and Asgharian (1995) created an asymmetric lung geometry based on measurements of Raabe *et al*. (1976).

A number of deposition models are available in the literature for the calculations of vapour uptake and particle deposition. Early deposition models were compartmental and limited in predictive capability. More realistic deposition models assumed the lung to expand and contract uniformly and resembled a trumpet in shape when symmetric lung geometry was assumed (Yu, 1978). These models have been validated for regional deposition fractions. The human lung has an asymmetric branching structure that affects both airflow and particle deposition. Asgharian *et al*. (2001) used the multiple-path analogy in 10 stochastically generated lungs of human adults to calculate site-specific and regional deposition of particles. The stochastic lungs were based on morphometric measurements of Raabe *et al*. (1976) and developed by Koblinger and Hofmann (1985). Significant dose variations among the lung structures were found, which indicated intersubject variability in the population to some extent.

Deposition models based on asymmetric lung geometries (Asgharian *et al*., 2001) offer an advantage over previous models in that lung physiology and morphometric variability within each generation are accounted for. These two parameters are shown to be most critical in accurate microdosimetry predictions of particles in the lung (Asgharian *et al*., 2001; Subramaniam, et al., 2003; Asgharian *et a*l., 2004).

Mechanistically-based computational models of fragrance materials particle deposition and vapour uptake were developed in the respiratory tracts of humans and rats. Modelling efforts focused on two components – consisting of the upper and lower respiratory tracts – since deposition and absorption into airway tissues are likely to occur in both sites. In addition, particle deposition and vapour uptake in the nasal passages are needed to determine the amount that enters the lung.

Human exposure to most inhaled materials will occur to both vapour and particle phases where the materials are generated by spray atomization (Rogers *et al*., 2005). For highly volatile components of the inhaled materials, one-way transfer of vapour from the particle to vapour phase occurs rapidly. On the other hand, low vapour pressure components of the fragrance materials tend to stay in particulate phase with little or no evaporation. Components with medium vapour pressure (near that of water) will equilibrate to stay in both the vapour and particulate phases. Additional phase change may occur for medium vapour pressure components of the fragrance materials during the transit of the fragrance materials through the respiratory tract.

Different approaches are needed for calculations of airborne material losses in the nose and lung depending on the vapour pressure of the compound. The most general approach is for medium vapour pressure compounds for which continuous vapour/liquid transfer occurs. The computation is fairly involved. Assessment of the delivered dose of medium vapour pressure components to the respiratory tract consist of simultaneous computations of the limiting cases and accounting for vapour transfer across the two phases. The approach to calculating lung deposition of uptake of inhaled materials is given in the Table 17.

Saturation Vapour Pressure	Comments
High	Due to their high saturation vapour pressure, these compounds will completely evaporate to the vapour phase upon inhalation. Concentration levels and tissue uptake rates will be determined throughout the respiratory tracts of rats and humans.
Medium	These compounds will be present in both the particulate and vapour phases, with equilibrium levels changing as they travel through the respiratory tract due to different deposition rates of the two phases. A new dosimetry modelling approach will be developed that accounts for particle-vapour interaction in the nose and lung.
Low	Due to their low saturation vapour pressure, these compounds will be assumed to stay in the particulate phase with no evaporation to the vapour phase. Particle deposition locations will be predicted in the nasal passages and in all airway generations of the lungs for rats and humans.

Table 17: Pressure characteristics for consideration

C.6. Summary of key parameters for the different models

Table 18 summarises the key parameters for each of the above-mentioned models for inhalation exposure estimation.

Model	Input parameters	Output parameters
BAMA/FEA Indoor Air model (one-box)	Room volume Ventilation rate Weight fraction compound Spray duration Mass generation (spray) rate	Concentration in [mg/m^3] 15-min TWA 4-hour TWA 8-hour TWA 16-hour TWA 24-hour TWA
RIVM ConsExpo 4.1 – 'spray' model (one-box)	Frequency Body weight Room volume Ventilation rate Exposure duration Spray duration Cloud volume Room height Mass generation rate Airborne fraction Weight fraction non-volatile Weight fraction compound Density non-volatile Initial droplet distribution Inhalation cut-off diameter Spray direction Uptake fraction Inhalation rate	Mean event concentration Mean concentration on day of exposure Mean concentration yearly Acute (internal) dose Chronic (internal) dose

Model	Input parameters	Output parameters
BAuA SprayExpo 2.0 model (one-box)	Released droplet spectrum Release rate Concentration of the non-volatile substance Spatial and temporal pattern of the release process Vapour pressure of the liquid Room volume Room ventilation rate Human minute ventilation	Inhaled dose [mg] Average air concentration [mg/m^3]
RIFM 2-Box Indoor Air Dispersion model (two-box)	Spray Rate Spray Duration Uses per day Duration of use per day Product used per day Residency time in room per day Residency time in the rest of house per day Inhalation rate Concentration of material of interest Volume: Room of Interest [m^3] Volume: Rest of House ([m^3)] Air Flow: Room of Interest → Outdoor [m^3/min] Air Flow: Rest of House → Outdoor [m^3/min] Air Flow: Room of Interest → Rest of House [m^3/min] Daily Duration: Room of Interest (min) Daily Duration: Rest of House [min]	Zone/Box1 Peak Concentration [mg/m^3] Zone/Box2 Peak Concentration [mg/m^3] Peak Exposure Rate [mg/min] Total Cumulative Exposure [mg] Total Exposure/Body Weight [mg/kg]

Model	Input parameters	Output parameters
RIFM Computational Fluid Dynamics (CFD) and Multiple Path Particle Deposition (MPPD) model	Material specific data	Head deposition fraction during inhalation Lung deposition fraction during inhalation Total lung deposition fraction during pause Head deposition fraction during exhalation Lung deposition fraction during exhalation Total head deposition fraction Total Tracheobronchial deposition fraction Total pulmonary deposition fraction Total deposition fraction Head deposited mass rate [µg/min] Tracheobronchial deposited mass rate [µg/min] Pulmonary deposited mass rate [µg/min] Total deposited mass rate [µg/min] Total deposition fraction in conducting airways Total deposition fraction in conducting airways during inhalation Total deposition fraction in conducting airways during pause Total deposition fraction in conducting airways during exhalation Total deposition fraction in alveolar region Total deposition fraction in alveolar region during inhalation Total deposition fraction in alveolar region during pause Total deposition fraction in alveolar region during exhalation Mass Deposition per Alveolus [mg] Mass Deposition per Macrophage [mg] Number of Particles per Alveolus Number of Particles per Macrophage Airway deposition fraction (Tracheobronchial + Alveolar)

Table 18: Most important parameters for some models

Appendix D – Worked example – Safety assessment with a 1-box model

The BAMA/FEA Indoor Air model has been used for the exposure assessment.

The tool can be downloaded at: http://www.bama.co.uk/viewPublication.php?id=18

Hazard assessment:

Ingredient A has a sufficient hazard which makes an exposure assessment necessary to demonstrate safety.

Exposure assessment:

Input parameters:

In this example, a spray product, containing an ingredient A at 0.5 %, is used once in a small bathroom.

The following use patterns have been arbitrarily chosen, but may be different depending of the spray product:

Room size [m^3]	Air changes [$hour^{-1}$]	Spray time [s]	Discharge rate[1] [g/s]
10	0.6	3	0.7

[1] including propellants and solvents.

Output parameters:

The estimated exposure calculated with the BAMA/FEA Indoor Air model is:

Ingredient A [% w/w]	Initial concentration [mg/m^3]	15-min TWA [mg/m^3]	8-hours TWA [mg/m^3]	24-hours TWA [mg/m^3]
0.5	1.1	1.0	0.2	0.1

Risk Characterisation

The safety assessment is completed by comparison of the calculated exposure with the relevant DNEL for this ingredient. For the purpose of this example assume that the spray product is used by consumers and the exposure being considered is 24 hours. If a 24 hour DNEL is available for the ingredient being considered then this is the relevant DNEL to use.

However if the relevant DNEL is not available it can be estimated using the methodology described in Appendix F – Derived No Effect Level. For example, Ingredient A has a reported short term exposure (15 minute) DNEL for inhalation of 50 mg/m^3 which needs to be converted to the relevant exposure time.

A DNEL for 24 hour exposure (assuming the same exposure scenario e.g. consumer use) can be derived using the linear extrapolation by modifying Equation 6 of Appendix F – Derived No Effect Level, i.e.:

$$24\text{h DNEL} = 15\text{Min DNEL} \sqrt[n]{\left(\frac{t1}{t2}\right)}$$

Where: t1 = 15 minutes, t2 = 1440 minutes (24 x 60 minutes), n =1.

In this example:

$$24\text{h DNEL} = 50\ \text{mg/m}^3 \text{ x } \frac{15}{1440} = 0.52\ \text{mg/m}^3$$

If the exposure scenarios are different (e.g. professional use versus consumer use) then appropriate Assessment Factors must be applied (see Table 21 in

Appendix F – Derived No Effect Level).

The Risk Characterisation Ration is then obtained by comparing the modelled exposure with the estimated DNEL:

$$\text{RCR(inhalation)} = \frac{\text{Exposure}}{\text{DNEL}} = \frac{0.1}{0.52} = 0.19$$

The RCR is < 1 and therefore there is no cause for concern or risk reduction measures are not necessary as far as the inhalation route is concerned.

Remark

For products sprayed away from the body, like aerosol air fresheners, the BAMA/FEA Indoor Air model is likely to over-predict short-term exposure because the 'breathing zone' will be outside of the spray cloud and 'breathed-in' concentrations will be lower than those modelled for the room volume as a whole. The model therefore gives rise to conservative short-term exposure estimates that may indicate a problem when in reality none exists.

Appendix E – Worked example – Safety assessment with a 2-box model

The RIFM 2-Box Indoor Air Dispersion model was used to determine consumer exposure to Ingredient A in a hairspray (nearfield) and an air freshener (farfield). The model is already prepopulated with default parameters for these two product types.

E.1. Consumer exposure to hairspray using the nearfield model

This scenario assumed that the consumer applied hairspray in the bathroom by spraying the product towards the body, specifically at the head (e.g. hairspray).

Scenario: An adult applies a hairspray and spends 2 minutes in 'head cloud' (during spraying) followed by 18 minutes in the bathroom. The data are used to calculate the air concentrations of Ingredient A (present at 0.5 % in the product) and its systemic exposure.

When entering values into the model, it should be noted that Ingredient A is present at 0.5% in this example as a component of the whole product which is considered 100%.

The input parameters and their references are summarised below.

Parameter	Value	Justifications and references
Zone 1 (and volume)	1 m^3	Head cloud – Sahmel *et al.,* 2009.
Zone 2 (and volume)	10 m^3	Bathroom – ConsExpo 4.1.
Air Flow rate (Zone 1 to Outdoors)	0 m^3/min	There is no air flow from the cloud (zone 1) to the outdoors. The exchange between the near field and far field within 2 minutes is minuscule and therefore set to be 0.
Air Flow rate (Zone 2 to Outdoors)	1.89 m^3/min	Calculated for bathroom to outdoors, confidential industry report.
Air Flow rate (Zone 1 to Zone 2)	7.24 m^3/min	Calculation using 3 m/min air flow velocity. (Indoor air velocities reported as 0.05 to 0.3 m/s in National Academy of Sciences *Clearing the Air: Asthma and Indoor Air Exposures Report, 2000*. Lower value from range was used as a conservative approach). To calculate air exchange from near field to far field considering 1 m^3 near field sphere and 3 m/min air velocity → Air exchange= (β) Beta= $1/2(4\pi*0.62^2)*3$ = 7.24 m^3/min (0.62m = radius of the near field sphere of 1 m^3). (Nicas, 1996).
Product spray rate	5330 mg/min	PCPC (US Personal Care Products Council) 90th percentile value for hairspray use per application.
Ingredient A spray rate	26.65 mg/min	Based on 0.5% Ingredient A in final product and the spray rate mentioned above.

Parameter	Value	Justifications and references
Duration of product discharge	0.24 min	The ConsExpo 4.1 spray duration is 0.24 min but whole numbers may be used as well.
Adult bodyweight	60 kg	Average ideal bodyweight for an adult.
Adult daily inhalation rate	9 L/min or 0.009 m^3/min	Assuming light to moderate activity (US EPA, 1996) Exposure Factors Handbook [Draft]. U.S. Environmental Protection Agency, National Center For Environmental Assessment, Washington D.C. EPA/600/P-95/002Ba).
Time spent in Zone 1	2 min	ConsExpo 4.1 assumes that during the use of the spray (the actual spraying) the breathing zone of the exposed person is located inside the cloud volume (page 16 RIVM Factsheet). The actual spray time can be set for 2 minutes as this would be the length of time a person would be within the cloud according to Rothe *et al.*, 2011. Note: '2 minutes' is not the default value in the model.
Time spent in Zone 2	18 min	Rothe *et al.*, 2011. Note that '18 minutes' is not the default value in the model.
Number of simulations	1	This is the default value in the 2-box model to inform that the simulation takes place over 1 day
Number of events/day	1.49	PCPC data average

Zone 1 Peak Concentration:	3.351 mg/m³
Zone 2 Peak Concentration:	0.579 mg/m³
Peak Exposure Rate:	0.030 mg/min
Total Cumulative Exposure:	0.040 mg
Total Exposure/Body Weight:	0.001 mg/kg

Table 19: Results summary

Alternative input parameters can also be used in the 2-box model for hairsprays. For example, the Dutch *National Institute for Public Health and the Environment* (RIVM) quotes a shorter exposure time of 5 minutes (Bremmer *et al.*, 2006a).

E.2. Consumer exposure to an air freshener using the farfield model

Input parameters used to model adult exposure to product sprayed into the air (e.g. aerosol air freshener) in a bathroom.

Scenario: Adult spends 54 minute in the bathroom during a 24 hour period with a total of 6.5 seconds of spray during the day. Evaluating the dispersion of 0.04% Ingredient B from the product. Aerosol air fresheners are most commonly used in the bathroom on an episodic basis. Spray rates are 1.5 g/second, and typical use suggests that these products are sprayed 6.5 seconds per day, which translates into a daily usage of 9.75 g of product.

When entering values into the model, it should be noted that Ingredient B is present at 0.04% in this example as a component of a portion of the formulation accounting for 0.5% of the total product.

Parameter	Value	Justifications and references
Zone 1 (and volume)	10 m^3	Bathroom- ConsExpo 4.1.
Zone 2 (and volume)	188.5 m^3	Rest of the residence. Calculated based on house/room volume assumptions (EU values) from ConsExpo and confidential industry data (see Table 10).
Air Flow rate (Zone 1 to Outdoors)	0.10 m^3/min	
Air Flow rate (Zone 2 to Outdoors)	1.89 m^3/min	Calculated for bathroom to outdoors, confidential industry report (see Table 10).
Air Flow rate (Zone 1 to Zone 2)	0.87 m^3/min	Calculated for bathroom to rest of residence, confidential industry report (see Table 10).
Product spray rate	1.5 g/s	Confidential industry data.
Ingredient B spray rate	0.0006 g/s	Based on 0.04% Ingredient B in final product and the spray rate above: 1.5 g/s x 0.04% = 0.0006 g/s.
Duration of product discharge	5 s	Torfs, *et al.*, 2008.
Adult bodyweight	60 kg	Average ideal bodyweight for an adult.
Adult daily inhalation rate	9 L/min or 0.009 m^3/min	Assuming light to moderate activity (US EPA (1996) Exposure Factors Handbook [Draft]. U.S. Environmental Protection Agency, National Center For Environmental Assessment, Washington D.C. EPA/600/P-95/002Ba).
Time spent in Zone 1	54 min	Torfs, *et al.*, 2008.
Time spent in Zone 2	936 min	Torfs, *et al.*, 2008.
Number of simulations	1	This is the default value in the 2-box model to inform that the simulation takes place over 1 day.
Number of events/day	1.3	Torfs, *et al.*, 2008 – note that 5 s x 1.3 events = 6.5 seconds use per day.

Zone 1 Peak Concentration:	0.00195 mg/m^3
Zone 2 Peak Concentration:	6.96484E-05 mg/m^3
Peak Exposure Rate:	0.00001755 mg/min
Total Cumulative Exposure:	0.000251693 mg
Total Exposure/Body Weight:	4.19488E-06 mg/kg

Table 20: Results summary

Appendix F – Derived No Effect Level

The Derived No-Effect Level (DNEL) is defined in the REACH Regulation as the level of exposure above which humans should not be exposed; it is based on the methodology used for the well-established ecotoxicological principle of the Predicted No-Effect Concentration (PNEC) which is the concentration of an ingredient below which adverse effects in the environmental sphere of concern are not expected to occur. The risk to humans can 'be considered to be controlled' if exposure levels predicted from the Exposure Scenarios for the intended use(s) do not exceed the appropriate DNEL(s).

DNELs are to be derived (data permitting) for all human health end points for the likely exposure routes, durations and frequency of exposure for all chemicals covered by REACH. Ideally DNEL should be based on toxicological data such as NOAEL or LOAEL for the various times of exposure and repeat doses likely to be experienced.

However, if human data is not available (as is likely in many cases), DNELs can be derived from data of toxicity studies on animals by the methods described in Chapter R.8 of the ECHA IR/CSA guidance (ECHA, 2012a). If suitable data is not available for the ingredient, then other techniques such as 'read across' of data from analogous chemicals may be used.

DNELs are required for both single (acute) exposures and repeated (long term) exposures. For inhalation; acute exposure usually means up to 4 hours, but for occupational exposure could be 15 minutes or 8 hours. Repeated exposure would be repeated 8 hours exposure for workers, but could be continuous 24 hours exposure for consumers. DNEL will also need to be derived from toxicity data for specific end-points[2] (local effect on the point of entry e.g. deposition in the thorax or lung) as well as for systemic effects to the body (i.e. cumulative exposure from all sources).

If no DNEL are available[3], other measured 'no effect' inhalation toxicological data, i.e. studies not to Good Laboratory Practice (GLP), could be used to estimate a NAEC. In the absence of that, Indoor Air Quality (IAQ) guidelines or workplace exposure guidelines (WEL) for the ingredients could be used.

Chapter R.8 of ECHA IR/CSA guidance describes the information requirements in the context of the risk characterisation according to REACH Regulation. It also provides advice on how to derive the data to fill gaps if all of the necessary DNELs are not available. In particular, Section R.8.4.2[4] provides methodologies for estimating NAEC from other data if specific inhalation toxicology endpoints are not available.

[2] ECHA IR/CSA guidance, Chapter R.8, pp8-9, 49, 51 and 56. (ECHA, 2012a).
[3] It is a stated aim to eventually develop agreed DNELs for all chemicals for all end points, but in the short to medium term these may not be available.
[4] ECHA IR/CSA guidance, Chapter R.8, pp18-22. (ECHA, 2012a).

As described in Chapter R.8[5] it is possible, for a given endpoint, to estimate concentrations for different exposure times using the modified Haber's Law (C^n t = k, where 'C' is the concentration, 'n' is a regression coefficient, 't' is the exposure time and 'k' is a constant).

Thus for a given end point, Equation 1, which is derived from Haber's law, can be used to extrapolate concentrations at any relevant exposure time.

$$\text{Estimated NAEC} = \text{Measured NOAEC} \times \sqrt[n]{\left(\frac{t1}{t2}\right)}$$

Where:

NAEC is the estimated no adverse effect concentration.

NOAEC is the measured no observed adverse effect concentration.

t1 is the time of measurement

t2 is the desired exposure time

n is a regression coefficient

Equation 6

The regression coefficient, n is based on empirical concentration-exposure duration relationships for relevant effects which are often difficult to establish. In the absence of suitable data for deriving values for n, a default value of n = 1 (i.e. a linear relationship) is recommended for extrapolating from shorter to longer exposure times. However, a more conservative value of n = 3 is recommended for extrapolating from longer to shorter exposure times.

By assuming that a measured NAEC is not species dependent i.e. that absorption by all species is 100% (the worst case default value), the ECHA guidance proposes that the NAEC for human inhalation is the same as that measured by animal inhalation test data.

In many cases inhalation data is not available; therefore the ECHA guidance proposes a methodology to allow a NAEC for systemic toxicity to be estimated from a human oral NOAEL.

This is done by multiplying by the body weight to calculate the dose and dividing by volume breathed in to give a concentration (see Example R.8-1[6])

$$\textbf{Inh NAEC} = \textbf{Oral NOAEL} \times \frac{\textbf{Body Weight}}{\textbf{Volume breathed in}}$$

Equation 7

Table R.8.-2[7] sets a default body weight for an adult as 70 kg and gives a range of breathed in volumes for different exposure times for consumers.

Further, if no suitable human toxicity data is available, Figure R.8-3[8] provides a methodology for estimating a NAEC for systemic toxicity from data on oral 'no effect' toxicity for other species. This approach is based on calculating a daily dose and adjusting it for the different metabolic rates and body weights using the principle of allometric (metabolic rate) scaling

[5] ECHA IR/CSA guidance, Chapter R.8, p103 (ECHA, 2012a)
[6] ECHA IR/CSA guidance, Chapter R.8, p58. (ECHA, 2012a).
[7] ECHA IR/CSA guidance, Chapter R.8, p20 (ECHA, 2012a).
[8] ECHA IR/CSA guidance, Chapter R.8, p21. (ECHA, 2012a).

between the species tested and humans. Table R.8-2 also provides factors (standard respiratory volume, sRV) to use when using data on rats, for example for data on daily dosage (24 h) the scaling factor is 1.15 m^3 per kg body weight.

Hence for a 24 h hour inhalation NAEC can be estimated from a measured daily rat oral NOAEL by:

$$\textbf{Human Inh NAEC} = \textbf{Oral Rat NOAEL} \times \frac{\mathbf{1}}{\mathbf{sRV}_{\text{rat}}} \times \frac{\mathbf{Absorbtion}_{\text{oral rat}}}{\mathbf{Absorbtion}_{\text{inh human}}}$$

Equation 8

In most cases the absorption factors will be unknown so should be assumed to be 100%.

DNEL can then be derived for specific endpoints by applying appropriate safety factors to the NAEC (see Section R.8.4.3)[9]. However, this last step requires expert judgement beyond the capabilities of many downstream user companies so it is recommended to follow the advice in Section R.8.4.3.1[10] to use a default factor of 2.5 for toxico-dynamic differences between species and a factor of 10 for human differences (i.e. to protect the wider population including children and the elderly). This means that for extrapolation of NAEC from animal data, a factor of 25 should be used, whilst for extrapolation from human data (including occupational limits) a factor of 10 should be used.

[9] ECHA IR/CSA guidance, Chapter R.8, pp22-33. (ECHA, 2012a).
[10] ECHA IR/CSA guidance, Chapter R.8, pp23-31. (ECHA, 2012a).

Table 21 gives an overview of the default assessment factors for extrapolating from animal data to man.

Assessment factor – accounting for differences in:		**Default value systemic effects**	**Default value local effects**
Interspecies	- Correction for differences in metabolic rate per body weight	AS [a, b]	--
	- Remaining differences	2.5	1 [f;] or 2.5 [g]
Intraspecies	- Worker	5	5
	- General population	10 [c]	10 [c]
Exposure duration	- Sub-acute to sub-chronic	3	3 [h]
	- Sub-chronic to chronic	2	2 [h]
	- Sub-acute to chronic	6	6 [h]
Dose-response	- Issues related to reliability of the dose-response, incl. LOAEL/NAEL extrapolation and severity effect	1 [d]	1 [d]
Quality of whole database	- Issues related to completeness and consistency of the available data	1 [d]	1 [d]
	- Issues related to reliability of the alternative data	1 [e]	1 [e]

[a] AS = factor for allometric scaling. For AS values, see ECHA IR/CSA Guidance, Chapter R.8, Table R.8-3.
[b] Caution should be taken when the starting point is an inhalation or diet study
[c] Not always covering for very young children; see text for deviations from default
[d] See text for deviations from default
[e] Special consideration needed on a case-by-case basis
[f] for effects on skin, eye and gastro-intestinal tract via simple destruction of membranes
[g] for effects on skin, eye and gastro-intestinal tract via local metabolism; for effects on respiratory tract
[h] for effects on respiratory tract.

Table 21: Default assessment factors (ECHA, 2012a, Table R.8-6)

Appendix G – Worked example – Risk assessment for consumer use of hair spray products based on data generation.

The safety assessment for hairspray polymers and resins involves determining the type of lung pathology that can be caused in animal inhalation exposure studies, and establishing the NOAEC for these pathologies. The human exposure to the consumer use of such a product is also determined by techniques which model the simulated exposure under 'in use' conditions for the aerosol or spray product. From these values of the threshold for inhalation effects and human exposure it is possible to derive the MoS for human exposure under the conditions of consumer use.

Characterisation of the toxicological hazard from inhaling hairspray polymers/resins

The potential hazards of polymers and resins used in aerosol or spray consumer products are determined by repeat dose inhalation toxicity testing using rats. The animals are exposed daily for 2-6 hours to an inhalable (<3.5 µm) aerosol of the polymer or resin usually in a subchronic regimen with recovery periods to assess whether any of the effects found are progressive or adaptive (reversible).

Because the effects of insoluble biopersistent resins and polymers in the lung are not apparent after short term exposure and evaluation, the experimental exposure period to determine the potential hazard of inhaling resins and polymers needs to be subacute (28 days), to allow the potential for chronic effects to develop in the deep lung.

The NOAEC for pathological effects in the lungs is derived from either the effects at 28 days in these studies, or subsequent recovery periods of up to 39 weeks. Recovery periods have been included in some studies to allow for the subsequent development of chronic lung pathology, from which the reversibility or progression of lung lesions can be assessed. This is because hairspray resins have the potential to persist in the lung, due to their poor solubility.
Chronic inflammation and granuloma formation have been associated with 13 week hairspray resin inhalation studies carried out in male rats. In some studies fibrosing granulomas and interstitial fibrosis have accompanied the chronic inflammatory response, during the recovery periods (Carthew *et al*., 2002).

Animals and inhalation exposure regimen

Male Wistar rats (weight range 150-275 g) in groups of 60 test animals, per exposure dose (range 1 mg/m^3 to 40 mg/m^3) and two control groups of 30 rats are exposed for 2 h/day, 5 days/week, receiving 65 exposures on consecutive working days during a 13 week period in a nose only inhalation chambers. All animals are individually housed in stainless steel cages with stainless steel sheet and wire mesh cages on mobile racks in individual environmentally controlled rooms connecting to the whole body inhalation chambers, when not being exposed to the test material. During the course of the study the animal room temperature should be maintained in the range 21 ± 2°C and the relative humidity in the range of 51-62% RH. A sham-exposed control group is exposed to clean air only and the vehicle exposed control group was exposed to nebulised solvent (ethanol/distilled water approximately 60:40 v/v).

Aerosol generation

The aerosols are generated from dilute solutions of the test material in ethanol (rectified spirit):distilled water, (usually 60:40 (v/v)) using a nebuliser. The aerosol is introduced into the exposure chamber through the centre of the top section and is diluted by air introduced through two inlets on opposite sides of the top section. This caused vortex mixing and drying of the aerosol before the test atmosphere was drawn through the chamber and exhausted through the base section under controlled vacuum. The volume of the chamber is approximately 1400 litres, which under the conditions as operated represents about 11 air change equivalents per hour. Chamber atmospheric conditions should be maintained within the temperature range 19-25°C and 30-70% RH.

During each exposure the actual airborne aerosol concentration in the breathing zone of the animals is measured gravimetrically using open faced filter holders and 5.5 cm diameter Whatman GF/C glass fibre filter discs sampling at 5 L/min.

The nominal chamber concentrations for resin and vehicle was calculated for each exposure by dividing the amount of material (both vehicle and resin) used by the nebulizer during the exposure by the total volume of air passing through the chamber [m^3] during the exposure.

The chamber concentrations of the ethanol vapour is monitored using a gas-tight syringe and charcoal absorption tubes. The samples are desorbed with carbon disulphide and analysed for ethanol by gas chromatography.

The particle size distribution of the airborne aerosol are measured using an aerodynamic particle sizer. The sizing analysis is recorded in terms of equivalent diameters and are represented as the Mass Median Aerodynamic Diameter (MMAD) ± Geometric Standard Deviation (GSD). The percentage of respirable particles (3.5 µm or less) can be computed using data obtained by the particle sizer. The respirable concentration of aerosol in the chambers (particles in range 0-3.5 µm expressed as mg/ m^3) is calculated from the airborne chamber concentration (measured gravimetrically) and the respirable percentage (as determined by the particle sizer). The percentage of particles in the size range of <3.5 µm (inhalable to rats) should be >90%. The temperature and humidity is measured each minute during the exposures in every exposure chamber using temperature and humidity monitors connected to a computer for data collection.

Necropsy and examinations

At the end of the 13 week exposure period, 6 rats from each of the control groups and 12 rats from each of the test groups are killed and necropsied. Selected organs are weighed and a comprehensive range of tissues should be taken for histological examination as well as respiratory tract tissue, inflated with fixative, for histological examination. Haematology and blood biochemistry are performed on cardiac blood samples taken immediately prior to necropsy.

The remaining rats in each group can be maintained without further treatment for up to 90 weeks after the last exposure to investigate the reversibility or development of any treatment-induced effects. At 13 and 39 weeks after the end of the exposure period 12 rats from each of the treatment groups, and 6 control animals are killed and a complete necropsy performed, lungs are weighed and selected respiratory tract tissue are inflated with fixative and taken for histological examination.

At 90 weeks of recovery from the initial 13 week exposure the remaining recovery groups (24 test and 12 control animals) are killed and necropsied. A comprehensive range of tissues

should be taken from all the rats for possible histopathological examination. Haematology and blood biochemistry are performed on cardiac blood samples taken from these animals immediately prior to necropsy.

Hairspray risk characterisation.

The risk assessment for hairspray resins is based on addressing the possible respiratory tract (local lung) effects, as there are no systemic effects from inhaling insoluble polymers or resins due to the lack of systemic exposure. The risk assessment is therefore based on measuring the incremental daily lung burden in rats at the NOAEC, and comparing this to the incremental daily lung burden in women using the hairspray, to derive a MoS.

Thus,

$$\text{MoS} = \frac{\text{Incremental daily lung burden in rats at the NOAEC}}{\text{Incremental daily lung burden in women}}$$

Equation 9

Exposure estimations for use in the risk assessment.

Exposure of rats during the inhalation toxicity test.

The method used for calculating total lung deposition depends on whether sufficient particle size data from the inhalation study are known. If it is not known it is calculated as follows:

$$\text{Total lung deposition [µg]} = \text{Exposure concentration [mg/m}^3\text{]} \times \text{Lung deposition [\%]} \times \text{Minute volume [m}^3\text{/min]} \times \text{Exposure time [min]} \times \text{No of exposures}$$

Key:

Exposure concentration = Exposure concentration at the NOAEC

Lung deposition = Assumed proportion of the resin which remains in the lungs (usually assumed to be 10% in the absence of detailed particle size data)

Minute volume = Average volume of air inhaled/minute. This is dependent on average weight of the strain of rats at 6-7 weeks.

Exposure time = Daily exposure time

Number of exposures = Number of exposures during the study

Equation 10

If sufficient particle size data are known the total concentration deposited can be adjusted accordingly, using the percentage deposition data derived by Raabe (Raabe *et al*., 1976).

Calculation of the daily incremental lung burden in the rat exposed during the inhalation study.

This is calculated at the NOAEL in a rat 90 day inhalation study using the following formula:

Incremental rat exposure/day

Daily lung burden [µg/g lung/day]	=	Total lung deposition [µg]	/	Average lung weight [g]	/	No of exposures

Key:

Average lung weight = Average lung weight of rats in the NOAEL dose group at end of exposure.

Number of exposures = Number of exposures during the study

Equation 11

Daily incremental lung burden in consumers under conditions of simulated use.

This is usually calculated from the simulated use data, using the following formula:

Incremental human exposure/day

Daily lung burden [µg/g lung/day]	=	RDose [µg/s spray]	×	Use [s/day]	×	[Lung deposition / Lung weight] [g]

Key:

RDose = Respirable dose

Use = Normal use (1x10 seconds/day) or heavy use (2 x 20 s/d)

Lung deposition = 0.2 (i.e. 20% of inhaled material is assumed to remain in the lungs)

Lung weight = 650 g (average lung weight for a small female).

Equation 12

The respirable dose is assessed by conducting a simulated use test with the hairspray product and measuring the amount of material which is less than 7 µm aerodynamic diameter (i.e. material that is small enough to penetrate the deep lung). The respirable dose (expressed in
µg resin/second spray) is then calculated using the following assumptions:

- Breathing rate is 20 L/min or other default considered appropriate to the exposure scenario and age of subject exposed (Ginsberg *et al*., 2010).
- The subject stays in the room for ten minutes (although most resin is inhaled during the first minute or two).

<u>Risk characterization for respiratory tract (local) effects in the lung.</u>

$$\text{MoS} = \frac{\text{Incremental daily lung burden in rats at the NOAEC}}{\text{Incremental daily lung burden in women}}$$

Equation 13

A margin of safety of >25 is considered satisfactory for the risk characterization of potential respiratory tract (local) effects in man.

Appendix H – Use of Derived Minimum Effect Level (DMEL)

DMEL (derived minimum effect level) is used for unavoidable contaminants in aerosol ingredients, such as genotoxic carcinogens with no threshold for effects.

A DMEL is not equivalent to a DNEL. DMELs are derived for non-threshold effects where there is a residual risk, even at very low levels of exposure.

If a no-effect-level cannot be established, a DMEL expresses an exposure level corresponding to a low, possibly theoretical, risk.

It was originally developed to assess the relative risk for exposure to unavoidable genotoxic carcinogen contaminants in foods (FAO/WHO, 2005; EFSA, 2005, O'Brien *et al*., 2006), and has been used to evaluate the carcinogenicity of a number of genotoxic carcinogen contaminants in food (Benford *et al*, 2010). It can equally well be used to evaluate very low levels of contaminants in cosmetics and home care consumer products, as detailed in the ECHA guidance for assessing carcinogenic risk (ECHA, 2012a).

Comparison of the BMDL10 (the lower confidence limit on the benchmark dose associated with a 10% response) from animal carcinogenicity study to the exposure gives a MoE for the non-threshold effect of cancer.

$$\mathrm{MoE} = \frac{\mathrm{BMDL10}}{\mathrm{Exposure}}$$

Equation 14

Larger MoEs are required for non-threshold effects, than for thresholded effects. Chemical contaminants known to be both genotoxic and carcinogenic, where there is no level of exposure that can be considered without some risk, can be safety assessed using this approach.

MoEs of >10,000 have been proposed as of low concern for risk management by the European Food Standards Agency (EFSA).

Appendix I – Sources of Hazard Information

Suppliers' literature on chemicals

ACGIH (American Conference of Governmental Industrial Hygienists) – Threshold Limit Values (fee required)
www.acgih.org/store/

BAMA (British Aerosol Manufacturers' Association) Hazard Summary Profiles: as part of work to prepare the UK aerosol industry for REACH, BAMA commissioned toxicological hazard summaries for a number of chemicals commonly used in aerosols. These summaries can be purchased from BAMA
www.bama.co.uk/bama_hazard_profiles/

EU – ECHA (European Chemicals Agency) Information on Registered Substances
http://apps.echa.europa.eu/registered/registered-sub.aspx

EU – ESIS (European Chemical Substance Information System) and ORATS (Online European Risk Assessment Tracking System)
http://ecb.jrc.ec.europa.eu/esis/

EU – EU-OSHA (European Agency for Safety and Health at Work) – European Occupational Exposure Limits (OEL)
http://osha.europa.eu/en/topics/ds/oel/
http://osha.europa.eu/en/publications/reports/OELs_table/view

HERA (Human and Environmental Risk Assessment on ingredients of household cleaning products) – Risk Assessments
http://www.heraproject.com/RiskAssessment.cfm

IARC (International Agency for Research on Cancer) – Publications
www.iarc.fr/en/publications/index.php

ICCA (International Council of Chemical Associations) – High Production Volume (HPV) assessment dossiers
http://webnet.oecd.org/hpv/ui/Default.aspx

Indoor Air Quality (IAQ) guidelines set by authorities, particularly relevant for chemical used in aerosols sold to the general public and for use in non-industrial locations

IPCS (International Programme on Chemical Safety) – Concise International Chemical Assessment Documents (CICADs)
www.inchem.org/pages/cicads.html

Japan – Japanese initial risk assessment reports of chemical substances
www.safe.nite.go.jp/risk/riskhykdl01.html

Japan – National Institute of Advanced Industrial Science and Technology, Risk Assessment Documents
http://unit.aist.go.jp/riss/crm/mainmenu/1.html

Japan – NITE (National Institute of Technology and Evaluation) – Chemical Risk Information Platform (CHRIP)
www.safe.nite.go.jp/japan/db.html

Japan – Recommendation of Occupational Exposure Limits issued by Japan Society for Occupational Health
http://joh.med.uoeh-u.ac.jp/oel/index.html

Japan – Working Environment Evaluation Standards under Industrial Safety and Health Act
www.jaish.gr.jp/anzen/hor/hombun/hor1-18/hor1-18-2-1-0.htm

Material Safety Data Sheets (check reliability)
www.eusdb.de/en

OECD (Organisation for Economic Co-operation and Development) eChem Portal
http://www.echemportal.org/

RIFM (Research Institute for Fragrance Materials**)** database (with subscription)
http://www.rifm.org/rifm-science-database.php?cat=4

US EPA (Environment Protection Agency) Design for the Environment (DfE)
http://www.epa.gov/dfe/

US EPA Integrated Risk Information System (IRIS)
http://www.epa.gov/iris/

US EPA Toxic Substance Control Act Test Submission Database
http://www.srcinc.com/what-we-do/databaseforms.aspx

US Hazardous Substances Data Bank (HSDB)
http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB

US National Toxicology Program (NTP) Health Assessment and Translation (formerly CERHR) Publications and Study Reports
http://cerhr.niehs.nih.gov/reports/index.html

http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm