Mini review

Principle considerations for the risk assessment of sprayed consumer products

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In recent years, the official regulation of chemicals and chemical products has been intensified. Explicitly for spray products enhanced requirements to assess the consumers’/professionals’ exposure to such product type have been introduced.

In this regard the Aerosol-Dispensers-Directive (75/324/EEC) with obligation for marketing aerosol dispensers, and the Cosmetic-Products-Regulation (1223/2009/EC) which obliges the insurance of a safety assessment, have to be mentioned. Both enactments, similar to the REACH regulation (1907/2006/EC), require a robust chemical safety assessment. From such assessment, appropriate risk management measures may be identified to adequately control the risk of these chemicals/products to human health and the environment when used.

Currently, the above-mentioned regulations lack the guidance on which data are needed for preparing a proper hazard analysis and safety assessment of spray products.

Mandatory in the process of inhalation risk and safety assessment is the determination and quantification of the actual exposure to the spray product and more specifically, its ingredients. In this respect the current article, prepared by the European Aerosol Federation (FEA, Brussels) task force "Inhalation Toxicology", intends to introduce toxicological principles and the state of the art in currently available exposure models adapted for typical application scenarios. This review on current methodologies is intended to guide safety assessors to better estimate inhalation exposure by using the most relevant data.

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1. Introduction

The human respiratory tract is a dynamic system responsible for the gas exchange and the filtering of airborne pathogens and foreign material (Salem and Katz, 2006).

To understand the specific defence mechanisms and filter function of the respiratory tract, some anatomical basics are introduced. The vestibular hairs in the nose, mucociliary clearance, and high-velocity clearance/reflex mechanisms (sneezing and coughing) are first mechanisms of such defence. Additional, non-ciliated airway secretions, blood/lymph clearance, immunological responses, contribute to this protective function.

As illustrated in Fig. 1, particle/droplet deposition throughout the respiratory tract is determined by the inhalation characteristics (duration, frequency, and strength), the size (aerodynamic diameter) of sprayed particles/droplets and their physicochemical properties and specific clearance mechanisms.

Particles/droplets exceeding a diameter of 30 \( \mu \text{m} \) are normally filtered in the nasopharyngeal passage and would not reach the lung. In contrast, smaller ones may reach the lower airways. The mucosal lining of the upper respiratory tract can serve as a protective barrier and a trap for such smaller particles/droplets. The mucociliary escalator, which promotes the movement of mucosal fluid up the extrathoracic region (nose, mouth and throat) plays a major role in the clearance process of inhaled material.

The German MAK Commission stated that the particles/droplets with an aerodynamic diameter of >15 \( \mu \text{m} \) are deposited almost exclusively in the extrathoracic region, and healthy humans will clear particles >7 \( \mu \text{m} \) within 24h from the tracheobronchial compartment. The threshold of particle/droplet diameters small enough to reach the alveoli is often set to be 5 \( \mu \text{m} \) (MAK, 2012). However, in this document particles/droplets with an aerodynamic diameter <10 \( \mu \text{m} \) are conservatively considered to be respirable and suspected to reach the deeper lung.

Beside the mentioned deposition of particles/droplets propellants (gases) and solvents (vapours), often used in spray products, could have an additional health impact which has to be taken into account for the overall hazard assessment of inhalable chemicals and products.

2. Aims

This article is intended to introduce important elements for the inhalation safety assessment, to enable safe use of spray products in both occupational and consumer settings, and help improve the understanding of relevant inhalation exposure scenarios in typical application environments. Product-type specific approaches for modelling the inhalation exposure of spray products will be reviewed.

A tiered (step-wise) approach for preparing a robust safety assessment is recommended, why detailed information on the ingredients hazard, the spray characteristics and data on the explicit exposure is needed. Both, local effects in the respiratory tract and the systemic inhalation toxicity have to be taken into account for the acute and repeated exposure.

It is essential to understand the realistic occupational or consumer exposure and application habits, in order to estimate the impact of other possible routes (such as dermal, oral and/or environmental background exposure) on the total systemic exposure and body burden.

3. Principles of the inhalation safety assessment

Four key elements have to be addressed:

3.1. Data collection

Available safety data for all ingredients and their specific regulation have to be evaluated.

3.2. Hazard assessment

The hazard assessment is processed in hazard identification and hazard characterization. Within hazard identification, ingredients are identified which are suspected to cause health concern when inhaled. For hazard characterization, the level of exposure due to the specific content of certain chemicals in the spray product is considered.

With this information, a decision should be made on the need of an explicit exposure assessment. If no hazardous chemicals are used in the spray product, or if they are only present at negligible, low concentrations, a risk characterization without an explicit exposure assessment could be sufficient.

3.3. Exposure assessment

To get knowledge on the realistic inhalation exposure to identified hazardous ingredients data on the room size in which the individual is present during spraying, and details on the spray application, e.g. frequency, duration and direction is needed. With one
of the following options a more sufficient exposure estimate could be reached:

- Screening assessment as worst-case exposure.
- Progressively more complex exposure modelling.
- Measuring the actual amount of spray inhaled, or potentially inhaled by simulating the realistic exposure scenario.

It is important to note that the final exposure is determined by the particle size and the distribution of particles/droplets in the exposure room under use conditions. The composition of the formulation and the technical details of the spray can (e.g., nozzle, size, propellant type) are of significant impact.

3.4. Risk characterization

Modelled or measured human inhalation exposure data has to be compared with suitable derived threshold values of no concern.

In case of an unfavourable risk characterization, there is a need to further refine the exposure assessment (e.g., using a more realistic approach), technically modify the spray characteristics, or to reformulate the product.

Fig. 2 illustrates the basic principles of this tiered safety assessment of spray products.

It is important to keep in mind that techniques and terminologies used in the safety assessment should be checked for their compliance with relevant legislation and official guidance.

4. Inhalation safety assessment in detail

4.1. Data collection

It is recommended to start a safety assessment of spray products with the acquisition of available hazard data of individual ingredients and the understanding of their specific content in the spray product.

The hazard identification of individual ingredients typically starts with the information given in related material safety data sheets (MSDS). Especially the toxicological classification according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS)/EU Classification, Labelling and Packaging Regulation (1272/2008/EC, CLP) could be a starting point to get knowledge on basic toxicological hazards. Additional data sources for the safety assessment could be found in related toxicological reports, official data files, safety studies, peer-reviewed articles, and opinions by regulatory bodies.

Fig. 1. Leading terms within the human respiratory tract.

Fig. 2. Tired approach for the Inhalation Safety Assessment (SCCS, 2012). Colour code in boxes: Blue related to ingredients. Yellow related to product exposure. (For interpretation of the references to color in figure legend, the reader is referred to the web version of the article.)
4.2. Hazard assessment

4.2.1. Hazard identification

With the mentioned data collection a useful understanding of the principle toxicological properties of the related chemicals could be reached, but for a scientifically robust safety assessment, detailed information on the following toxicological endpoints may be needed:

- Acute systemic toxicity after oral, dermal or inhalation exposure.
- irritation/corrosion (local effects) after mucosal, dermal and/or inhalation exposure.
- Dermal and respiratory sensitization.
- Mutagenic/genotoxic potential.
- Repeated dose toxicity (e.g. 28-day/90-day studies) when orally, or topically exposed, or when inhaled, with the corresponding thresholds identified: No-Observed-Adverse-Effect-Level (NOAEL)/No-Observed-Effect-Level (NOEL), or No-Observed-Adverse-Effect-Concentration (NOAEC)/No-Observed-Effect-Concentration (NOEC).
- Reproductive/developmental toxicity (maternal/foetal).

The reliability and robustness of the final hazard identification is related to the quality of individual information used (Schneider et al., 2009), why the most robust studies should be preferred, ideally those directly related to inhalation (e.g. OECD testing guideline #412 or #413).

In case inhalation data are lacking, this data gap might be bridged by other appropriate toxicological information in a Weight of Evidence approach (WoE). In this approach e.g. robust oral toxicity data, may function as an adequate surrogate with a route-to-route extrapolation as described in the European Chemicals Agency (ECHA) guidance (ECHA, 2012a).

4.2.2. Hazard characterization

For the hazard characterization all compiled toxicity data, systemic as well as local ones, have to be considered and determined by adequate dose descriptors like [mg/kg bw/day] for systemic and [mg/cm² lung surface area] or [mg/g lung weight] for local effects. Usually these descriptors are expressed as a NOAEC (for local and systemic effects) or LC₅₀ (acute lethal concentration), respectively.

Once the overall hazard has been determined for the individual ingredients, its health impact during product inhalation can be estimated related to their individual content. The likelihood of reactivity between individual ingredients should be considered.

In cases where the content of certain ingredients is very low an Exposure-Based-Waiving (EBW) approach could be applied (Carthew et al., 2009) as a justification for concluding that there is no risk. The application of such an approach requires expert knowledge and a detailed understanding about its restrictions and limitations.

4.3. Exposure assessment

Spray products have a wide variety of applications and the actual health related risk to humans (workers, professionals, consumers) depends on the hazard and exposure to the sprayed chemicals at specified use conditions. Therefore, a proper exposure assessment is crucial and should be based on detailed knowledge of the use conditions established from data on habits and practices.

Generally, the exposure to inhalable substances is determined by:

\[
\text{Exposure} = \frac{\text{weight of ingredient in the released spray formulation [mg]}}{\text{room volume [m}^3\text{]}}
\]

For practical reasons only those data, which are expected to have a relevant impact on the specific exposure have to be taken into account.

4.3.1. Screening approach

ECHA has published some guidance for the exposure estimation to spray products (ECHA, 2012b). For screening purposes, a rough estimate of the exposure to a certain sprayed product/chemical could be sufficient or even appropriate. In such first screening assessment, it is assumed that exposure is to a certain ingredient quantity which released the dispenser instantaneously. An immediate homogenous distribution in a fixed exposure room is assumed.

\[
\text{Concentration (exposure)} = \frac{\text{weight of ingredient in the released spray formulation [mg]}}{\text{room volume [m}^3\text{]}}
\]

This conservative approach will provide overestimated exposure for volatile substances (fixed room volume without air exchange), but will underestimate short-term local exposure for particles/droplets (inhomogeneous distribution shortly after spraying) as the sprayed formulation needs a while to become homogeneously distributed in the room.

The distribution/exposure scenario has to be representative for the specific product type. For cosmetic and personal care products, which are sprayed towards the body, it is assumed that the total amount of the sprayed product enters immediately and homogeneously the “personal zone”/“breathing zone”, of about 2 m².

For many hazardous ingredients in spray products such simple exposure assessment may be appropriate to prepare a reliable risk characterization.

4.3.2. Exposure Modelling

Based on the diversity of spray products and their variability in applications, a number of models for a more realistic exposure assessment, varying in complexity, have been developed and are in use. An understanding of certain individual strengths and weaknesses of these models is needed for a proper choice.

For a robust exposure assessment the amount of sprayed product/chemical in a given time and realistic room conditions should be taken into account. The initial air concentration, dilution by
ventilation and sedimentation are additional important parameters to describe the ‘real use’ conditions. In this regard, the Time-Weighted-Average concentration (TWA) expresses the time-dependent change of product concentration in the exposure room after spraying.

Typical spraying values of some common consumer products are given in the following tables (Tables 1—3), however, some of these parameters are triggered by individual habits and any two people may use the same product type differently (Steiling et al., 2012). To build realistic exposure scenarios it is therefore important to understand how spray products are realistically used (Table 1).

<table>
<thead>
<tr>
<th>Consumer product</th>
<th>Discharge rate (g/s)</th>
<th>Spray time (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hairspray</td>
<td>0.7</td>
<td>3—4</td>
</tr>
<tr>
<td>Antiperspirant/deodorant spray (90th percentile)</td>
<td>0.8</td>
<td>1.4</td>
</tr>
<tr>
<td>Air freshener</td>
<td>1.5—1.8</td>
<td>4—5</td>
</tr>
<tr>
<td>Furniture polish</td>
<td>1.8</td>
<td>2—3</td>
</tr>
<tr>
<td>All-purpose cleaning spray</td>
<td>1.2</td>
<td>24</td>
</tr>
<tr>
<td>Starch</td>
<td>2.0</td>
<td>2—3</td>
</tr>
<tr>
<td>Carpet cleaner</td>
<td>2.0</td>
<td>20—30</td>
</tr>
<tr>
<td>Oven cleaner</td>
<td>2.0</td>
<td>10—15</td>
</tr>
<tr>
<td>Flying insect killer</td>
<td>1.5</td>
<td>10</td>
</tr>
<tr>
<td>Crawling insect killer</td>
<td>1.5</td>
<td>60—90</td>
</tr>
<tr>
<td>De-icer</td>
<td>2.5</td>
<td>15—20</td>
</tr>
<tr>
<td>Paints</td>
<td>0.8</td>
<td>30—40</td>
</tr>
</tbody>
</table>

* BAMA (2008).
* Bremmer et al. (2006).
* Steiling et al. (2012).
* Weerdsteijn et al. (1999).

Values for the daily applied amounts and the application frequency of some cosmetic products are given in Table 2. The amount per application represents the total amount of product including the related propellant and solvent content (can weight loss), but not the quantity of product landing on the skin or hair, which is much lower (Steiling et al., 2012).

<table>
<thead>
<tr>
<th>Product application</th>
<th>Amount/day (g)</th>
<th>Frequency of application/day</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deodorant (aerosol)</td>
<td>6.1 (90th percentile)</td>
<td>2</td>
<td>McNamara et al. (2007) and Hall et al. (2007)</td>
</tr>
<tr>
<td>Hairspray (aerosol)</td>
<td>6.8 (75th percentile)</td>
<td>1</td>
<td>Bremmer (2006)</td>
</tr>
<tr>
<td>Hairspray (pump spray)</td>
<td>3.6</td>
<td>1</td>
<td>Loretz et al. (2006)</td>
</tr>
</tbody>
</table>

Typical exposure data of some household aerosol products are given in Table 3.

<table>
<thead>
<tr>
<th>Products</th>
<th>Mean spraying duration per use (min)</th>
<th>90th percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spray shoe polish</td>
<td>7.49</td>
<td>18</td>
</tr>
<tr>
<td>Aerosol spray paint</td>
<td>39.54</td>
<td>60</td>
</tr>
<tr>
<td>Aerosol rust remover</td>
<td>18.57</td>
<td>60</td>
</tr>
<tr>
<td>Aerosol spray paints for cars</td>
<td>42.77</td>
<td>120</td>
</tr>
<tr>
<td>Spray lubricant for cars</td>
<td>9.90</td>
<td>15</td>
</tr>
</tbody>
</table>

Beside the aforementioned conservative exposure calculation, using standard values of well designed surveys and specific studies on typical application/use habits, several computational exposure models have been developed in parallel.

Such computer programmes, developed to calculate the expected inhalation exposure varies from simple ones to sophisticated models. Later takes into account various factors to determine most realistically how much of a spray/chemical is actually inhaled, exhaled, is reaching deeper lung are or is deposited. Currently, the following models have been established with preferred application to certain exposure scenarios:

a) BAMA/FEA Indoor Air model (one-box).
b) RIVM Cons Expo 4.1 models (one-box).
c) BAAU 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.

The most obvious differences between these models are the number of assumed exposure rooms (boxes). Some are utilizing a single exposure room, others use two or more zones/rooms.

4.3.2.1. One-box models. The one-box model (Fig. 3) is based on the assumption that particles/droplets are homogeneously distributed in an exposure room of known volume. Concentrations are calculated as a function of the sprayed amount, the room volume and the ventilation rate as well as the time elapsed from the start of the emission and staying in this room.

**Fig. 3.** Theoretical behaviour of a sprayed product in a room.

4.3.2.2. Two-box models. A more sophisticated approach is the two-box model, which assumes 2 different zones/rooms (Box A and Box B) in which the emitted material is homogeneously dispersed as illustrated in Fig. 4. This scenario automatically results in two separate exposure environments which have to be taken into account when calculating the overall exposure.

Although the air concentration will be higher in Box A, total exposure will depend on the residency time in each box. The amount of material which could be inhaled is determined by its concentration in individual boxes, the specific residency times and the
4.3.2.4. Multiple particle path deposition model. The Multiple Path Particle Deposition (MPPD) model is a higher tier exposure assessment model utilizing a computational model of human and rat specific anatomical differences in the respiratory tract (the nasal cavity and lung airways). The MPPD allows the direct extrapolation of laboratory animal data to human exposure and is capable to estimate dose-related kinetics of inhaled material (Schroeter and Kimbell, 2006a,b; Martonen and Schroeter, 2003; García and Kimbell, 2009; Schroeter, 2009). The MPPD model allows the specific determination of the dose deposited at various sites of the respiratory tract, and to calculate the dose which can be systemically uptaken across the tissue surface in the lung. The correct quantification of the deposited/penetrated amount of material requires the use of respiratory or at least dermal penetration coefficients and sufficient knowledge on physicochemical characteristics of the individual chemical.

During the last couple of years, some of these models became publicly available such as the BAMA/FEA Indoor Air Model, RIVM ConsExpo 4.1, SprayExpo (Koch et al., 2012) and BG-Spray (Eickmann, 2007) and found to be useful for determining systemic exposure. Model-specific advantages and drawbacks are described in the literature (Eickmann et al., 2007).

The product-specific application of these models is summarized in Table 4.

4.3.2.4. Example for using the one-box model. To better understand the various exposure modelling methods discussed, an example is given for calculating the user's exposure to a hypothetical spray air freshener (AF) with ingredient “A” (chemical of interest) formulated at a content of 0.5%. Following the content of Table 4, the BAMA/FEA Indoor Air model, a one-box model, should suffice to calculate exposure for such a scenario.

The typical spraying time for an AF is 5 s with a product release of 1.5 g/s (BAMA, 2008). The room in which an AF is more commonly sprayed is the bathroom. A small bathroom has a volume of 10 m³ (RIVM, 2006). For this scenario we also assume an adult with a respiration rate of 13 L/min for light activity (Salem and Katz, 2006) and a body weight (bw) of 65 kg. If the person stays in this bathroom for 30 min, the amount this person will be exposed to ingredient “A” is calculated as follows:

<table>
<thead>
<tr>
<th>Exposure model</th>
<th>Products for which the model is useful</th>
</tr>
</thead>
<tbody>
<tr>
<td>BAMA/FEA Indoor Air model (one-box)</td>
<td>Products sprayed into the air (e.g. air freshener) Products sprayed onto a horizontal surface (e.g. carpet cleaner)</td>
</tr>
<tr>
<td>RIVM ConsExpo 4.1 model (one-box) (RIVM, 2007)</td>
<td>Products sprayed into the air (e.g. air freshener) Products sprayed at the body (e.g. cosmetic products) Products sprayed at a vertical surface (e.g. paints) Products sprayed on to a horizontal surface (e.g. carpet cleaner)</td>
</tr>
<tr>
<td>BfA SprayExpo 2.0 model (one-box)</td>
<td>Products sprayed into the air (e.g. air freshener) Products sprayed towards a surface (e.g. paints)</td>
</tr>
<tr>
<td>RIVM 2-Boxes Indoor Air Dispersion model (two-boxes)</td>
<td>Products sprayed into the air (e.g. air freshener) Products sprayed at the body (e.g. cosmetic products) Products that are combustible (candles) Products that are passive or heated diffusers</td>
</tr>
<tr>
<td>RIVM Computational-Fluid-Dynamics (CFD) and MPPD model</td>
<td>Products sprayed into the air (e.g. air freshener) Products sprayed at the body (e.g. cosmetic products) Products sprayed at a vertical surface (e.g. paints) Products sprayed on to a horizontal surface (e.g. carpet cleaner)</td>
</tr>
</tbody>
</table>

1. 1.5 g/s product release for 5 s spraying (1.5 g/s × 5 s) ends up in 7.5 g product released.
2. 0.5% of ingredient “A” in the air freshener (7.5 g × 0.005 = 0.037 g) results in 37.5 mg.
3. Assuming this amount is homogenously distributed in 10 m³ bathroom, this gives an initial concentration of 0.00375 mg/L ([37.5 mg/10 m³]/1000 L).
4. Assuming no ventilation (i.e. “sealed room”), and a respiration rate of 13 L/min (0.00375 mg/L × 13 L/min) comes to 0.04875 mg/min of inhaled substance “A”. 5. For the duration of 30 min spent in the bathroom the person will be exposed to (0.04875 mg/min × 30 min) 1.4625 mg of substance “A” or 22.5 μg/kg for a 65 kg person (1.4625 mg/65 kg = 0.0225 mg/kg bw or 22.5 μg/kg bw).

However when running the mentioned BAMA/FEA Indoor Air model this worst-case exposure scenario will become more realistic by incorporating an air exchange of 2 times per hour, the ventilation rate associated with a bathroom (RIVM, 2006). Taking this air exchange into consideration, a 30 min time weighted average bathroom concentration (30 min TWA) for chemical “A” is calculated to be 2.4 mg/m³. With this TWA value, the modelling calculates the 30 min exposure to ingredient “A” to be 0.936 mg or 14.4 μg/kg bw (vs. 22.5 μg/kg bw as calculated above). This refinement is more realistic than the previously calculated value, but remains conservative, as other relevant information (such as particle size distribution) are not considered. Following the scheme given in Fig. 1, for a robust risk assessment, the more details one considers the more realistic will be the estimate of the respirable fraction and ultimate local or systemic exposure to the substance of interest.
4.3.3. Exposure measurement

For some applications and/or products computational modelling data may not give a sufficient level of confidence necessary to be taken in the risk characterization. For exposure scenarios where the spray is directed to men (e.g. a hair spray) experimental measurements of the respirable fraction of the spray into the ‘breathing zone’ of this individual may be needed.

For such measurement it should be understood that particle/droplet size could be dynamic due to the evaporation of e.g. the solvent after releasing the spray container. During such maturation of particle size larger particles/droplets become smaller and under specific conditions particles/droplets could become bigger by aggregation (EAF, 2009). In either case, droplet size and density directly affect their settling velocity and elimination from the “breathing zone.” Product spray clouds are complex and their description is time-related and determined by e.g. the product composition and geometry of the spraying dispenser. Currently, no computational modelling is available to conduct a sufficiently reliable simulation of this particle/droplet maturation; this is why it is necessary to resort to measurement.

4.3.3.1. Measurement of spray exposure under simulated use conditions. Mannequins with simulated anatomical features, equipped with an aerosol sampler in the modelled upper respiratory tract are properly connected to a particle size spectrometer (Fig. 6), to measure the respirable dose, small enough to reach the deeper lung. Individual use conditions (adult, child) and habits and practices of spraying (frequency and duration) could be simulated with such model. The aerodynamic diameter and the number of individual particles/droplets in a defined volume per minute can be measured, even specifically in the ‘breathing zone’ over a certain time period. The resulted particle size distribution data allows the extrapolation of the respirable dose for that given formulation under that application conditions (Cartthew et al., 2002).

In cases where spray products are not intentionally directed towards men, a slightly different measurement procedure could be useful. For such application the product has to be sprayed into a cabinet of defined volume and an installed impactor will collect specifically defined airborne fraction on integrated filters with defined mesh-sizes. The respirable fraction deposited on the corresponding impactor inlet is typically gravimetrically measured or chemically analyzed.

4.4. Risk characterization

Once the exposure to the relevant spray fraction is reliably understood, by estimation, modelling or measurements, the risk to human health at that level of exposure can be reliably assessed. For the final risk characterization regulators often require their specific safety factors and calculations for getting their acceptance. In this regard the most commonly used values for the risk assessments of chemicals are the Margin-of-Safety (MoS) and the Risk-Characterization-Ratio (RCR).

In a quantitative risk assessment it has to be decided if the identified hazards are linked to a certain threshold or not. A threshold in this regard is defined as a dose below which no statistically significant increase in adverse effects on the exposed organism can be identified. Adverse effects without a threshold are for example genotoxic carcinogens. A method developed by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) for assessing non-threshold effects of genotoxic carcinogens (Barlow et al., 2006) could be applied to characterize the risk of possibly unavoidable non-threshold contaminants in sprays.

4.4.1. Risk-characterization-ratio (RCR)

Under REACH a risk assessment is part of a challenging process which is known as a Chemical Safety Assessment (CSA). Details how this has to be achieved and in particular, how to estimate e.g. inhalation exposure is given in the ECHA IR/CSA guidance (ECHA, 2012b).

Important in such CSA risk assessment is the calculated RCR, the ratio between the actual exposure and the estimated derived no effect level (DNEL) for certain adverse effects. Thus, for a given exposure to an individual ingredient the RCR is defined by:

\[
\text{RCR} = \frac{\text{Exposure}}{\text{DNEL}}
\]

RCR values < 1 are interpreted as of no concern and risk reduction measures are not necessary. In cases of RCR > 1, a refinement of exposure is required or risk reduction measures are necessary (e.g. modification of the spray characteristics or reformulation of the product) (ECHA, 2012a).

4.4.2. Margin of safety (MoS)

The MoS is commonly 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 between the estimated or measured Systemic-Exposure-Dose (SED) for the exposed person and the NOAEL/NOAEC determined in appropriate animal tests. Usually, the NOAEC represents the highest systemic concentration for which a test chemical does not induce an adverse effect in the test animal when exposed repeatedly (e.g. for 90 days) to that concentration.

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

![Mannequin with particle sizer spectrometer.](image-url)
Besides 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 NOAEC are given as [mg/kg bw/d]. For inhalation, the NOAEC are typically given as [mg/m³] or [ppm].

\[
\text{MoS} = \frac{\text{NOAEL (or NOAEC)}}{\text{SED}}
\]

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. The same factor is currently requested by the US EPA for demonstrating chemical safety.

For the safety assessment of spray products, the MoS calculation is more complex compared to other applications, in addition to the dose the physical nature of the particles (e.g. size) will have a significant impact on the exposure as explained before. Finally, technical details determine where exposure occurs in the respiratory tract (see Fig. 1; different cell types in the different regions of the respiratory tract may be affected uniquely). As both, the site of exposure and the particle/droplet size influence the local exposure [mg/cm² lung tissue], a risk assessment based on a “simple” MoS calculation may not be appropriate.

Specific exposure data for certain areas in the respiratory tract and appropriate information (dose–response-relationship) on both systemic and local effects from standard toxicity tests are useful in a proper risk assessment of sprayed products.

5. Discussion

Products and in particular, consumer products have to be safe under conditions of foreseeable use as required by numerous regulations. Consequently, it is important to agree on the key data needed for an informed and representative risk assessment. During the last few decades, both industry partners and regulators have built expertise in the risk assessment of consumer products which come into contact with the skin or could be occasionally ingested. For spray products, a risk assessment is essentially more complex, due to the number of variables influencing the exposure as well as the nature of the particles/droplets released during a spraying event.

For uptake via the inhalation route, the particle/droplet sizes and velocity dictate if exposure will be mainly local sedimentation in the upper respiratory tract or diffusion in the alveolar region. The size of particle/droplets and velocity of a spray is influenced by technical details such as the pressure in the spray can, the can size and even the geometry of the spray nozzle. In addition, product composition such as propellant and solvent use may trigger an exposure episode in particular areas of the respiratory tract. As the final exposure scenario is sensitive to all the above parameters, and is often not comparable to the exposure scenario used in standard inhalation studies (e.g. OECD #413), a more appropriate exposure characterization is necessary for a robust and reliable risk assessment.

6. Conclusion

This review summarizes current best practices on how to evaluate the risk of inhaled ingredients from spray products. Using a tiered approach, based on consideration of exposure, the discussed evaluation strategy is useful and appropriate in providing a robust risk assessment for both the consumer and the occupational use of spray products. The particular requirements of the various regulatory bodies involved in the safety evaluations of spray products have been described. This should enable companies and agencies to prepare risk assessments for spray products with an approach relevant to the level of concern. This could be based on modelling exposure for the particular formulation and application scenario, or at a higher tier, to measure real exposure under simulated use conditions for a more accurate exposure characterization. The introduced ranked hierarchy of approaches will be useful to better ensure safety of spray products.

Conflict of interest

The Authors report no conflicts of interest. The Authors are employees of the organizations and companies: Henkel AG & Co KGaA, Montana Air Sl, Unilever UK, Ardgath Group, SC Johnson, European Aerosol Federation (FEA), British Aerosol Manufacturers Association (BAMA), L’Oreal, Procter & Gamble Service GmbH, Research Institute for Fragrance Materials Inc. (RIFM).

Transparency document

The Transparency document associated with this article can be found in the online version.

References


