Applying the Threshold of Toxicological Concern (TTC) to Low Level Ingredients in Air Fresheners

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Introduction

Humans are exposed to numerous chemicals through sources such as foods, medicines and consumer products. Consumer safety is of paramount importance. In some cases, detailed toxicological data may be lacking for chemicals present in consumer products at low levels. This represents a challenge in assuring consumer safety at a time of strong public and regulatory pressure to increasingly rely on alternative testing methodologies. However, validated alternatives allowing assessment and prediction of repeated dose toxicity of chemical exposures in humans are unlikely to be available in the near future. This limits the ability of new product innovations without investigations requiring considerable amount of testing for materials present at these low levels.

The concept of the toxicological threshold of concern (TTC) is widely seen as a useful concept that provides assurance of safety even in the absence of substantial chemical-specific toxicity data, provided that an exposure level can be defined below which there is no significant risk to humans.

Air fresheners may contain fragrance mixtures, emulsifiers and/or gelling components amongst other ingredients. The actual product concentrations of most of these ingredients, and hence, potential consumer exposure is rather low. The objective of this paper is to examine whether within its remits, the TTC concept allows establishing a *de minimis* level for systemic toxicity of air freshener ingredients below which they can be assumed to be safe under normal and foreseeable product use conditions.

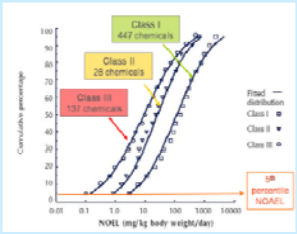
The basic paradigm of the TTC concept

The TTC is a pragmatic risk assessment tool that is based on the principle that a human exposure threshold value can be established for all chemicals that are not potent carcinogen nor bioaccumulative substances, below which there is a very low probability of an appreciable risk to human health (Kroes *et al.*, 2004).

Derivation of TTC for non-genotoxic chemicals based on structural class

- Munro *et al.* (1996) developed a database of 612 structurally well-defined organic chemicals, divided into three structural classes as defined by Cramer *et al.* (1978):
  - Class I: Substances with simple chemical structures and efficient modes of metabolism, suggesting a low order of oral toxicity (137 substances in database)
  - Class II: Substances which possess structures that are less innocuous than Class I but do not contain structural features suggestive of toxicity like those in Class III (28 substances in database)
  - Class III: Substances with a chemical structure that permits no strong initial assumptions of safety or may even suggest significant toxicity or have reactive functional groups (447 compounds in database)
- Most sensitive species, sex, and toxicological endpoint considered for each substance
- NOELs are converted to TTC by multiplying the NOEL by 60 kg body weight and dividing by a safety factor of 100

Figure 1: Plotted distribution of NOELs for each structural class



- **Structural Class I**
  - 5th percentile NOEL: 3.0 mg/kg bw/day
  - TTC: 1800 µg/person/day
- **Structural Class II**
  - 5th percentile NOEL: 0.91 mg/kg bw/day
  - TTC: 540 µg/person/day
- **Structural Class III**
  - 5th percentile NOEL: 0.15 mg/kg bw/day
  - TTC: 90 µg/person/day

Consumer exposure assessment to low level ingredients released from air freshener

This investigation focuses on three types of air freshener:

- **Continuous action products (CAP)** – are based on gel, membrane or wick-technology containing fragrances, surfactants and/or other gelling components.
- **Scented candles** – are on the market in a wide range of forms and with a wide range of fragrances. Generally scented candles contain a total fragrance level of about 3-6%, the balance being wax and other minor ingredients.
- **Spray aerosols** – are traditional sprays which are in a pressurized can and supplied either in a semi-concentrated or regular form. Typically these sprays contain the fragrance, emulsifiers, water and the propellant gas.

Consumer exposure scenarios

The following conservative consumer exposure scenarios were taken into account in the exposure assessment. Table 1 summarises the exposure scenarios chosen for this evaluation.

Table 1: Consumer exposure scenarios

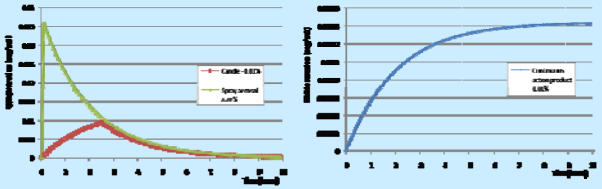
	Release Rate	Daily Exposure Time	Use Frequency	Room Size	Air Exchange
CAP	1g product per day	10 hours in living room*	Daily	Living 58 m^3	0.5 per hour
Spray	1.5g product per use	10 minutes directly after use	1.3 times per day	Bathroom 4 m^3	2.0 per hour
Candle	3.8 g product per hour	2.5 hr burning 10 hours stay	2 candles per week	Living 58 m^3	0.5 per hour

* Consumer research commissioned by the Belgium Ministry of Health (VITO, 2008) indicated an average stay of 4 hrs in a living room

Consumer exposure modelling

Using the above exposure scenarios, consumer exposures to emissions of low level ingredients released from air freshener were estimated by using the consumer exposure assessment model ConsExpo, Version 4.1, that has been developed by the Dutch Health Ministry (RIVM, 2009).

Figures 2a and 2b: Modelled time-concentration curves for Candles, Aerosols & CAP



Consumer exposure assessment

Consumer exposures were modelled for 3 ingredient concentrations using the vapour module: 0.01%, 0.05% or 0.1%. The rationale for using these percentages is that 0.01% and 0.1% are commonly used as *de minimis* levels by regulatory agencies. ConsExpo calculates the 'inhalation mean event concentration' (IMEC). The following assumptions were made in the exposure assessment:

Breathing rate:	12.2 m^3/day (ConsExpo default value for 'Rest')
Absorption:	100% of inhaled ingredient is systemically available
Body weight:	60 kg

Table 2: Modelled consumer's 'inhalation mean event concentration' (IMEC) and associated estimated internal dose/exposure values

	IMEC (µg/m^3)	Daily Internal Dose (µg/day)	Daily Internal Exposure (µg/kg bw/day)
CAP – 0.1%	1.15	5.8	0.1
CAP – 0.05%	0.58	2.9	0.05
CAP – 0.01%	0.12	0.6	0.01
Candle – 0.1%	32.3	47	0.78
Candle – 0.05%	16.2	23	0.39
Candle – 0.01%	3.23	4.7	0.08
Spray – 0. 1%	320	35	0.6
Spray – 0.05%	160	17	0.3
Spray – 0.01%	32	3.5	0.06

Comparison of consumer dose estimates to TTC levels

Under the assumptions being made in the exposure scenarios, estimated consumer doses to emissions of a 'fictitious' ingredient present in either continuous action products, candles or spray aerosols at levels up to 0.1% are below the lowest TTC level of 90 µg per day which has been established for Class III chemicals. This represents a 100-fold safety factor over the NOELs for Class III chemicals.

Discussion

- The TTC concept can be used to establish a *de minimis* level for consumer exposures to air freshener ingredients that are within the remit of the TTC and below which an acceptable risk to consumer can be assumed:
  - Consumer exposure is well understood and can be conservatively modelled;
  - Some structural, toxicological and toxicokinetic info is available for air freshener ingredients;
  - Genotoxic ingredients are not directly added to air fresheners;
  - TTC Class III level is the most conservative class;
- Comparing TTC levels which have been derived from oral toxicity studies to inhalation exposure, may require an additional assessment factor for route to route extrapolation to ensure appropriate conservatism;
- TTC concept does not allow for assessment of local effects such as respiratory or skin sensitisation.

Conclusion

- Considering an additional assessment factor of 5 for route to route extrapolation leading to a conservative TTC level of 18 µg per day , the application of the TTC concept suggests the establishment of *de minimis* level for AF Ingredients:
  - < 0.1% Continuous action products
  - < 0.05% Spray aerosols
  - < 0.01% Scented candles
- *De minimis* levels apply to systemic endpoints; local effects such as respiratory irritation or sensitisation are not addressed and require additional assessments.
- TTC should not be applied to potent carcinogens and bioaccumulative substances

References

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