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Exposure based waiving: The application of the toxicological threshold of concern (TTC) to inhalation exposure for aerosol ingredients in consumer products

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ABSTRACT

The inhalation toxicology studies available in the public domain have been reviewed to establish a database for inhalation toxicology and derive thresholds of toxicological concern (TTC) for effects in the respiratory tract and systemically for Cramer class 1 and 3 chemicals. These TTCs can be used as the basis for developing an exposure based waiving (EBW) approach to evaluating the potential for adverse effects from exposure to ingredients in aerosol products, used by consumers. The measurement of consumer exposure in simulated product use is key to the application of an exposure based waiving approach to evaluating potential consumer risk. The detailed exposure evaluation for aerosol ingredients with defined use scenarios, in conjunction with an evaluation of the potential structure activity relationship for toxicity and the TTCs for inhalation exposure could be used to waive undertaking inhalation toxicology studies under REACH. Not all classes of chemicals are suitable for such an approach, but for chemicals with a predictable low potential toxicity, and very low levels of exposure, this approach, could reduce the amount of inhalation toxicology studies required for the implementation of the European REACH legislation. Such an approach is consistent with the concept of developing 'intelligent testing strategies' for REACH.

1. Introduction

1.1. Key changes in the regulation of chemicals in the European Union

The recent implementation of two key pieces of European legislation will have a significant impact on the safety evaluation of aerosol products developed for consumer use. The REACH legislation (Registration, Evaluation and Authorisation of Chemicals) requires the safety assessment of chemicals manufactured or imported into Europe on a tonnage basis, with the scope and cost of toxicology testing increasing with the amount of tonnage used. The aim of this legislation is to ensure the safe use of chemicals with respect to human health and the environment, while at the same time minimising the additional animal based toxicology testing that is implicit in the evaluation of the safety of chemicals. The second piece of legislation passed recently is the 7th amendment to the Cosmetic Directive. The 7th amendment to the Cosmetic's Directive, bans the repeat dose toxicology testing of cosmetic ingredients after 2013. To continue to evaluate the safety of ingredients in aerosol products for consumer use an alternative approach to evaluating the toxicological safety of ingredients for use in aerosols needs to be developed, which does not use repeat dose inhalation toxicology testing.

1.2. An approach to safety evaluation using exposure based waiving

When simulated in use exposure measurements for consumer inhalation exposure to substances and chemicals in aerosols are carried out it is known that the respiratory tract exposure is low. The key question is how low would exposure need to be before it could be considered to constitute no appreciable risk of toxic hazard to the consumer? For regulatory purposes 'exposure based waiving' means exemption from conducting studies when the justification for the waiving is based on the fact that there is no relevant exposure of humans and environment. Relevant exposure is interpreted as meaning that exposure remains within acceptable burden limits, and it can be assumed that the exposure is not associated with any hazard potential for human health and the environment (REACH, Exposure Based Waiving, 2006). The way to test whether exposure based waiving could be used in the safety assessment of aerosol ingredients would be to examine the inhalation toxicology study data for gases and chemicals with a view to establishing a threshold of toxicological concern (TTC) for inhalation exposure.

If a threshold of toxicologic concern for inhalable ingredients could be established, below which it could be confidently assumed that there was no potential hazard, then aerosols could be

Abbreviations: TTC, threshold of toxicological concern; EBW, exposure based waiving; REACH TGD, Registration Evaluation and Authorisation of Chemicals Technical Guidance Document; NOAEL, no observed adverse effect level; NOAEC, no observed adverse effect concentration; LOAEL, lowest observed adverse effect level.

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designed to minimise the exposure to ingredients to the point where inhalation testing would not be considered necessary. This would avoid the use of animals in a 'safety by design' approach to aerosol safety evaluation.

1.3. Establishing a toxicological threshold of concern for inhalables

To establish a TTC for inhalation exposure we need to assess the potential for local toxic effects in the respiratory tract, the portal of entry of an aerosol ingredient for consumer exposure, as well as the possibility of systemic effects, when the ingredient is absorbed and becomes bioavailable throughout the body. By examining the available inhalation toxicology studies on a wide range of chemicals that are available through the safety programs of government agencies worldwide, we can build up a picture of the existing knowledge of the local and systemic toxicity of these chemicals, which could be considered to represent the likely and even unlikely ingredients in consumer aerosols. Considering the available inhalation toxicology study data for chemicals allows us to compile a database of toxicology NOAECs (no observable adverse effect concentrations) and NOAELs (no observable adverse effect levels) for both local and systemic adverse effects respectively and determine an appropriate benchmark dose (5th percentile) to use in determining a safe level of exposure to an ingredient with no inhalation toxicology data. Application of an appropriate safety factor to this benchmark value of the local and systemic NOAECs and NOAELs will give a threshold of toxicologic concern (TTC) for any local and systemic toxic effects below which there would be no safety concern for exposure. The recent draft opinion of the DG SANCO Scientific Committees on the TTC approach to safety assessment of chemical substances highlighted the need for work to be done in the area of inhalation toxicology (DG SANCO, 2008) (see Figs. 1–3).

1.4. Precedent for the use of the TTC in exposure based waiving

This principle has been used previously in the area of oral exposure to food contact materials and flavourings, to develop a threshold of toxicologic concern (TTC) (Barlow et al., 1999; Cheeseman et al., 1999; Cramer et al., 1978; Kroes et al., 2000, 2004, 2005, 2007; Munro et al., 1996, 1999; Renwick, 2004). This is a proposed level of exposure below which there is considered to be no concern for a lifetime exposure to a chemical from a toxicology perspective. More recently, the TTC concept has been advocated and used for determining the safety of cosmetic ingredients when there is systemic exposure through dermal application. However, the expert working group did not address the question of deriving a local dermal TTC (Kroes et al., 2007). To apply this concept to the use of ingredients in consumer aerosols the toxicity of inhalable chemicals to the respiratory tract has been evaluated, as well as systemic toxic effects.

Some categories of chemicals have been excluded from this type of evaluation, such as known genotoxic carcinogens, protein allergens, some neurotoxic chemicals (organophosphates) and metals and dioxins. None of these types of chemicals would be considered for use in a consumer aerosol for obvious safety reasons. If they were potential protein allergens they would be evaluated specifically for potential respiratory sensitisation.

2. Methods

2.1. Analysis of the available inhalation toxicology data for chemicals to derive TTC values for local and systemic effects

There is an extensive inhalation toxicology database of over one hundred rodent (mostly rat) studies that have been conducted by industry and government agencies to evaluate the toxic potential of both gases and less volatile chemicals in aerosols. Some studies used were on particulate matter (amorphous silica) or were

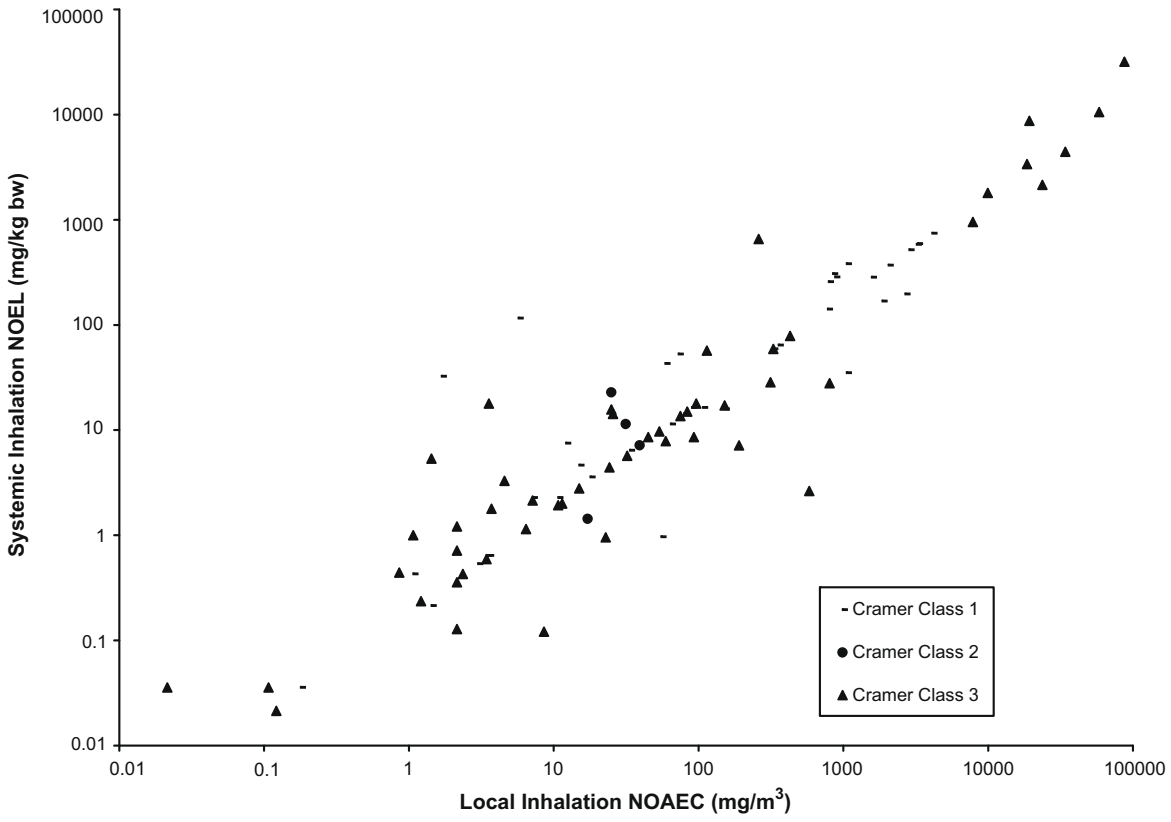

Fig. 1. Relationship between local inhalation NOAECs and systemic NOAELs derived from the inhalation database for chemicals in the 3 Cramer classes.

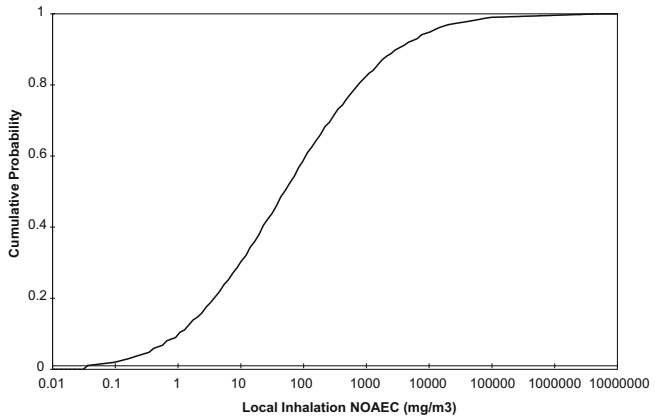

Fig. 2. Cumulative distribution of the most conservative inhalation NOAECs for compounds in the inhalation database.

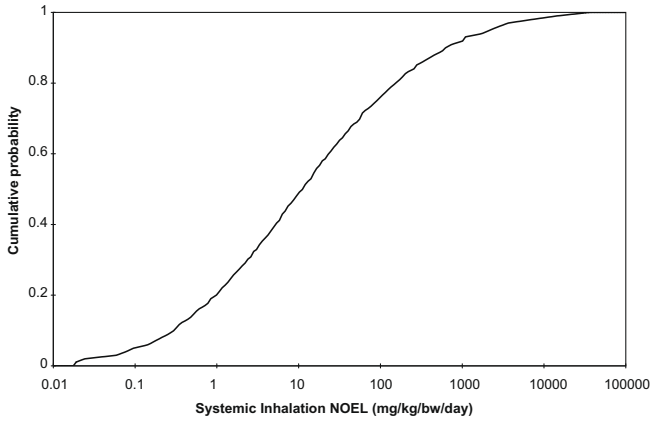

Fig. 3. Cumulative distribution of the most conservative systemic NOELs for compounds in the inhalation database.

carried out on the solid form of the chemical such as benzoic acid dust, for determining a safe level for occupational exposure. Some chemicals were also prepared as aerosols and the respirable exposure determined as part of the study. For rat inhalation studies complimentary studies on the particle size distribution to determine the MMAD (mass median aerodynamic diameter) and GSD (geometric standard deviation) are also conducted, to ensure that the exposures for non-gaseous chemicals are in the respirable range for rats (<3.5 μm). The inhalation studies used are publically available through the US EPA High Production Volume Chemicals reports (Screening Initial Data Sets; SIDS reports) and through published evaluations carried out by agencies and organisations such as the BfR (German Federal Institute for Risk Assessment), TNO (Netherlands Organisation for Applied Scientific Research) and ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals) reports on specific chemicals.

2.2. Excluded chemicals and substances

In reviewing these studies for respiratory tract and systemic effects certain types of chemicals were excluded as they were not considered representative of the ingredients that are, or could be used, in aerosols for consumer use.

Those chemicals that were excluded were chemicals where there was existing evidence that they were:

1. Genotoxic carcinogens
2. In vivo mutagens (presumed carcinogens)
3. Heavy metals (neurotoxic)
4. Dioxins and PCBs (accumulative and biopersistant)
5. Organophosphates (neurotoxic)
6. Polymers (require substance specific data)

Most of these categories of chemicals have been excluded from previous TTC evaluations because of the potency of the particular toxicity associated with them. Genotoxic carcinogens (and hence in vivo mutagens, which are presumed to be genotoxic carcinogens, in the absence of bioassay data), are not considered to have a threshold for their effect. Polymers are a special additional case where the biopersistence in the respiratory tract would cause additional concern, necessitating substance specific data to complete the risk assessment (Carthew et al., 2002, 2006).

2.3. Studies evaluated

Because the derivation of the NOAEC should be very conservative (lifetime of exposure) only inhalation studies that were subacute, or subchronic were used (other than existing two year studies), as the NOAECs from these studies could be corrected to a lower NOAEC for chronic exposure using the well documented and justified adjustment factors (REACH Technical Guidance Document (TGD), 2008). Inhalation studies using the rat were used because this represents the majority of the available data prepared to OECD guidelines for inhalation testing and is usually done to GLP (good laboratory practice) standards.

Twenty or so inhalation studies were excluded from analysis because they were on genotoxic carcinogens and use of such substances is banned under the EU Cosmetics Directive (Directive 2003/15/EC). A total of 92 rat inhalation studies were reviewed using this set of criteria. In the rare instance where no NOAEC was identified, the range of endpoints was reviewed and the incidence and severity grading was used to apply an additional uncertainty factor to extrapolate from a LOAEL to a NOAEL. This was 10 for both cases in this dataset.

2.4. Derivation of group NOAECs /NOAELs from the NOAECs for local and systemic effects from inhalation studies

As in previous work to derive a group NOAEL for use in deriving a subsequent TTC, the 5th percentile has been used to derive, in this case, a NOAEC for local effects and also a NOAEL for systemic effects by using the default values for breathing rate and time of exposure (corrected to a 6 h per day standard and five days a week exposure). A designation of the Cramer class of the chemical was obtained using the Toxtree program. The ninety two chemicals split roughly into 40% class one and 54% class three with only four chemicals in class two (Appendix A).

2.5. Derivation of the TTC for local and systemic effects

The previous TTCs for systemic effects based on oral studies were derived by applying uncertainty factors for interspecies variation in toxicokinetics and toxicodynamic (10-fold) and also an additional uncertainty factor of 10 for intraspecies differences in toxickinetics and toxicodynamics, to a 5th percentile of the NOAELs derived from oral toxicology studies (Renwick et al., 2003). Using the analogous REACH (European Registration Evaluation Authorisation of Chemicals) process a DNEL (derived no effect level) is derived by applying adjustment (uncertainty) factors to the benchmark dose (5th percentile NOAEC/NOAEL) for a chemical. As the same process would be used, on the benchmark dose, the TTC is equivalent to the group DNEL for a Cramer class derived using a 5th percentile benchmark, rather than a chemical specific NOAEL.

This overall uncertainty factor should be adjusted for differences between rat and human exposure. The REACH TGD specifies an uncetainty factor of 10 for inter-individual variations in human toxicokinetic and toxicodynamic responses. A further uncertainty factor of 2.5 is used for interspecies differences in response, for inhalation exposure, making a total of 25. Allometric scaling is not required as part of the evaluation as this has already been considered in the exposure metric for inhalation of mg/m^3 (REACH TGD, 2008). The overall uncertainty factor of 25 is the same as used in the derivation of the systemic TTC from inhalation studies on the RepDose chemicals database, evaluated by the Fraunhofer Institute (poster exhibited at Eurotox 2008, Rhodes, Greece).

3. Results

Appendix A shows the corrected NOAECs for respiratory tract (local) effects and NOAEL for systemic effects for each of the 92 chemicals classified by the Cramer groups 1–3. Tables 1 and 2 show the derived 5th percentile values of the NOAECs and NOAELs for local and systemic effects by Cramer class and overall for the 92 chemicals reviewed. Table 3 lists the TTC obtained from the Cramer classes, individually and in total, for the respective local NOAECs and systemic NOAELs.

3.1. Comparison of systemic inhalation based TTCs with the TTCs derived for the Cramer classes from oral toxicology studies

The TTCs for systemic effects with Cramer classes 1 and 3 based on inhalation data lie between the class 1 and 3 values based on

Table 1
Local NOAELs for the individual and all Cramer class chemicals derived from inhalation studies. Local effect in respiratory tract.

Cramer class	Number in class	5th percentile for local effects NOAEC (mg/m^3) for 6 h day	5th % NOAEL for local effects μg /g lung tissue/day[a]
1	38	1.4	54
3	50	0.47	18
1+2+3	92	0.97	38

[a] Assuming a rat lung weight of 1.4 g.

Table 2
Systemic NOAELs for the individual and all Cramer class chemicals derived from inhalation studies. Systemic effects.

Cramer class	Number in class	5th percentile for systemic effects NOAEL (mg/kg/day)	5th % NOAEL for systemic effects μg/kg/day[a]
1	38	0.41	410
3	50	0.07	70
1+2+3	92	0.13	130

[a] Body weight used 60 kg.

Table 3
Local and systemic TTCs derived for the individual and all Cramer classes from inhalation studies.

Cramer class	Number in class	TTC for local effects μg /g lung tissue/day	TTC for systemic effects μg/kg/day
1	38	2.1	16.4
3	50	0.73	2.8
1+2+3	92	1.6	5.1

Table 4
TTC for systemic and local effects derived from oral and inhalation studies (60 kg subject).

Cramer class	TTC for systemic effects μg/day from inhalation exposure	TTC for systemic effects μg/day from oral exposure	TTC for local effects μg/day from inhalation exposure[a]
1	980	1800	1400
3	170	90	470
1+2+3	300	–	1000

[a] Using human lung weight of 650 g.

studies carried out by the oral route (Table 4). This is not surprising since the inhalation dose is assumed to be 100% while the applied absorption factor of 50% (REACH TGD) is probably an overestimate of bioavailability. The systemic effect of inhaled doses is therefore likely to be greater than the equivalent oral exposure, due to higher internal dose. While this seems to be the case for class 1 chemicals by inhalation the TTC is higher for class 3, where the presumption of toxicity is often a default for chemicals with no structural alerts, and therefore less likely to be the case. It is reassuring that there is no huge difference between the systemic TTCs derived by data from inhalation studies compared to the TTCs derived from oral studies, and that the values for inhalation systemic TTCs lie within the range of 1800–90 μg/day for the oral Cramer classes 1 and 3 (least and most toxic) TTC values. The effect of using all of the data in the inhalation database on the NOAECs, NOAELs and TTCs for local and systemic effects is also shown in Tables 1–4 for comparative purposes (Cramer 1+2+3). The spread of the Cramer classes 1 and 3 is much lower for inhalation toxicity than for oral toxicity, being consistent with the findings of the 3-fold variation between Cramer class 1 and 3 in the Fraunhofer RepDose work analysing inhalation toxicology studies for systemic TTCs (Escher et al., 2008).

4. Discussion

4.1. Chemicals with NOAECs or NOAELs below the 5th percentile

There were only five chemicals with local NOAECs below the 5th percentile.

These were sulphuric acid, trimellitic acid, glutaraldehyde, hydrogen peroxide and 1,2-dichloro-4-nitrobenzene. For systemic effects sulphuric acid, trimellitic acid, glutaraldehyde, and 1,2-dichloro-4-nitrobenzene plus 2,2'-dimethyl-4,4'methylenebis(cyclohexylamine) were below the 5th percentile for the NOAEL.

It was not surprising that the chemicals that fell below the 5th percentile for both local and systemic effects were strong acids or bases which would cause severe local irritancy in the respiratory tract, a chlorinated benzene derivative, glutaraldehyde and 2,2'-dimethyl-4,4'methylenebis(cyclohexylamine), which is a severe respiratory and skin irritant. None of these chemicals would be considered as suitable ingredients in consumer aerosols, based on their physicochemical properties, as strong acids or bases, or potential chemical reactivity and would have been excluded from consideration on this basis alone.

This indicates that the identified 5th percentile for deriving a TTC for inhalable ingredient in consumer aerosols would not miss any chemicals with an unacceptable local lung toxicity, and this TTC value could be used with confidence to compare the simulated consumer exposure to carry out a risk characterisation. The RepDose database derived inhalation TTC for systemic effects is lower, but this could be due to the inclusion of additional chemicals relevant to occupational exposure, which are likely to be intrinsically more toxic, reducing the overall TTC for systemic exposure by inhalation. The full details of the chemicals included in the RepDose inhalation database have not as yet been published (Escher et al., 2008). An approach has also been developed to establishing a Concentration of No Toxicological Concern (CoNTC) as a risk assessment screening tool for air toxicants (Drew and Frangos, 2007). The value derived for the CoNTC is conservative and precautionary for protection of public health, so it is very low (0.03 mg/m^3). This is because it is based on the generic threshold of toxicity for carcinogens, including those that may act via a mutagenic mode of action. Clearly, this would not be relevant for ingredients in consumer aerosol products, which would not include any known carcinogens.

In the present paper, the approach proposed to deriving a TTC for local and systemic effects from inhalable chemical substances uses a targeted approach to safety evaluation, rather than considering the entire world of chemicals, which would include genotoxic carcinogens and other chemicals with a toxicology profile which would automatically make them unacceptable for use in a consumer product. To achieve this, an approach based on a series of preliminary exclusion criteria has been developed.

In terms of the exclusion criteria, in a tiered approach to the safety evaluation of chemicals suitable for consideration in the TTC approach to aerosols, strong acids and bases would also be excluded at the preliminary stage in the evaluation, on the basis of their physicochemical properties. Chemicals where there is existing evidence of skin sensitisation, or with reactive groups (such as aldehydes) where irritation or respiratory sensitisation would be suspected would be evaluated on a data specific basis.

A structured approach to inhalation safety for a chemical in a consumer aerosol product can be summarised in the following steps.

4.2. Risk characterisation for the potential inhalation toxicity of an ingredient in an aerosol product

4.2.1. Preliminary review of the structure activity relationship for the chemical

Exclude;

1. Genotoxic carcinogens
2. In vivo mutagens (presumed carcinogens)
3. Heavy metals (neurotoxic)
4. Dioxins and PCBs (accumulative and biopersistent)
5. Organophosphates (neurotoxic)
6. Polymers (require substance specific data)
7. Substances with properties of a strong acid or base
8. Potential respiratory sensitisers
9. Irritants (strong acids or bases)
10. Pharmacological actives

Review existing mutagenicity data, skin irritation and sensitisation data. If negative, continue with exposure estimation.

4.2.2. Obtain exposure data for simulated use of aerosol ingredient

The importance of exposure, in terms of deciding whether the risk characterisation is acceptable, has been highlighted as part of implementing REACH (Bernauer et al., 2008). The question is whether the exposure is relevant (i.e. detrimental or adverse) or non-relevant (de minimus) becomes the critical issue (Bernauer et al., 2008). This consideration means that the more refined the exposure is, preferably based on actual measurements, the more accurate the risk characterisation will be.

The best way to achieve this is to measure the actual human Respirable Dose (RDose) for the inhalable range of particle sizes (<20 μm) under conditions of simulated consumer use (μg/second spray) (Carthew et al., 2002). The consumer exposure is then calculated from the application, i.e. number of seconds use × inhalable dose (<20 μm particle size), for local respiratory tract exposure in μg/g lung tissue and μg/kg body weight/day, assuming a human lung weight of 650 g, a body weight of 60 kg and 100% retention in the respiratory tract and absorption, systemically (Carthew et al., 2002).

4.2.3. Risk characterisation for consumer exposure

The simulated, measured, human exposure estimate should be compared to the acceptable TTC (DNEL) derived from the rat inhalation toxicology database, for both local and systemic effects. For local effects the TTC for Cramer class 1 substances could be used (1400 μg/day), or if a more precautionary approach was considered appropriate, the lower Cramer class 3 value (470 μg/day) would apply. Similarly, the appropriate Cramer class TTC for systemic effects can be used for the risk characterisation.

If the risk characterisation shows the human daily simulated exposure to the ingredient for the particular application and formulation is less than the appropriate TTC (DNEL) the risk would be considered negligible. This would mean that, using the exposure based waiving principle, inhalation specific data would not have to be generated for the chemical/substance, and a repeat dose inhalation toxicology study would be unnecessary.

5. Conclusions

Using the available inhalation data, thresholds of toxicologic concern (TTCs, or REACH equivalent DNELs) have been derived for both local and systemic effects, arising from inhalation exposure to chemicals. The values for local effects differ only by a factor of 3-fold with the least and most toxic Cramer classes (1 and 3), and by 6-fold for the threshold for systemic effects. Comparing the exposure to ingredients from consumer aerosol products to the acceptable TTC (DNEL) for local and systemic effects from inhalable chemicals allows us to characterise the risk for aerosol ingredients.

Applying this approach to the safety assessment of selected aerosol ingredients, specific toxicology inhalation testing would not be considered necessary when the consumer exposure is lower than the TTC for local effects in the respiratory tract, at the proposed level of use in an aerosol application. Additional systemic exposure from dermal absorption would have to be evaluated and either compared to the systemic TTC, or a NOAEL (DNEL under REACH) from a subacute, or subchronic toxicology study, if this is available. While it is possible to use this approach to examine the possible exposure related approval of ingredients in consumer aerosol products, there are some important classes and types of chemicals and materials (polymers in particular) where this approach should not currently be employed.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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Appendix A. List of chemicals evaluated for local and systemic effects from the available subacute, subchronic and chronic inhalation toxicology studies

No.	Chemical	Local NOAEC[a] (mg/m^3)	Systemic NOAEL (mg/kg/day)	Reference
Cramer class 1				
1	Benzene alkylate 225	39	7	Monsanto Report BD-84-277, OECD SIDS (1995)
2	Benzoic acid	3	0.5	OECD SIDS (2001a), IRDC (1981)
3	1,4-Butanediol	79	14	Stasenkova (1965), OECD SIDS (2000a)
4	*n*-Butyl acetate	847	307	David et al. (2001)
5	Butyraldehyde (isobutyraldehyde)	1052	35	Abdo et al. (1998)
6	2-Butoxyethanol	107	16	Dodd et al. (1983)
7	Diethylene glycol butyl ether	34	6.4	OECD SIDS (2005a)
8	Diethylene glycol ethyl ether	11	2.3	OECD SIDS (2005a)
9	*N*,*N*-Dimethylacetamide	64	11	Malley et al. (1995)

(*continued on next page*)

Appendix A (*continued*)

No.	Chemical	Local NOAEC[a] (mg/m^3)	Systemic NOAEL (mg/kg/day)	Reference
10	Dimethyl Terephthalate	3.6	0.6	Krasavage et al. (1973)
11	Ethylene	4110	743	CIIT (1977), Hamm et al. (1984)
12	Ethylene glycol hexyl ether	151	16	Klonne et al. (1987)
13	Ethylene glycol propyl ether	327	59	Katz et al. (1984)
14	Ethylacetate	90	16	Christoph et al. (2003)
15	Ethylbenzene	1857	169	National Toxicology Program Report TR-466 (1992)
16	2-Ethylhexanol	152	28	Klimisch et al. (1998)
17	Glutaraldehyde	0.18	0.036	Gross et al. (1994)
18	Glycerol	59	43	Renne et al. (1992)
19	Hydroxypropyl Acrylate	1.1	0.4	Quast et al. (1983), OECD SIDS (2005c)
20	Isobutanol	2679	196	Branch et al. (1996)
21	Isobutylene	3270	593	National Toxicology Program Report TR 487 (1998)
22	Isophthalic Acid	1.4	0.2	IITRI (1988)
23	Methanol	779	140	WHO (1997)
24	3-Methylbutanal (Isovaleraldehyde)	1052	382	Abdo et al. (1998)
25	3-Methyl-2-butenal	12	7.5	BASF (1994)
26	Methyl methacrylate	73	53	Lomax et al. (1997)
27	4-Methylpentan-2-ol (methyl isobutyl carbinol)	3207	581	Blair (1982)
28	Methyl isobutyl ketone (MIBK).	1570	248	Phillips et al. (1987)
29	Mineral oils	18	3.6	Dalbey and Biles (2003)
30	Pentaerythritol	2857	518	Keplinger and Kay (1964), OECD SIDS (1998)
31	2-Propanol	876	286	Burleigh-Flayer et al. (1997)
32	Propylene	2050	370	Quest et al. (1984)
33	Propylene glycol (1,2-dihydroxypropane)	5.7	116	Suber et al. (1989)
34	Polyethyene glycol 200	357	64	Crook et al. (1981)
35	Terephthalic acid	7	2.3	OECD SIDS (2001b)
36	Triethanolamine (TEA)	1.7	33	Gamer et al. (2008)
37	1,2,3,4-Tetrahydronaphthalene	15	4.6	OECD SIDS (2004b)
38	Triacetin	793	257	Fassett (1955), OECD SIDS (2002b)
Cramer class 2				
39	Benzene Alkylate 215	39	7	Monsanto Report ML-82-1, OECD SIDS (1995)
40	Methylacrylic acid	25	23	CIIT (1984), OECD SIDS (2000b)
41	2-Propen-1-ol	17	1.4	Dunlap et al. (1958)
42	3,5,5-Trimethylcyclohex-2-enone (isophorone)	31	11.4	OECD SIDS (2003e,g)
Cramer class 3				
43	Acetic anhydride	1.4	5.4	Huntingdon (1996), OECD SIDS (1997)
44	Ammonium persulphate	3.7	1.8	Last et al. (1982)
45	Benzene, 1-chloro-2-(chloromethyl)	2.4	0.4	OECD SIDS (2003a)
46	Bisphenol A	3.6	18	NTP-CERHR, 2007
47	2-Butene, 1,3-dichloro-	7.1	2.1	OECD SIDS (2006a)
48	t-Butyl alcohol	15	2.8	NTP (1997)
49	*N*-tert-butylbenzothiazole-2-sulphenamide	3.4	0.6	OECD SIDS (2003f)
50	ε-Caprolactam	25	16	Reinhold et al. (1998)
51	ε-Caprolactone	26	14	Norris and Kintigh (1992), OECD SIDS (2004)
52	1-Chloro-1,1-difluoroethane	58,400	10,600	Kelly and Trochimowicz (1976), OECD SIDS (2001c)
53	3-Chloropropyltrimethoxysilane	580	2.6	Dow Corning (1993), OECD SIDS (2006b)
54	1-Chloro-1,2,2,2-tetrafluoroethane (HCFC-124)	9900	1800	Haskell Laboratory for Toxicology and Industrial Medicines (1991), OECD SIDS (2003b)
55	Chloromethane	330	59	CIIT (1981)
56	3-Chloropropene (allylchloride)	23	1	OECD SIDS (1996a)
57	Decamethylcyclopentasiloxane (D5)	150	17	Burns-Naas et al. (1998)
58	Diacetone Alcohol	800	28	OECD SIDS (2002a)
59	1,1-dichloro-1-fluoroethane (HCFC 141b)	34200	4430	Brock et al. (1995)
60	1,2-Dichloro-4-nitrobenzene	0.12	0.02	OECD SIDS (2003c)

Appendix A (*continued*)

No.	Chemical	Local NOAEC[a] (mg/m^3)	Systemic NOAEL (mg/kg/day)	Reference
61	1,4-Dicyanobutane	11	2	OECD SIDS (1993)
62	Dicyclopentadiene	96	18	Bevan et al. (1992)
63	Diethanolamine	1.1	1	Gamer et al. (2008)
64	Diethylenetriaminepentaacetate	2	1.3	Unilever (2002)
65	1,1-Difluoroethane (HFC-152a)	19,300	8,700	Dupont (1982), OECD SIDS (2007)
66	1,1-Difluoroethylene	18,600	3,400	Arts et al. (1991), OECD SIDS (2003d)
67	*N*-(1,3-dimethylbutyl)-*N*′-phenyl-1,4-phenylenediamine	6.4	1.1	Monsanto (1976), OECD SIDS (2005b)
68	Dimethylformamide	54	10	Malley et al. (1994)
69	2,2'-dimethyl-4,4'methylenebis(cyclohexylamine)	8.6	0.1	OECD SIDS (2001d)
70	Dipropylene Glycol Methyl Ether (DPGME)	430	79	Landry and Yano (1984)
71	5-Ethylidene-2-norbornene	93	8.6	Ballantyne et al. (1997)
72	2-Furanmethanol, tetrahydro	75	14	OECD SIDS (2005d)
73	Hexamethyldisiloxane (D6)	23,700	2140	Cassidy et al. (2001)
74	Hexamethylenediamine	4.6	3.3	OECD SIDS (1996b)
75	Hydrogen chloride	11	2	Toxigenics (1984), OECD SIDS (2002c)
76	Hydrogen peroxide	0.9	0.4	Kondrashov (1977)
77	3-Methoxy-3-methyl-1-butanol (MMB)	190	7	OECD SIDS (2005e)
78	Propylene glycol monomethyl ether (PGME)	7860	950	ECETOC (1995)
79	Methylacrylonitrile	114	57	Pozzani et al. (1968)
80	Methyl bromide	84	15	Reuzel et al. (1991b)
81	2-nitroaniline	1.2	0.2	Nair (1983)
82	Octamethylcyclotetrasiloxane (D4)	260	660	Burns-Naas et al. (2002)
83	2,4-Pentanedione	314	29	Dodd et al. (1986)
84	1,1,1,2,2-Pentafluoroethane (HFC-125)	87,500	31,800	OECD SIDS (2006c), Nakayama (1993)
85	Permethrin	45	8.6	Metker (1978)
86	Phosphorus trichloride	2	1.2	Monsanto (1983), OECD SIDS (2004a)
87	Propylene dichloride (1,2-dichloropropane)	24	4.4	Parker et al. (1982)
88	Silicon dioxide (synthetic amorphous silica)	2	0.7	Reuzel et al. (1991a)
89	Sulphuric acid	0.02	0.04	Kilgour et al. (2002)
90	1,1,2-Trichloroethane	59	8	OECD SIDS (2002d)
91	Trimellitic Acid	0.11	0.04	IITR (1989), OECD SIDS (2002e)
92	*N*-vinyl-2-pyrrolidone	32	5.7	Klimisch et al. (1997)

[a] NOAEC for 6 h/day exposure corrected to a value for chronic exposure and for 5 days per week.

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