Recommendation no. 11

of the BPC Ad hoc Working Group on Human Exposure

Proposal for harmonising the assessment of human exposure to repellents (PT19)

(Agreed at the Human Health Working Group III on 25 May 2016, revision agreed at Human Health Working Group V on 22 November 2017)

Publication date: 18 January 2018[1]

[1] For the rules on the applicability of new guidance, please consult the CA document "Relevance of new guidance guidance becoming available during the process of authorisation and mutual recognition of authorisations of biocidal products" (CA-July12-Doc.6.2d – Final) for biocidal products and the BPC document "Applicability time of new guidance and guidance-related documents in active substance approval" (BPC-13-2015-17) for active substances.

Document history		
Version	**Changes**	**Date**
1	First version	Agreed at WGIII 2016
2	Changes to the document: • Modification of uncovered body surface area to 55% • Inclusion of reference to Bremmer and Van Veen, 2000 • Modification Table 1 assuming 55% uncovered body surface area and including new age category (children 2 < 6 years old) • Inclusion Table 5 (exposed skin surface area when long-sleeved shirts and trousers are worn, for adults) • Reordering of paragraphs and modification of headings.	Agreed at WGIV 2017
2.1	Changes to the document: • Alignment between application rates used in efficacy and human exposure assessment • Replacing reference to HEEG Opinion 17 by HEAdhoc Recommendation 14	Agreed at WGV 2017

1. Introduction

According to the Pest Control Products Fact Sheet[2], repellents (biocidal products of PT19) are supplied as liquids (milk, gel, lotion) in plastic bottles, as impregnated cloths, as sticks or as sprays. All of these biocidal products are ready to use. They must be applied to the skin and are meant to keep insects away from the skin. They are normally applied to those parts of the body that are not covered by clothing. Sometimes users apply the biocidal products to their clothes to keep away crawling insects such as ticks, or to prevent mosquitoes from biting through the clothes. The use of these biocidal products results particularly in exposure of the skin. Oral exposure can also occur as a result of hand-mouth contact if hands are not washed after applying the biocidal product. Inhalation exposure to aerosols, e.g. from spray application, is also possible.

This recommendation proposes the models currently available for assessing human exposure to repellents. It has to be noted that the proposal made in the recommendation is not legally binding. Applicants and assessors can choose the model to apply and the relevant recent discussions on repellents within the CG with regard to human exposure assessment and risk mitigation measures should be taken into account.

2. Aim of the recommendation

The aim of this recommendation is to make a proposal for harmonising the assessment of human exposure to repellents. The discussion covers approaches based on default values and existing data and approaches based on data generated by the applicant.

3. Proposal for harmonization

3.1. Oral exposure

Underlying data for assessment of oral exposure

Oral exposure due to hand-to-mouth contact is a realistic route of exposure especially for children and infants. Hand-to-mouth transfer could also happen in adults, as the products are applied to the skin with bare hands. It is considered that a reverse reference scenario for oral ingestion should be used for exposure assessment. According to the Pest Control Products Fact Sheet, the oral route is also important for adults as the products are applied to the skin with bare hands. It is expected that children will ingest the entire amount that is rubbed onto their hands, and that adults will ingest the amount on their fingers.

[2] The former Technical Notes for Guidance on Human Exposure to Biocidal Products 2002 (TNsG 2002) reflected the general considerations and values reported in the Pest Control Products Fact Sheet in relation to repellents. Since the TNsG 2002 is now incorporated in the Biocides Human Health Exposure Methodology document, reference only to the Pest Control Products Fact Sheet is made in this recommendation, where relevant.

Taking into account the default human factor values agreed in the HEAdhoc Recommendation 14, the surface of the hands is approximately 8 % of the total particular treated body surface (head, hands, arms, legs and feet) for infants, toddler, children and adults. As it is expected that adults will ingest the amount on their fingers only, the factor of 4 % of the total treated body surface (head, hands, arms, legs and feet) can be used as a rough estimation (50 % surface of the hands).
Regarding the default assumptions of ingesting the entire amount rubbed onto the hands (100 % transfer coefficient), it has to be highlighted that no saliva extraction factor is taken into consideration.

Approach to assess oral exposure

A reverse reference scenario for oral ingestion using the below mentioned default values for skin surface area should be considered for exposure assessment. Nevertheless, the content of an ingredient that acts as a strong deterrent for ingestion (e. g. denatonium benzoate) is important to prevent ingestion of the biocidal product. For infants and older children, 8 % of the total applied product amount with a transfer coefficient of 100 % should be used for oral exposure assessment due to hand-to-mouth contact even if an aversive agent is added to the biocidal product and exposure of hands cannot be excluded (no saliva extraction factor considered). For adults 4 % of the total applied product amount (only fingers would be licked) with a transfer coefficient of 100 % should be applied if no aversive agent is added (no saliva extraction factor considered). In addition, appropriate label statements should be indicated as risk mitigation measures to minimise oral ingestion due to hand-to-mouth contact.

Deterrent/ Aversive agents

Adding an ingredient that acts as a strong deterrent for ingestion (e.g. denatonium benzoate) is important. However, efficacy in preventing ingestion of the biocidal product formulation in all age groups should be considered. Sometimes, a self-deterrent is added to denature the alcohol component, but the content of that deterrent might be too low for the purpose of preventing ingestion. It is known that some persons cannot taste denatonium benzoate, particularly young children and infants. In addition, for young children it takes time for the ability to taste the deterrent to develop. Therefore, inclusion of the taste deterrent will not restrict ingestion by all persons. Nonetheless, aversive agents should be included in repellent products applied to human skin to act as taste deterrents for ingestion. Moreover, further risk mitigation measures (e.g. application by adults, washing of hands, non-application on hands, no application by infants and younger children) are required. In cases where denatonium benzoate is added as an aversive agent, the ingestion of the entire amount rubbed onto the hands is unrealistic, so a reduction of 100 % ingestion of hand exposure might be possible. Due to missing data concerning this reduction, no proposal is made here.

In addition to adding an aversive agent, a label claim like “For children 2 to 12 years: The repellent must be applied by adults. Do not apply to children's hands” and “Keep out of reach

of children" may be a suitable risk mitigation measures to minimise oral ingestion due to hand-to-mouth contact[3].

3.2 Inhalation exposure

Underlying data for assessment of inhalation exposure

Inhalation exposure may be possible resulting from inhaling aerosols or pump sprays after spraying. According to the Biocides Human Health Exposure Methodology, particles smaller than 5 µm in diameter are respirable for humans. In general the cut-off the respirable fraction is 10 µm (de Winter-Sorkina and Cassee, 2002) and assumption is made in ConsExpo 4.1 that the inhalable fraction is 50 µm. Non-respirable particles/droplets may be ingested orally.

Moreover, exposure via inhalation (including oral uptake of non-respirable particles), if applied outdoors or in well/ventilated areas, is normally considered lower or negligible. This also applies for aerosol sprays. It is recommended to assess inhalation exposure by ConsExpo 4.1 (exposure to spray) or according to the Biocides Human Health Exposure Methodology (page 220, hand-held trigger spray or pre-pressurised aerosol spray can depending on the spray device).

Exposure via inhalation cannot be fully ruled out, therefore a recommendation on ventilation is considered necessary for spray formulations (e.g. safety phrases comparable to S23, S51). Appropriate label statements should also be indicated as risk mitigation measures to minimise inhalation exposure.

Approach to assess inhalation exposure

Inhalation exposure can be assessed using ConsExpo 4.1 (exposure to spray) or the Biocides Human Health Exposure Methodology (page 220, hand-held trigger spray or pre-pressurised aerosol spray can depending on the spray device). For ConsExpo the following default parameters are proposed: spray duration 15 s (ConsExpo default for hair spray); exposure duration: 1 min; room volume 20 m^3; room height 2.5 m; ventilation rate: 2.5 h^{-1} (if use in bedrooms with opened windows is assumed, ConsExpo General Fact Sheet, 2014) or 6 h^{-1} (if use in well-ventilated areas like outdoors is assumed, rounded maximum value from ConsExpo General Fact Sheet, 2014); spraying towards exposed person; cloud volume: 0.0625 m^3 (ConsExpo default for hair spray and other cosmetics); volume mass generation rate: 0.8 g/s for trigger spray and 1.1 g/s for pre-pressurised aerosol spray can (ConsExpo defaults for pest control products). Appropriate label statements should also be indicated as risk mitigation measures to minimise inhalation exposure.

3 Discussions are ongoing within the Coordination Group (CG) to define a harmonised position at EU level regarding the acceptability of risk mitigation measures (RMMs) and label instructions for repellents. Therefore, the label statements indicated in this recommendation to minimise oral exposure may be subject to changes once the harmonised approach for RMMs is reached.

3.3. Dermal exposure

Approach to assess dermal exposure

The proposed approach refers to potential systemic exposure assessment. Local effects assessments (e.g. for irritancy/sensitisation) are not addressed in this recommendation, but need to be considered during product evaluation.

In assessment of dermal exposure the results of the repellent usage study (Boomsma and Parthasarathy, 1990) are considered acceptable and can be used, provided that a letter of access is available. If a letter of access is not available, data from the US-EPA SOP for Residential Exposure Assessment (2012) can be used. In this case, a distinction between different devices (pump spray, aerosol, lotion) is possible. Due to the reasons given below (section 2), the 95th percentiles are acceptable. As a worst case scenario it should be assumed that non-professionals may apply the repellent active ingredient on skin and clothing (see table 1). For further refinement, values for applying the repellent active ingredient to skin only (see table 2) might be appropriate presuming that it is accepted that application can be limited to skin by additional labelling. However, using the values for applying the repellent active ingredient to skin only (see table 2) only results in a 5 % reduction of exposure compared to values used for application on skin and clothing.

If a risk is identified using the below product application amounts, further approaches taking into account the application rate, such as the UK Proforma, can be used in the exposure assessment. It has to be noted that the implementation of the approaches based on application rates should be in line with the conclusions agreed during the CG-16 meeting, mentioned in part 4. "Approaches based on data generated by the applicant" below.

In any case, efficacy data should support the values used for the exposure assessment.

The default human factor values agreed in the HEAdhoc Recommendation 14 are recommended to be applied in the assessment.

It has to be noted that, if exposure through clothes needs to be assessed, the 50% protection factor[4] could be applied as a refinement, according to the HEAdhoc Recommendation no. 8

Underlying data for assessment of dermal exposure

The following data sources give different product application amounts (dermal exposure) for repellents used as pump spray or aerosol and will be discussed here:

1. Repellent usage study of Boomsma and Parthasarathy (1990)
2. US-EPA SOP for Residential Exposure Assessment (2012)
3. Pest Control Products Fact Sheet
4. Approach based on data generated by the applicant

[4] The protection factor of 50% represents the capacity of clothes to reduce exposure for the covered parts and does not represent the area of skin covered by clothes.

1. Repellent usage study of Boomsma and Parthasarathy (1990)

The study of Boomsma and Parthasarathy (1990) obtained data from three sources: a mail survey giving information on incidence and frequency of repellent product use, a usage study giving information on DEET repellent product dosage per application and product use, and syndicated market data.

The information gathered from the usage study is used in this recommendation to get realistic product or active substance amounts per application. The study involved a total of 540 subjects who were partitioned into analyzable subsamples of adult males, adult females and children (age: 13-17 years, and age: 12 year or younger). People were asked to apply a product typically once to themselves, or, in the case of very young children, parents were asked to apply the product once to the child. All children 12 years or younger were accompanied by a parent during the application process. The amount of used product was estimated by determining the weight difference of the container before and after product use. The amount of insect repellent product and DEET (content of the product according to label information) used per application was determined from data taken over two months (June and July). Due to the use of different repellent formulations (aerosol, pump spray, lotion etc.) several times during this time frame (e.g. 3 times aerosol, 2 times pump spray), data were not split into formulation type. Amounts of DEET exposure are broken down by application to both skin and clothing, and to skin only. Based on the mean values of usage data presented in the study it must be assumed that exposure is significantly higher for aerosol application compared to other devices.

Wargenau (2001) presents a quantile estimation (90 % and 95 % quantiles) for the criteria (a) amount of DEET (g) used on skin and clothing (table 49 of repellent usage study, table 1 of this recommendation), (b) amount of DEET (mg) used on skin only (table 50 of repellent usage study; table 2 of this recommendation), and (c) amount of product (mg) used on skin and clothing (table 46 of repellent usage study; table 3 of this recommendation). The results of Wargenau (2001) are used in this recommendation to calculate the 75th percentile. The 75th percentile was considered acceptable for Annex I inclusion of DEET, since the user study had a large number of study subjects.

Wargenau (2001) tried to fit an exponential distribution to the data describing the amount of DEET; for the amount of products used the chi-square distribution was considered to improve the model fit. Although it is unclear why Wargenau is fitting an exponential distribution and the chi-square distribution to the data as a first step, and not a lognormal distribution, the chosen distributions are accepted due to the data range. In addition, effects on the 75th percentile might be negligible. Accepting the calculated parameters (λ for exponential distribution, and λ, ν for the chi-square distribution) of Wargenau (2001, appendix B), the 90th, 95th and 75th percentiles can be estimated (see tables 1 to 3). The used R-code is given in annex 1.

Table 1: Quantile estimation for amount of DEET (mg *) used (on skin and clothing)

Percentile	Total population	Adult male	Adult female	Child ≤ 12 years	Child 13 – 17 years
90th	2797	3083	2367	2829	3018
95th	**3639**	**4011**	**3079**	**3681**	**3927**
75th	1684	1856	1425	1703	1817

* the average content of DEET (26.113 %) in the applied repellent products has to be taken into account for exposure estimation of other products

Table 2: Quantile estimation for amount of DEET (mg *) used (on skin only)

Percentile	Total population	Adult male	Adult female	Child ≤ 12 years	Child 13 – 17 years
90th	2643	2537	1519	2344	2539
95th	**3439**	**3301**	**1977**	**3049**	**3304**
75th	1591	1527	914	1411	1529

* the average content of DEET (26.113 %) in the applied repellent products has to be taken into account for exposure estimation of other products

Table 3: Quantile estimation for amount of product (mg) used (on skin and clothing)

Percentile	Total population	Adult male	Adult female	Child ≤ 12 years	Child 13 – 17 years
90th	10250	10720	9620	10720	10080
95th	**12616**	**13133**	**11876**	**13133**	**12425**
75th	6873	7263	6421	7263	6738

Scaling up the data per year using market data and the mail survey is not preferred because the time frame of the usage study (two months: June and July) is considered to illustrate realistic application frequency. Scaling up per year would underestimate exposure.

The default body weight for adults within the EU is 60 kg. However, this value is chosen to encompass both genders. In the CAR for DEET exposure has been estimated for males and females separately via the usage study. Mean body weights of 70 kg and 60 kg were used for

males and females, respectively. The mean body weights of male and female in the study were 82 kg and 67 kg, respectively. The mean body weights of children ≥ 12 years and children ≤ 12 years in the study were 61 kg and 30 kg, respectively. In the CAR of DEET body weights of 62.8 kg and 25.5 kg were used.

One shortcoming of the user study is the lack of raw data. Differences between the calculated product amounts (skin and clothing) and the calculated DEET amount (skin and clothing) can not be explained due to missing raw data.

Another shortcoming of the study is that it is not possible to distinguish between the various formulations used. The results show that there are differences in the applied amount using an aerosol, a pump spray, a lotion, a stick or a liquid. Using an aerosol results in higher application amounts (only mean values are given). Therefore, it is not possible to calculate the active substance amount/product amount applied using aerosols or pump spray or lotions for the different user categories. According to the study results, 73 % of the tested products were aerosols, and only 16 % were pump sprays. Based on given mean exposure in the study, aerosols are somewhat underestimated (see Boomsma and Parthasarathy (1990), table 46 and 49 of repellent usage study) for the different user categories. The other tested formulations are well covered. Comparing the given mean values the product amount applied by aerosols would be approximately 20 % higher. To compensate this shortcoming and to cover all application types the 95th percentile is considered acceptable and should be used.

2. US-EPA SOP for Residential Exposure Assessment (2012)

The US-EPA SOP for Residential Exposure Assessment (2012) recommends the following product application amounts for aerosols and pump sprays (95th percentile, section 6.2.2):

Aerosols:	2.9 mg product/cm²
Pump sprays:	1.5 mg product/cm²
Lotion:	3.5 mg product/cm²

According to Pest Control Products Fact Sheet, insect repellents are applied on the uncovered skin (head, hands, arms, legs and feet.) The surface of these body parts is 64% of the total body surface (Bremmer and Van Veen, 2000)5. However it is considered unrealistic that a person would expose head, hands, arms, full legs and full arms during a mid-term exposure to repellents, as the normal outdoor clothing assumes people wearing short-sleeved shirt and shorts which cover thighs and upper arms.

Assuming that during the whole season (mid-term exposure within a year) a short-sleeved shirt (i.e. T-shirt) and shorts are worn, 55% of the total body surface remains uncovered and is treated with repellent.

According to the default human factor values agreed in the HEAdhoc Recommendation 14, the following surface to body ratios should be used:

Adult (female, 60 kg):	277 cm²/kg

[5] Bremmer, H.J., M.P. van Veen, 2000. Factsheet Algemeen. Randvoorwaarden en etrouwbaarheid, ventilatie, kamergrootte, lichaamsoppervlak. Bilthoven, The Netherlands: National Institute for Public Health and the Environment (RIVM). Report no. 612810009

Children (6 to <11 years, 23.9 kg): 385 cm²/kg

Children (2 to <6 years, 15.6 kg): 436 cm²/kg

Toddler (1 to <2 years, 10 kg): 480 cm²/kg

Infant (6 to < 12 months, 8 kg): 513 cm²/kg

Calculating the resulting applied product amounts according to the formula

mg b.p./application =

amount product/cm² x body surface area [cm²/kg] x body weight [kg] x uncovered skin [%]

gives the following results:

Table 4: calculated product amounts acc. to US-EPA SOP for Residential Exposure Assessment (2012), assuming 55% uncovered body surface area

User category	**Pump spray: mg b.p. per application**	**Pump spray: mg a.s. assuming a content of 20 %**	**Aerosol: mg b.p. per application**	**Aerosol: mg a.s. assuming a content of 20 %**	**Lotion: mg b.p. per application**	**Lotion: mg a.s. assuming a content of 20 %**
Adult (female, 60 kg)	13711.5 mg b.p.	2742.3 mg a.s.	26508.9 mg b.p.	5301.8 mg a.s.	32993.5 mg b.p.	6398.7 mg a.s.
Children (6 to <11 years, 23.9 kg)	7591.2 mg b.p.	1518.2 mg a.s.	14676.4 mg b.p.	2935.3 mg a.s.	17712.9 mg b.p.	3542.6 mg a.s.
Children (2 to <6 years, 15.6 kg)	5611.3 mg b.p.	1122.3 mg a.s.	10848.6 mg b.p.	2169.7 mg a.s.	13093.1 mg b.p.	2618.6 mg a.s.
Toddler (1 to <2 years, 10 kg)	3960.0 mg b.p.	792.0 mg a.s.	7656 mg b.p.	1531.2 mg a.s.	9240.0 mg b.p.	1848.0 mg a.s.
Infant (6 to < 12 months, 8 kg)	3385.8 mg b.p.	677.2 mg a.s.	6545.9 mg b.p.	1309.2 mg a.s.	7900.2 mg b.p.	1580.0 mg a.s.

Efficacy studies for DEET were used as the basis for the given application rates. It is assumed that these studies are laboratory studies, and therefore the result might not reflect realistic application amounts. In addition, no information about user categories or specific exposure data for children, toddler and infants is given. Therefore, the 95th percentiles should be used for exposure assessment.

3. Pest Control Products Fact Sheet[6]

The default is based on the assumption that the application rates of sunscreen and repellent products are comparable. The application amount for sunscreen (8-10 g) given in the Cosmetics Fact Sheet (2006), is assumed to be an amount used to cover the entire body. In the case of repellents, normally only uncovered body surfaces are treated representing about 64 % of the total body surface. The proportional adjustment of the sunscreen amount yields an application amount of 5-6 g repellent product. The upper estimate of 6 g was adopted as default for adults. For infants (10.5 months old), an amount of 1.5 g is estimated assuming a linear relationship between the body surface and the amount of repellent used.

In addition, based on the US EPA RED document for DEET, a use rate of 5.8 g repellent product (containing 20 % active substance) is estimated. This supports the default values extrapolated from the use of sunscreen products. On the other hand, the data in the following sections provide higher estimates for repellent use.

However, the default values of 6 g for adults and 1.5 g for infants have some deficiencies due to the derivation from sunscreen application rates. Sunscreen needs to be applied in large amounts to be sufficiently protective, and, in addition, the viscosity of sunscreen might be much higher than that of a repellent product, which allows much thicker layers to be applied onto skin. In addition, no specific exposure data are given for children.

4. Approaches based on data generated by the applicant

Further approaches are based on the use of application rates. An example is the UK Proforma, which defines the maximum skin area that can be treated "safely" for three age groups (children <12 years of age, children ≥12 years and adults[7]), using standard reverse reference exposure/risk calculations based on the toxicologically-determined AEL for the particular active substance. In other words, this approach defines the maximum dose that can be applied to body parts without exceeding the AEL derived for the active substance contained in the product (see Annex 2). The applicant would be required to provide details of the application device used to deliver the product to the skin. This should include the amount of product per cm^2 of skin delivered; these values should be derived from data and/or by logical deduction. The provision of these data should allow for the consideration of formulations other than sprays.

It has to be noted that the approaches based on application rates may imply specific labelling instructions for biocidal products to define the body parts to be treated. This aspect is linked to the exposed area of the skin where the repellent is applied. It is considered that the exposed body surface area of an adult represents 55% % of the total body surface (derived using the

[6] The default values indicated in this section were also reported and used in the TNsG 2002.
[7] UK explained that the Proforma approach attempts to mirror the conclusions of the CAR, namely that DEET products are for restricted use on children between 2 and twelve years old, and not for use on children less than 2 years of age. The age group described as <12 years of age is indeed assessed using the HEAdhoc Recommendation 14 for the toddler (female 1 to <2 years old). The selection of this parameter ensures that the determination of body areas to which the product may be safely applied are protective of children aged 2 years and above. In fact, children aged 2 years and above and <12 years of age are considered. Children ≥12 years are assessed as a separate group, as are adults.

values of the body part surface areas from the HEAdhoc Recommendation 14). This corresponds to the situation when normal outdoor clothing (short-sleeved shirt (i.e. T-shirt) and shorts) are worn. This type of clothing leaves the following body parts exposed: head, neck, hands (palms and backs), lower arms, lower legs, feet and 70% of upper arms and thighs. It is assumed that for mid-term scenarios, which are those relevant for exposure to insect repellents, the normal outdoor clothing will be worn.

When long-sleeved shirts and trousers are worn, the exposed skin represents 20%(Table 5) of the total body surface of an adult, since the exposed body parts of a person wearing such type of clothing would include, as a worst case, the head, neck, hands (palms and backs of hands), and feet. A person wearing long-sleeved shirts and trousers would not expose his lower arms and lower legs to repellents. The same approach can be followed to derive body surface areas of children ≥12 years and children<12 years.

Table 5: Exposed skin surface area when long-sleeved shirts and trousers are worn (for adults), according to HEAdhoc Recommendation 14

	Neck	**Head**	**Hands**	**Feet**	**Exposed surface area**	**Total body surface area**	**Percentage exposed surface area**
Surface area (cm^2)	230	1110	820	1130	3290	16600	3290/ 16600 = 19.8%

During the CG-16 meeting, it was concluded that wearing long-sleeved shirts and trousers was not considered to be an acceptable RMM to reduce the exposure to repellents to acceptable levels, in case a risk is identified. Therefore, in line with the conclusions of the CG, the implementation of the approaches based on application rates is acceptable as long as the use of long-sleeved shirts and trousers to define the maximum skin area that can be treated with the repellent, is not foreseen.

When approaches based on application rates are used, the application rates can be refined to a lower value, thus resulting in a lower amount of product delivered. Nonetheless, any application rates should be supported by efficacy data.

Alternatively, applicants may submit an exposure study. If applicable, it should fulfil the quality criteria as laid down in the Guidance on the Biocidal Products Regulation Volume III Human Health - Part B Risk Assessment. Such a study should allow assessing exposure of the corresponding biocidal product with sufficient reliability. Among others the following prerequisites must be fulfilled:

The way of application in the study should comply with the intended use as described in the instructions for use or with the foreseeable use of the biocidal product submitted for application, taking into account the possible routes of exposure. It must be clear, which parts of the body surface will be treated and how users estimate the dose applied (instruction of use or no instruction). The number of participants must allow a reliable exposure assessment for all

relevant user groups (e.g. adults, adolescents, children). The exposure may depend on individual parameters as bodyweight, gender and age. Therefore, parameters, which may influence individual exposure, should be recorded. The type of application (aerosol spray, pump spray lotion etc.) and data specific to the particular delivery device should be also recorded.

4. References

- Bremmer, H.J., M.P. van Veen, 2000. Factsheet Algemeen. Randvoorwaarden en betrouwbaarheid, ventilatie, kamergrootte, lichaamsoppervlak. Bilthoven, The Netherlands: National Institute for Public Health and the Environment (RIVM). Report no. 612810009
- Biocides Human Health Exposure Methodology, October 2015. http://echa.europa.eu/about-us/who-we-are/biocidal-products-committee/working-groups/human-exposure
- Boomsma, J. C., Parthasarathy, M., Human Use & Exposure to Insect Repellents containing DEET. 1990; DEET Joint Venture/Chemical Specialties Manufacturers Association
- Cosmetics Fact Sheet, Bremmer, H.J., Prud'homme de Lodder, L.C.H.,van Engelen, J.G.M., 2006, RIVM report 320104001/2006. http://www.rivm.nl/bibliotheek/rapporten/320104001.pdf
- de Winter-Sorkina, R., Cassee, F. R. From concentration to dose: factors influencing airborne particulate matter deposition in humans and rats. 2002. RIVM report 650010031/2002 http://rivm.openrepository.com/rivm/bitstream/10029/9272/1/650010031.pdf
- Guidance on the Biocidal Products Regulation Volume III Human Health - Part B Risk Assessment, Version 2.3, October 2015. http://echa.europa.eu/guidance-documents/guidance-on-biocides-legislation?panel=vol3partB#vol3
- HEAdhoc Recommendation no. 8 - Consumer use of biocidal product and protection from typical clothing. http://echa.europa.eu/web/guest/view-article/-/journal_content/title/recommendations-of-the-ad-hoc-working-group-on-human-exposure
- HEAdhoc Recommendation 14 - Default human factor values for use in exposure assessments for biocidal products. https://echa.europa.eu/view-article/-/journal_content/title/recommendations-of-the-ad-hoc-working-group-on-human-exposure
- Pest Control Products Fact Sheet, Bremmer, H.J., Blom, W.M., van Hoeven-Arentzen, P.H., Prud'homme de Lodder, L.C.H., van Raaij, M.T.M., Straetmans, E.H.F.M. van Veen, M.P., van Engelen, J.G.M., 2006, RIVM report 320005002/2006.
- U.S. Environmental Protection Agency, Reregistration Eligibility Decision (RED) DEET, EPA738-R-98-010, 1998, http://www.epa.gov/oppsrrd1/REDs/0002red.pdf
- U.S. Environmental Protection Agency, Standard Operating Procedures for Residential Pesticide Exposure Assessment; 2012; http://www.epa.gov/pesticides/science/USEPA-OPP-HED_Residential%20SOPs_Oct2012.pdf
- Wargenau, M., Expert Report – Quantile Estimation Concerning Exposure to Insect Repellents Containing DEET; 2001; M.A.R.C.O. Institute for Biomedical Statistics, Sponsor: Bayer AG

Annex 1: R-Code to calculate percentiles from Wargenau (2001)

```
### 2014-06-26
mu <- c(total=1.215, male=1.339, female=1.028, children=1.229, teens=1.311)
rbind("90%"=qexp(.90,1/mu), "95%"=qexp(.95,1/mu), "75%"=qexp(.75,1/mu))
##
mu <- c(total=1.148, male=1.102, female=0.660, children=1.018, teens=1.103)
rbind("90%"=qexp(.90,1/mu), "95%"=qexp(.95,1/mu), "75%"=qexp(.75,1/mu))
##
lambda <- c(total=2.9, male=3.1, female=2.3, children=3.1, teens=2.8)
nu <- c(total=2.0, male=2.1, female=2.3, children=2.1, teens=2.0)
rbind("90%"=qchisq(.90,nu,lambda), "95%"=qchisq(.95,nu,lambda),
"75%"=qchisq(.75,nu,lambda))
```

Annex 2: UK Proforma approach

The UK Proforma approach defines the maximum skin area that can be treated 'safely' for three age groups (children <12 years of age, children ≥12 years, and adults[8]); using standard reverse reference exposure/risk calculations based on the toxicologically-determined AEL for the particular active substance.

Where the demonstrated effective repellency rate is used in the calculations, the Proforma shows the product is also able to afford protection to treated skin. The Proforma defines areas to be treated by named body part. This allows the Applicant flexibility to determine which particular market to aim for.

The Proforma approach requires the provision of the following information;

i. The concentration of active substance (% w/w) in the in-use product.
ii. Details of the application device used to deliver the product to the skin. This should include the amount of product per cm^2 of skin delivered; values should be derived from data and/or by logical deduction.
iii. The amount of product to be applied per cm^2 of skin [g/cm^2] so as to be efficacious.
iv. The toxicologically-determined AEL for the particular active substance.
v. The dermal penetration value for the particular product.

Oral route

In regards to children, oral exposure is only expected to occur if the product does not include a deterrent (such as denatonium benzoate) or where the labelling does not carry recommendations restricting application on children's' hands. Where these risk mitigation measures are employed there is no need to assess oral exposure. The following label phrases would be considered suitable risk mitigation measures:

i. "For children 2 to 12 years: The repellent must be applied by adults"
ii. "Do not apply to children's hands"
iii. "Keep out of reach of children"

Where the product is applied specifically to a child's hands or it does not contain a deterrent, oral exposure due to hand-to-mouth contact is a realistic route of exposure. In such instances it is expected that children will ingest the entire amount (100%) that is applied to the hands. A reverse reference calculation for oral ingestion can be performed considering the product application rate (g/cm^2 of skin), the relevant HEAdhoc Recommendation 14 default hand surface area (cm^2) values and a transfer efficiency of 100%.

The oral route is also pertinent for adults, as products are applied to the skin using bare hands. Whilst adults are advised to wash hands after application, this may not always be practicable.

[8] Please see footnote 6.

It is therefore assumed that an adult will ingest the amount of product on their fingers only (50% of the total hand surface area).

Inhalation route

Exposure via inhalation (including oral uptake of non-respirable particles) is considered low or absent if applied outdoors or in well-ventilated areas, therefore a recommendation on ventilation is considered necessary for spray formulations (e.g. safety phrases comparable to S23, S51).

Dermal route

The following calculation may be used to determine the maximum amount of product (limit dose expressed in mg/person/day) that can be safely applied directly to the skin for each identified age group:

Limit dose of product (mg/person/day) = *AEL x BW / DA / AS*

Where:
AEL = acceptable exposure limit (mg/kg bw/day)
BW = bodyweight (60kg adult, 23.9 kg child ≥ 12yrs, 10 kg child <12 yrs)
DA = dermal penetration value (%)
AS = active substance content of applied product (% w/w)

For the purposes of the product label, the limit dose of product should be expressed in terms that are easily understood by the user. The product application delivery data submitted by the applicant may be used to derive a spray duration or number of spray pump strokes that will dispense the limit dose.

To aid application of the product by the user, the limit dose (mg/person/day) can be expressed as a body surface area (cm^2) that may be safely treated using the following calculation:

Skin area treated [cm^2] = LD/AR

Where:
LD= Limit dose of product (mg/person/day)
AR = target product application rate [mg/cm^2]

The total skin area (cm^2) that may be safely treated may be described in terms of relevant body parts using the surface area values detailed in HEAdhoc Recommendation 14. Users can readily identify named body parts (e.g. lower legs, neck etc.) rather than attempting to estimate skin area (cm^2).

o0o