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Guideline on user safety of topically administered veterinary medicinal products

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This guideline will supplement the existing 'Guideline on user safety for pharmaceutical veterinary medicinal products' (EMA/CVMP/543/03-Rev.1).

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Guideline on user safety of topically administered veterinary medicinal products

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Executive summary

The guideline on user safety of topically administered products has been written to provide specific guidance and advice on how user risk assessments should be conducted for such products. This guideline should be used in conjunction with the 'Guideline on user safety for pharmaceutical veterinary medicinal products' (EMA/CVMP/543/03-Rev.1).

1. Introduction (background)

Applications for marketing authorisations for veterinary medicinal products (VMPs) in the European Union are issued in accordance with Directive 2001/82/EC as amended by Directive 2004/28/EC and Directive 2009/9/EC. This legislation requires that applications for pharmaceutical veterinary medicinal products include safety documentation. Annex I of Directive 2001/82/EC (replaced by the Annex to Directive 2009/9/EC) states that "the safety documentation shall show the potential risks which may result from the exposure of human beings to the veterinary medicinal product, for example during its administration to the animal".

The legislation does not give specific guidance on data requirements and assessment methods to be used to identify the risks or on the measures for risk reduction for users. The Guideline on user safety for pharmaceutical veterinary medicinal products provides general guidance on the evaluation of risks to the user, applicable to all types of veterinary medicinal products. This new guideline provides additional guidance and advice on how risk to users can be assessed for topically administered products.

The increase in the number of applications for topically administered products in recent years has highlighted the need for a coherent and common approach on how exposure to such products should be assessed.

Exposure to topically administered products may occur via direct exposure to the product (accidental ingestion or accidental spillage including hand-to-mouth contact (HTM)), or when pet owners, other household members or any other person including children come into contact with the treated animals after administration of a topical product. Exposure can be divided into short-term exposure (once or for a short time) and long-term exposure (over a longer period). While worst case exposure can be estimated based on conservative default assumptions, more accurate estimations of exposure can be achieved through the generation of experimental data.

2. Scope

This guideline focuses specifically on how user safety for topically administered VMPs that may remain on the surface of the animal's body is assessed and should be read in conjunction with the current version of the CVMP general 'Guideline on user safety for pharmaceutical veterinary medicinal products'. The focus of the assessment is on VMPs intended for companion animals. However, the principles of this guideline, for example in relation to the (pre-)application phase, may also be applicable to VMPs for food producing animals or other topical VMPs that do not spread over the animal's body.

This guideline is not intended to be applied retrospectively (i.e. to products marketed prior to adoption of this guideline). However, some types of post-approval changes may warrant a reassessment of user safety, e.g.

- Changes to the clinical use of the authorised products resulting in a significant increase in handled dose including duration of use;
- Identification of new information impacting on the assessment of the risks of the VMP such as new hazard data on the ingredients of a product including new excipients;
- Change of packaging material resulting in increased potential for user exposure, especially taking into account volumes to be spilled and the child resistant properties.

For a generic product a full user risk assessment would not normally be expected as the conclusion on user safety of the product and appropriate user safety warnings should reflect the user safety evaluation undertaken for the reference product. However, where there are aspects of the generic product that differ from the reference product (eg, if excipients differ), then the impact of these differences on user safety should be addressed.

As per the CVMP 'Guideline on user safety for pharmaceutical veterinary medicinal products', this guideline does not cover occupational safety during the manufacture of veterinary medicinal products.

Note: in this guideline the term 'product' refers to 'veterinary medicinal product' i.e. the whole formulation including excipients and the term 'residues' refers to 'residues of the active substance(s), excipients and/or impurities' when present.

3. Legal basis

Requirements for safety testing for a marketing authorisation application are laid down in Directive 2001/82/EC of the European Parliament and of the Council.

This guideline concerns the application of the requirements of Annex I of Directive 2001/82/EC, now replaced by the Annex of Directive 2009/9/EC, given in Part 3 of Title I, User safety: "This section shall include a discussion of the effects found in the preceding sections and relate this to the type and extent of human exposure to the product with a view to formulating appropriate user warnings and other risk management measures."

4. Principles of the assessment

In preparation of this new guideline, the CVMP considered the US EPA 'Standard Operating Procedures for Residential Pesticide Exposure Assessment' (2012) as the basis for the estimation of both dermal and oral exposure of users. However, the algorithms and some of the default values have been modified for use in this guideline. The CVMP also utilised data and information available from the National Institute for Public Health and Environment (RIVM) in the Netherlands.

In accordance with the provisions of Directive 2010/63/EU on the protection of animals used for scientific purpose, the conduct and design of *in-vivo* experimental studies should take account of 3Rs (replacement, reduction and refinement) principles.

4.1. The aspects involved in user risk assessments for topically administered products

The main aspects involved are similar to those outlined in the original CVMP 'Guideline on user safety for pharmaceutical veterinary medicinal products'. An assessment of the risk from the VMP to those handling and administering it or become exposed via contact with a treated animal, should be presented by incorporating the following aspects:

- an appraisal of the inherent toxicity of the VMP and the identification of the most relevant toxicological reference values (TRVs);
- an appraisal of how and when the user will be exposed to the VMP – identifying the different exposure scenarios and estimating user exposure for each scenario;
- assessment of the level of risk by establishing margins of exposure (MOEs) based on a comparison of the exposure levels with the toxicological reference values;
- the proposal of appropriate and practical risk mitigation measures where appropriate.

4.2. Establishing Toxicological Reference Values (TRVs) for all scenarios

The first step of the user safety assessment corresponds to the hazard identification and characterization of each active substance(s) and excipients and/or final product formulation as per the CVMP 'Guideline on user safety for pharmaceutical veterinary medicinal products', in order to derive TRVs with respect to the identified exposure scenarios.

This process should be based on the assessment of all available scientific data that are presented in the safety part of a marketing authorisation (MA) dossier (Part IIIA Safety Documentation). The overall assessment of the data allows a conclusion to be made on whether available data are sufficient or insufficient for use in the risk assessment. The need for any additional studies depends on any identified gaps in the dataset. If appropriate TRVs cannot be established for a particular route of exposure, new studies should be performed to generate them if extrapolation from route to route is not possible.

The studies used to define TRVs should be carried out in accordance with VICH/OECD guidelines and current methodology. Data from studies reported in the scientific literature may be accepted where these data have been published by a reputable source and are reported in sufficient detail to allow the competent authority to satisfy itself that the TRVs have been correctly set. These studies should provide sufficient data for the assessment of the toxicity of the substance of concern for short-term exposure (i.e. highest exposure levels) and long-term exposure scenarios (where relevant) and to consider effects such as reproductive toxicity including developmental toxicity, genotoxicity and carcinogenicity. In addition, studies on specific effects, such as neurotoxicity, may be necessary. It is considered that the use of LD_{50} values as TRVs is not appropriate. The risk assessment of short-term exposure should be based on acute NO(A)ELs or, if not available, on sub-acute or sub-chronic NO(A)ELs, the latter representing in general a worst case approach. In addition, the TRV may be based on information from long-term studies if in such studies acute effects have been observed on the first day(s) of dosing. For the risk assessment of long-term exposure, the use of a sub-chronic NO(A)EL or chronic TRV can be considered acceptable.

In most cases, data from animal studies allows a quantitative dose-response analysis to be made. Use of the benchmark dose (BMD) approach is encouraged as this provides a quantitative dose-response assessment taking into account the variability of the data and the slope of the dose-response curve. Available human data can also be considered for derivation of TRVs if these studies are relevant from a scientific point of view and, if generated experimentally, the applicant can confirm that the studies were accepted as ethically acceptable[1]. However, for any given substance, the accepted therapeutic dose used in human medicine does not imply an absence of risk and, therefore, it is generally not

[1] If data are provided from studies conducted in humans it should be confirmed that the study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki.

acceptable as a TRV. Interaction (if using data from single actives) should be addressed as per the EMA 'Guideline on pharmaceutical fixed combination products' (EMEA/CVMP/83804/2005).

In addition, the final product formulation should be evaluated for its irritating, corrosive or skin sensitising properties (see 'Guideline on user safety for pharmaceutical veterinary medicinal products').

The results of the studies should be assessed in order to identify the potential adverse health effects that can be caused by exposure to the substance(s) of concern.

In every case, TRVs are established for all relevant toxicological endpoints (critical effects), and are specific to a substance, duration of exposure (acute, sub-chronic or chronic) and a route of exposure (oral, dermal and inhalation; the latter in the case of topical sprays, aerosols and powders). The appropriate toxicological study and TRV for quantitative risk assessment is to be selected considering the route of user exposure, the duration of user exposure and the component concerned. If more than one NOAEL is available for a given exposure scenario, the choice of the NOAEL to be used as the TRV should be fully justified. In the context of a risk assessment, these values should be compared to exposure levels of the substance(s) of concern that corresponded to similar duration and route of exposure conditions. In the absence of a TRV for a specific route of exposure (for example, dermal), the use of a TRV defined from an oral study can be considered using route to route extrapolation with appropriate adjustments to address differences in bioavailability (see section 4.3 'Identifying exposure scenarios and estimating corresponding exposure levels', below). Even if the NO(A)EL is based on the most critical sensitive effect, other effects could also be taken into consideration (e.g. reproductive or developmental effects) in order to focus the user safety risk assessment on specific scenarios or users.

In summary, the establishment of TRVs should include relevant toxicological end points that relate to the different exposure scenarios. Therefore, TRVs for both short-term and long-term exposure scenarios should be included as follows:

A.	Short-term dermal	→	Contact during administration or general contact with the product → Contact with the treated animal in the acute phase	TRV based on acute dermal toxicity study or, if not available, to be based on the most relevant sub-acute or sub-chronic dermal toxicity study preferably using the final product formulation. In the absence of a dermal toxicity study using the final product formulation, TRV will be based on (sub)acute or sub-chronic oral toxicity study with the active substance and possibly excipients of concern, adjusted for dermal/oral absorption (see 'Factors that influence dermal penetration' below)
B.	Short-term oral	→	Accidental ingestion of the product → Hand-to-mouth exposure following contact with the treated animal in the acute phase	TRV based on acute oral toxicity study or, if not available, to be based on sub-acute or sub-chronic oral toxicity study
C.	Long-term dermal	→	Repeated contact with treated animal during the period of efficacy	TRV based on sub-chronic or chronic dermal toxicity study or, if not available, to be based on the most relevant sub-chronic or chronic oral toxicity study adjusted for dermal/oral absorption
D.	Long-term oral	→	Repeated hand to mouth exposure after contact with treated animal during the period of efficacy	TRV based on sub-chronic or chronic oral toxicity study

Factors that influence dermal penetration

Topically administered products may be formulated in such a way that dermal absorption is affected (for example, use of penetration enhancers). In such cases, a TRV from a dermal study using the final product formulation should be used used to assess short-term exposure following spilling or following touching a wet application site. In instances where no final product formulation specific TRV is available the impact of the final formulation on absorption should be addressed.

For long-term, post-application exposure scenarios for liquid formulations (of which the solvents have evaporated from the application site) it is considered that in general the excipients do not influence dermal absorption in the user. In that case, it would be acceptable to use TRVs from dermal studies with the active substance. In the absence of dermal studies, a TRV from an oral study with the active substance adjusted for oral and dermal bioavailability may be accepted. If no data on bioavailability are available, the TRV from an oral study might be used as a surrogate, assuming that in general a TRV from a dermal study will not be lower than a TRV from an oral study.

4.3. Identifying exposure scenarios and estimating corresponding exposure levels

4.3.1. Exposure scenarios

For the exposure assessment, all tasks and situations that may lead to exposure of users within the scope of this guideline should be identified. General guidance is given in the 'Guideline on user safety for pharmaceutical medicinal products'. Several scenarios are possible depending on the type of product.

The table below represents the main exposure scenarios for topically administered VMPs.

Phases	User	Details	Routes of exposure	Component of exposure	Duration/frequency of exposure
Contact with the product (further detailed in paragraph 4.3.2)					
Pre-application phase	Child	Accidental access to product	Oral and dermal	Whole formulation	Accidental Once
Application phase	Adult	Opening / application of product	dermal including HTM	Whole formulation	Once or short-term
	Child	Not relevant since the product is to be applied by an adult.			
Post-application phase	Child	Accidental access to residual product	Oral and dermal	Whole formulation	Accidental Once
		Exposure during the pre-application phase for children is considered to be worst case. Additional calculation for post-application exposure is therefore not necessary.			
Contact with the treated animal (further detailed in paragraph 4.3.3)					
Post-application phase (short-term)	Child	Handling/stroking of the treated animal	dermal including HTM	Whole formulation	Once or short-term
Post-application phase (long-term)	Child	Handling/stroking of the treated animal	dermal including HTM	Residues	Long-term Repeated

	Adult	Exposure during the post-application phase for children is considered to be worst case due to their lower bodyweight. Additional calculations for adults are therefore not necessary, except when the substance may pose a risk for specific populations e.g. pregnant women or women of childbearing age.

HTM = Hand-to-mouth contact (transfer of dermal loading to mouth)

In addition, skin irritation/corrosion and skin sensitisation after dermal exposure should be considered. Direct ocular exposure and hand-to-eye contact after dermal exposure is also possible and the ocular irritancy/corrosion of the product should be addressed. Exposure via eye contact is not considered to result in significant systemic exposure levels and/or subsequent adverse systemic effects. For some products, e.g. sprays, aerosols, powders, exposure by inhalation may be relevant and needs to be taken into consideration. No guidance is provided on assessment of risks via the inhalation route of exposure, which should be addressed on a case by case basis.

4.3.2 Exposure assessment for short-term dermal and oral exposure scenarios after direct contact with the product

The following paragraphs focus on the most sensitive population i.e. children when both adult and children could be exposed**.** Additional calculations for adults are therefore not necessary, except when the substance may pose a risk for specific populations e.g. pregnant women or women of childbearing age. Then, in addition to exposure during application, the post-application exposure i.e. stroking a treated animal should also be considered for this population. As a default it is assumed that only one animal will be treated. This is appropriate as the guideline uses worst case exposure scenarios, considered to be sufficiently conservative to overcome the need to routinely assume that more than one animal will be treated.

Phases:

A. Pre-application phase

Accidental oral exposure due to unintended access to the product by a child (bodyweight 12.5 kg) should be considered. This might occur if the product is left out on a surface whilst an adult is restraining an animal or if the product is accessible by a child (i.e. if the product is not in child-resistant packaging). Collars are usually provided in different sizes to fit different size animals. A child could chew on part of a collar or swallow any cut off excess length. Oral exposure to the collar whilst it is attached to an animal is considered an unlikely scenario. Oral exposure is considered to represent the worst case scenario for children during pre-application phase and consequently if no risk mitigation measures are needed in relation to oral exposure it is accepted that none are needed in relation to accidental dermal exposure. If child-resistant packaging is used in order to mitigate against oral exposure, this will also mitigate against dermal exposure during the pre-application phase.

The following assumptions are made as a conservative approach:

- For child exposure, direct oral exposure to the product (i.e. final product formulation) will be a maximum of 10% of a spot-on pipette, 10% of a collar or 10% of shampoo contents, with an upper volume of 5 ml for liquids and 2 cm for collars (swallow volume). Where appropriately justified, refinements can be made to these default values.

B. Application phase

Accidental dermal and indirect oral exposure of an adult (bodyweight 60 kg) is possible if the product comes into contact with the user's skin during administration and then is subsequently transferred to the mouth. It is considered that the product would be administered by an adult only.

- Direct dermal exposure to the final product formulation during application will be 10% of the administered dose as a default. A refinement of this value may be accepted in cases where the type of product and packaging justify this. Also actual measurements on transferability of the substance of concern while handling the product can be used for refinement.
- Indirect oral exposure might occur following dermal exposure of product and subsequent hand-to-mouth transfer of this dermal loading to the mouth. For the purposes of assessing the acute oral risk, it is suggested that as a reasonable worst case, oral exposure to final product formulation will be to a maximum of 10% dermal loading being transferred to the mouth, i.e. 1% of the administered dose.

C. Post-application phase

Accidental oral exposure of a child with residual contents of a used product container (e.g. pipette) is possible. Exposure during the pre-application phase is considered to represent the worst case scenario and no further calculation is necessary for the post-application exposure. However, if a risk is identified for the pre-application phase necessitating risk mitigation measures for the pre-application phase, a warning should be included regarding proper and immediate disposal of the used product.

Calculations:

The following equation should be used to calculate exposure due to contact with the product:

$$D = \frac{\mathrm{AR} * \mathrm{FA}}{\mathrm{BW}}$$

D = Dose to which the user is exposed corrected for bodyweight (mg/kg body weight)

AR = Application Rate (mg)
For children this is the amount (of substance of concern) present in the product.
For adults it is the amount (of substance of concern) applied to animal in the largest collar, largest pipette or largest shampoo dose applied to the animal).

FA = Fraction available for exposure by the relevant route and scenario.

Pre-application (direct oral exposure) for spot-on, collar or shampoo, FA = 0.1 (bearing in mind the default upper volume of 5 ml for liquids and 2 cm of length for collars).

During application (direct dermal exposure), FA = 0.1

During application (indirect oral exposure), FA = 0.01

The default values may be modified if justified by the provision of adequate information, e.g. from studies on leaching of collars.

BW = Body weight
For children: 12.5 kg (default considered to represent a child of 2 to <3 year old which is active in exploring their environment. This value is derived from a study in the Dutch population (considered to be representative for the European population) and corresponds to the 25th percentile of the Dutch population; 12.4 kg (RIVM report 090013003/2014) rounded

up to 12.5 kg).
For adults: 60 kg (the default value used by CVMP).

4.3.3 Exposure assessment for post application exposure scenarios after contact with the treated animal

It is assumed that residues on the animal are transferred to the skin of the user that comes into contact with treated animal during stroking. Children may additionally become orally exposed via hand-to-mouth contact. The exposure to children is considered to be the worst case, due to their low bodyweight. Therefore additional calculations for the exposure of adults are normally not necessary except when there are specific concerns (e.g. related to reproduction or developmental toxicity). As a result the following scenarios have to be considered:

- **dermal exposure of children after contact with the treated animal**
- **oral exposure of children due to hand to mouth contact**

Both scenarios should be considered for short-term exposure and long-term exposure to a treated animal. Short term exposure reflects exposure to the highest residue levels observed, which are generally the residues immediately after administration of the product and during the first 12 hours after treatment, but could be later. Long-term exposure reflects daily exposure to the average residue levels during the period of claimed efficacy. For risk assessment of long-term exposure, the potential that the product may be used repeatedly will inform the decision on which TRV to use for the risk assessment.

4.3.3.1 Dermal exposure of children after contact with the animal

The method for determining dermal exposure of children after contact with a treated animal is based on the principles of the US EPA guidance (2012) for determining the relationship between the amounts applied and contact activities with the animal. However, while the US EPA approach uses a default Transfer Coefficient to represent contact activity with the animal, the CVMP considers that use of a child's surface area in contact with the treated animal provides a more direct estimation of dermal exposure. Accordingly, it is assumed that the dislodgeable residue equals the transferable residue. Further a one-to-one relationship between dislodgeable/transferable residue on the animal (spread over its surface area) and the surface area in contact with the user is assumed, so the concentration of residues per cm^2 on the animal surface equals the concentration per cm^2 on human surface.

The residues to which a child may be exposed after the topical treatment of an animal are mainly residues of active ingredient(s). For acute exposure, also excipients may need to be taken into account if adverse effects can be expected from exposure to these substances.

Dermal exposure of a child in contact with a treated animal should be calculated as follows:

$$\mathrm{DE}_{bw-corr} = \frac{\mathrm{TR} * \mathrm{SA}_{contact}}{\mathrm{BW}}$$

Where:

$DE_{bw\text{-}corr}$ = Dermal Exposure corrected for body weight (mg/kg bw /day);

TR = Transferable Residue, which is the concentration of the active substance per surface area of the treated animal that may transfer to the child (mg/cm^2). See below;

$SA_{contact}$ = the surface area of a child in contact with the animal per day (cm^2).
The default is set to 1790 cm^2. This value represents the surface area of the unprotected

body parts, which are considered to be both hands, both arms and the head including neck of a 2 to <3 year old child. This value is derived from a study in the Dutch population (considered to be representative for the European population) and corresponds to the 25th percentile of the Dutch population, which is correlated to the 25th percentile chosen for body weight (RIVM report 090013003/2014). It should be noted that the default is expressed as contact area per day and not per event, while actually more events per day with smaller surface contact areas may occur.

BW = Body Weight of a child.
Default: 12.5 kg (see section 4.3.2)

The Transferable Residue is calculated as follows. It is assumed that one animal is contacted. If more animals are present, it is expected that total contact activity remains the same.

$$TR = \frac{AR * F_{AR}}{SA_{animal}}$$

Where:

TR = Transferable Residue, which is the concentration of the active substance per surface area of the treated animal that may transfer to the child (mg/cm^2);

AR = Application Rate, the amount of active substance applied to the animal (mg).
The recommended application rate that gives highest active dose to surface area ratio should be used;

F_{AR} = Fraction of the Application Rate available as transferable residue.
The nominal defaults are set to respectively 0.15 (15%) for short-term exposure and 0.02 (2%) for long-term exposure. These defaults are considered sufficiently conservative based on review of company-submitted data. Refinements can be made by deriving actual data on the final product formulation in wipe tests (see section 4.5);

SA_{animal} = Surface Area of the animal (cm^2).
The surface area of animal that gives worst case active dose to surface area ratio should be used. By using this surface area, it is assumed that the active substance will evenly distribute over the animals whole body surface[2].

Species	**Size**	**Surface area (cm^2)**
Dog	Large (> 20 kg)	11,000
	medium (10 – 20 kg)	7,000
	Small (<10 kg)	3,000
Cat	Large (> 6 kg)	4,000
	medium (3 – 6 kg)	2,500
	Small (< 3 kg)	1,500

[2] It is noted that in practice the highest residues are anticipated on the head and trunk of an animal and these are the areas predominantly stroked during typical contact behaviour with pet animals. Therefore the assumption of even distribution might result in an underestimation of the risk. However, considering all assumptions taken into account, the final outcome of the calculations is considered to be sufficiently conservative.

4.3.3.2 Oral exposure of children due to hand-to-mouth contact

This scenario assumes that part of the total residues to which a child is dermally exposed will be on the hands and may subsequently be ingested due to hand-to-mouth contact. The oral exposure is calculated by using the results from the dermal exposure assessment. Only a fraction of the dermal residue concentration is expected to be on the hands. As a result of hand-to-mouth (HTM) or actually hand-into-mouth contact (HIM), part of the residues on the hand may be ingested. Especially in young children, HTM-contact may result in significant exposure.

The method for determining oral exposure due to hand-to-mouth contact is based on dermal exposure and subsequently estimating the hand residue loading (per cm^2) multiplied by the surface area mouthed and unloaded per day.

It is assumed that the hands contain 15%[3] of the total dermal exposure, simply based on surface area (270/1790 cm^2; the surface area of both hands of a child/surface area of the unprotected body parts of a child).

The part that will be ingested depends on the surface area actually mouthed, the frequency of mouthing, unloading of the surface area and reloading of the surface area due to repeated contact with the animals in one day. Recent European data on HTM contact, including actual HIM contact and mouthed surface area, are available and these values are used in calculating the estimated exposure (RIVM report 320005004/2007).

The following equations are used to calculate oral exposure of a child contacting a treated animal:

$$OE = \frac{HR * SA_m * HTM * HIM}{BW}$$

Where:

OE = Oral exposure due to hand-to-mouth contact (mg/kg bw/day);

HR = Hand Residue loading (mg/cm^2), the amount of residues on the hand per cm^2 of hand. See below;

SA_m = Surface Area mouthed.
Default: 7 cm^2 for a 2-3 year old child, corresponding to the average surface area of two fingers as generally 2 fingers appeared to be mouthed (RIVM report 320005004/2007). It is assumed that the total content of this area is unloaded as this surface area represents actual hand-into-mouth contact;

HTM = Hand-to-Mouth contacts per day (day^{-1}).
Default: 20 per hour for a 2-3 year old child. This value corresponds to the 75th percentile of HTM/h derived from a review of HTM studies: 17 rounded up to 20 as a default (RIVM report 320005004/2007). The default is extrapolated to contacts per day i.e. 20 per day as for this calculation the mouthed area is assumed to be fully loaded every time HTM contact occurs;

HIM = Hand-into-Mouth contact. Fraction of HTM which actually results in hand-into-mouth contact.
Default: 0.4 for a 2-3 year old child (RIVM report 320005004/2007);

BW = Body weight of a child.
Default: 12.5 kg (see section 4.3.2).

[3] Under real conditions, it will be mostly the surface of the hands that are in contact with the animal. Assuming that 15% of the total dermal exposure is on the hands is therefore not worst case; however, it is considered reasonable given all the assumptions that have been taken into account when developing the equation and defaults.

This approach assumes that exposure time of a child to a treated animal is spread over the day; therefore reloading will occur during the day and as a result it is assumed that hands are loaded every time hand-into-mouth contact occurs.

$$HR = \frac{DE * F_h}{SA_h}$$

Where:

HR = Hand Residue loading (mg/cm^2), the amount of residues on the hand per cm^2 of hands;

DE = Dermal exposure (mg), not corrected for body weight;

F_h = Fraction of total dermal exposure expected to be on the hands. Default: 0.15 (15%) based on surface area comparison (see above);

SA_h = Surface Area of both hands of a child. Default: 270 cm^2 for a 2-3 year old child. The value corresponds to the 25th percentile of the Dutch population (considered to be representative for the European population) (RIVM report 090013003/2014).

4.3.3.3 Combined exposure by different routes.

If more than one route of exposure is involved in a single situation (i.e. within one scenario; for example dermal exposure and hand-to-mouth contact), the total systemic exposure (sum of routes) should be calculated.

4.4. Estimating exposure levels – Wipe tests (Transferable Residue study/Residue Dislodgeability study)

To make a quantitative user risk assessment for dermal and subsequent oral hand-to-mouth exposure, it is necessary to have a measure of the amount of active substance that is anticipated to transfer to an exposed person from handling / stroking a treated animal when the active substance is present on the animal's skin or fur (including to touch the collar when stroking). While estimations of transferable residue can be calculated on the basis of default values (see section 4.3.3.1), there is the possibility of refining calculations based on data derived from a suitable product specific *in vivo* exposure study, i.e. a pet animal wipe test. It has to be noted that the methodology of the wipe test will have a large influence on the results obtained. Therefore, this section was added to provide guidance on a methodology for a transferable residue study that will be acceptable to the competent authority, improve consistency of approach and harmonise the assessment of user safety of topically administered VMPs.

The applicant may use an alternative design if justified.

In devising or using a wipe test protocol, applicants should be aware of the following main points:

Documentation

The wipe test should be conducted under GLP. The methodology should be adequately described and justified.

Test Item

The wipe test should be conducted using the final product formulation administered/applied to the test animals as recommended in the proposed SPC.

Species

Wipe tests should be performed in the target animal species, usually dogs or cats. For products intended for use in both dogs and cats, a wipe test study performed on dogs would be sufficient as this will be considered worst case. The derived data may then also be used for cats.

Experimental design

Animals should not be bathed after application of test item (unless required according to the proposed conditions of use e.g. for shampoos).

The number of animals, breed, hair length and body weight should be documented. A minimum of eight test animals is recommended. The animals should be housed in groups as far as possible in order to respect animal welfare. However, individual housing must be used during the critical phase after treatment, i.e. the period during which there may be cross-contamination due to the potential for residue transfer between animals. The duration of this period should be as short as possible based on 3Rs considerations, but as long as necessary in order to ensure the scientific validity of the study. In any case it should be justified by the applicant.

Application of the test item

Animals should be treated in accordance with the proposed conditions of use.

For spot-on products, the dose that gives the highest active substance to surface area ratio should be used as determined for small, medium and large animals when the product is intended for various animal sizes (see table under 4.3.3.1.). This dose is to be applied to the test animals, which are in general medium sized animals (where the dose is to be corrected for difference in bodyweight). To obtain the highest active substance to surface area dose, the test animals should be dosed with the worst case amount (mg/kg) recommended in the SPC. For example, when in accordance with the proposed conditions of use, a 2ml pipette is recommended for a medium sized animal of 10 to 20 kg bw, the highest active dose to surface area will be 2ml applied to 10kg animals. In case the test animals in the wipe test weigh 20kg, a dose of 4ml should be applied.

Sample Collection and Handling

Careful consideration needs to be given to sampling time points, as the information from a transferable residue study may be used to formulate risk mitigation measures (RMMs) specifying that treated animals should not be handled for a certain time after treatment. Generally, the time points up to and including 12 hours after treatment are considered to cover the short-term exposure scenario and time points beyond 12 hours would cover the long-term exposure scenario. However, for certain product types (e.g., flea collars) the highest exposure may occur later. A short-term exposure estimation should be undertaken using the single highest value observed at any time point measured.

Generally, for products where a finite dose is applied and depletes until the whole dose is removed, the highest residues are expected at the start of treatment. Sampling time points should be prior to treatment and at 1, 4, 12 hours, 1, 2, 4, 7, 14, 21, and 28 days or for the claimed duration of efficacy. These time points cover the short-term and long-term exposure scenarios. Pharmacokinetic knowledge on the final product formulation and/or the active ingredient(s) can be taken into account to select appropriate sampling time points. For instance, collars contain a reservoir of active substance that does not show a depletion profile in the same way as a spot on. The highest residues are expected at later time points when the active has undergone a period of sustained release. Therefore, other sampling time points may need to be chosen taking into account the period of claimed efficacy. Sampling at time points beyond the claimed period of efficacy is not recommended.

One dye free 100% cotton glove should be used to collect the transferable residues and this should be placed over an impermeable glove. It is considered appropriate to use a gloved human hand as this will represent a realistic interaction with a treated animal; although the use of a mannequin hand is also considered acceptable. It is acknowledged that cotton gloves used as dosimeters overestimate exposure, because they are absorbent, unlike human skin.

Stroking procedure

At each time point, the sampler should carry out at least 10 petting simulations, in a manner determined to mimic normal petting actions. The sampler should stroke the specific body parts using the palmar surface of the gloved hand (cotton and impermeable gloves) with splayed fingers with uniform medium pressure using motions which run with the lay of the hair coat. One petting simulation will consist of 3 strokes to cover the whole body surface, starting at the head in each stroke and finishing at the base of the tail. The 3 strokes should be in the following order

- one stroke on the right side (along the ribcage)
- one stroke on the left side (along the ribcage)
- one stroke on the length of the back line from the crown to base of the tail

The strokes should include the application site(s) for spot-on products and the collar for medicated collars (not just over the fur adjacent to the collar).

The cotton and impermeable glove should be removed carefully by turning each glove inside out and placing in separate containers for storage / analysis.

Analysis of samples

Methods used for analysis of residues (i.e. active substances and/or substance of concern) must be adequately validated. The amount of residue on the cotton and impermeable gloves should be determined. If samples were stored prior to analysis, stability under the conditions of storage should be demonstrated.

Presentation of results

The amounts (expressed as mg or µg) of active substance applied to each animal should be recorded as well as the amount of residue dislodged (collected on the cotton and impermeable gloves) at each time point as well as animal body weight, breed and hair length. During the petting procedure, if there is any visible wetness on the application site and/or cotton glove covering the hand it should be recorded in the raw data. This will provide information on the time period until the application site has fully dried.

Individual results should be presented for each animal at every time point for the total amount of residue dislodged, expressed as mg or µg and as a percentage of applied dose.

A summary table of results should be provided including the time weighted average (TWA) and maximum of dislodged residue for each animal.

To compensate for the fact that only a limited number of animals are included in the wipe test, the upper tolerance limit should be calculated.

For short-term exposure scenarios, the upper tolerance limit should be calculated based on the highest residue value of each individual animal.

For long-term exposure scenarios, the upper tolerance limit should be calculated based on the TWA of each individual animal. The TWA should be calculated using all time points from the wipe test (1, 4, 12 hours …up to 28 days or the claimed duration of efficacy or until two subsequent measurements are below the LOQ). However, for products of which data show a MOE <100 in the acute phase, and for which risk mitigation measures limiting exposure in the acute phase are considered necessary (e.g. not to handle the animal for at least 4 or 12 hours), the TWA for chronic exposure should then be considered from the point after the acute phase (i.e. after 4 or 12 hours), since the risk mitigation measure(s) should reduce the likelihood of exposure during the acute phase. For collars, it is expected that the exposure during the period of efficacy remains steady because of the sustained release of the substance of concern from the collar.

See section 'definitions' for more detailed information on the calculation of the TWA and the upper tolerance limit.

4.5. Quantitative Risk Assessment – Margin of Exposure

The procedure for the quantitative risk assessment should follow that detailed in the 'Guideline on user safety for pharmaceutical veterinary medicinal products'. For non-quantifiable risks, a qualitative risk characterisation should be conducted.

The procedure for the quantitative risk assessment consists of comparing the exposure levels to which the user is exposed or is likely to be exposed with the exposure levels at which no adverse effects are expected to occur. This is generally done by comparing the estimated exposure to the relevant NOAEL.

Where the exposure estimate is higher than or equal to the NOAEL, the risk for the user is considered to be unacceptably high.

Where the exposure estimate is less than the NO(A)EL, the magnitude by which the NO(A)EL exceeds the estimated exposure (i.e. the margin of exposure (MOE)) needs to be considered taking account of the following parameters:

- the intra- and interspecies variation[4];
- the nature and severity of effect;
- the human population to which the exposure information applies;
- the differences in exposure (route, duration, frequency) compared to that applied in the study from which the TRV was derived;
- the dose-response relationship observed;
- the overall confidence in the database.

Where the MOE is more than needed in view of the parameters mentioned above, the risk for the user is considered acceptable. In other cases, risk management options should be proposed and evaluated.

Where appropriate and justified, available toxicological limit values or exposure limit values (for example, AOEL or other occupational limits, ADI) may be used as alternatives for the MOE approach as described above.

[4] To account for uncertainty related to interspecies variation (i.e. extrapolation from animals to humans) a standard factor of x10 is used unless there is reliable data to deviate from this.
To account for uncertainty related to intraspecies variation (i.e. differences in human susceptibility) a standard factor of x10 is used unless there is reliable data to deviate from this.
When alternative factors are proposed, consideration must be given to the guidance document published by the IPCS/WHO (IPCS/WHO, 2005).

4.6. Risk Mitigation Measures

If it is determined that the MOE is below that considered to be acceptable, a potential risk to the user has been identified. At this point, risk control options to reduce or eliminate the risk(s) need to be considered.

When considering how a risk can be controlled, the general approach detailed in the 'Guideline on user safety for pharmaceutical veterinary medicinal products' should be followed. The key criteria are that the risk mitigation measure (RMM) should reduce exposure to an acceptable level and that the measures be practicable. It should be noted that not all risks can be mitigated. This section provides some specific examples for controlling risks arising from exposure to topical veterinary medicinal products for companion animals. The examples are not intended to be exhaustive.

It is recommended that the concerned risks are communicated following the A, B, C, D format presented in section 5.3.3 of the 'Guideline on user safety for pharmaceutical veterinary medicinal products'.

Pre-Application

Pre-application situations where exposure can occur include storing or accessing the product or preparing it for use. The potential for, and the nature of, exposure will depend on e.g. packaging design, storage, or skills of the user. The type of exposure of concern is acute dermal and/or oral. The primary concerns are children being exposed to the product. Consideration should be given to the possibility of using child-resistant packaging as a risk mitigation measure. Other examples of mitigation measures that can reduce the risk include:

- Keep out of sight and reach of children.
- Keep the sachet with the <collar><pipette> in the outer carton until ready to use.
- Stored pipettes must be kept in the original packaging.
- Dispose of any surplus collar immediately.
- In case of accidental ingestion, seek medical advice immediately and show the package leaflet or label to the physician.

A packaging can be claimed as child-resistant packaging, only if it has been demonstrated to be child-resistant in accordance with the European Standard EN14375 for non-reclosable packaging or EN8317 for reclosable packaging.

Application

Situations where exposure can occur include administering the product to the animal. The type of exposure of concern is primarily acute dermal, oral, inhalation as well as ocular depending on the pharmaceutical form. Examples of mitigation measures that can reduce an identified risk include:

- Personal protective equipment consisting of {specify} should be worn when handling the veterinary medicinal product.
- Avoid contact with skin, eye and mouth, including hand-to-mouth and hand-to-eye contact. Do not smoke, drink or eat during application. Wash hands after use. In case of contact with the skin or eyes rinse immediately with water.
- Spray animals in the open air or a well-ventilated room.

Personal protective equipment

It is considered unreasonable to expect a pet-owner to have access to personal protective equipment beyond normal house-hold gloves. Therefore, measures requiring additional personal protective equipment for pet-owners may be considered unacceptable unless provided with the product.

Post-application

The post-application phase consists of both short-term and long-term dermal and oral exposure. The handling of animals following treatment including contact with a medicinal collar poses potential exposure risks. Consideration should also be given to children accessing veterinary medicinal product waste after treatment. Examples include:

- <Used applicators><Excess waste collar> should be disposed of immediately and not left within the sight or reach of children.
- In order to prevent children from gaining access to used <pipettes><excess waste collar>, dispose of waste material immediately.

Following the treatment of an animal, the use of personal protective equipment is not considered to be a practicable measure to reduce risk. Measures to minimise contact with the treated animal(s) should be considered. This can include avoiding contact during the time period in which exposure is expected to be greatest. For example:

- Avoid direct contact with the application site. Children should not be allowed to play with treated dogs/cats until the application site is dry.
- Treated animals must not be handled <until the application site is dry><for at least X hours after application of the product>. It is therefore recommended to treat the animal in the evening. Treated animals should not be allowed to sleep with their owners, especially children, on the day of (or for X days after) treatment.

A particular risk arises where the treated animal is in regular contact with the user e.g., topical products for companion animals are likely to have a prolonged post-application risk to multiple user types, including children. Examples of risk mitigation measures include:

- Avoid letting children touch the collar, play with it or put it into their mouth.
- Care should be taken not to allow young children to have prolonged intensive contact with (e.g. sleeping with) an animal wearing a collar.

Examples of impracticable measures would be the washing of hands each time after stroking or handling animals, in particular for children, or isolating animals for an extended period of time in a domestic environment. Keeping the animal away from people, particularly children, beyond the overnight period of 12-hours is also not generally considered practical.

In some cases it may not be possible to reduce the risks for all users exposed to the product to an acceptable level. Where this is the case the feasibility of restricting use to avoid exposure of vulnerable users needs to be considered.

In all cases, the applicant should justify that the proposed risk mitigation measures are feasible and reduce exposure to an acceptable level. Any identified risk to the user, proposed measures to mitigate those risks and the feasibility of the RMMs proposed will be considered in the context of the overall benefit:risk assessment.

The communication of user warnings and risk mitigation measures (RMMs) is important. For guidance on the presentation of user warnings in the product information, the reader is referred to the most recent version of the Quality Review of Documents veterinary product information template.

Definitions

Toxicological Reference Value (TRV): A toxicological index that, when compared to exposure, is used to quantify a risk for human health. TRVs are established for a given critical effect and are specific to a substance, duration of exposure and route of exposure (e.g. NOEL, NOAEL).

No observed effect level (NOEL): The highest administered dose that was observed not to cause an effect in a particular study.

No observed adverse effect level (NOAEL): The highest administered dose that was observed not to cause an adverse effect in a particular study.

Lowest observed effect level (LOEL): The lowest administered dose that was observed to cause an effect in a particular study.

Lowest observed adverse effect level (LOAEL): The lowest administered dose that was observed to cause an adverse effect in a particular study.

Acute reference dose (ARfD): An estimate of the exposure to a substance, expressed on a body weight basis, that can occur in a period of 24 hours or less without adverse effects or harm to the user. The route of exposure for which an ARfD applies should be specified.

Acceptable daily intake (ADI): an estimate of the substance and/or its residues, expressed in terms of µg or mg per kg bodyweight, that can be ingested daily over a lifetime without any appreciable health risk to exposed individuals.

Exposure: Contact with a substance by swallowing, breathing, or contacting the skin or eyes. Exposure in the context of this guideline may be short-term (once or for a short time), or long-term (repeated exposure for a longer period).

Short-term exposure: Contact with a substance that occurs once or repeatedly for only a short time. In the context of this guideline, short-term exposure covers from the time of treatment until the time point at which the highest exposure occurs. This is likely to be up to 12 hours but could be later.

Long-term exposure: Contact with a substance that occurs over a longer period. In the context of this guideline, long-term exposure covers the period of claimed efficacy.

Acute toxicity study The test substance is administered as one or more doses in a 24 hour period. Observations may continue for up to 14 days.

Sub-acute toxicity study: The test substance is administered daily in graduated doses to several groups of experimental animals for a period of up to 28 days.

Sub-chronic toxicity study: The test substance is administered daily in graduated doses to several groups of experimental animals for a period of 30 to 90 days.

Chronic toxicity study: The test substance is administered daily in graduated doses to several groups of experimental animals for a period of longer than 90 days.

Uncertainty factor (UF): Typically UFs are intended to account for uncertainty in extrapolating animal data to humans (inter-species variability), the variation in sensitivity among humans (inter-individual variability), quality of data, severity of response, or other concerns.

Margin of exposure (MOE): The ratio of the no-observed-(adverse)-effect level (NO(A)EL) or benchmark dose lower confidence limit (BMDL) for the critical effect to the theoretical, predicted, or estimated exposure.

Upper tolerance limit (T): The 95% upper confidence bound of the 95th percentile of the dislodgeable amount in the (infinite) population of animals.
The equation is given by

$$\log(T_{upper}) = \text{mean of } \log(Y) + k * \text{standard deviation of } \log(Y)$$

where Y represents the highest measured dislodgeable amount (for the short-term exposure scenario) or the TWA (for the long-term exposure scenario) in each individual animal; where k is the 95/95 tolerance limit factor. The value of k depends on the number of animals included in the test; for 8 animals it is 3.188 (see Note for guidance for the determination of withdrawal periods for milk; EMEA/CVMP/473/1998-FINAL).

Time weighted average (TWA): Dislodgeable amount per individual animal averaged over the time until claimed length of efficacy or until two subsequent measurements are below LOQ, with setting measurements below LOQ to half LOQ.

If t1, t2, …, tn are the time points of the stroke tests, and c1, c2, …, cn the corresponding dislodgeable amount, then the time weighted average is given by

$$\frac{\sum_{i=1}^{n-1}(t_{i+1} - t_i) \cdot (c_i + c_{i+1})/2}{t_n - t_1}$$

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Annex

Worked example

In order to illustrate the principles and approaches described in this guideline, a worked example is provided below. The values used for TRV, absorption and 'wipe test' are fictional figures.

A spot on pipette intended for medium sized dogs contains 134 mg active substance while the largest pipette (5 ml) contains 700 mg of active substance. The highest active dose to surface area ratio was determined for the medium sized dogs (therefore 134 mg can be used as AR when calculating contact with the treated animal). The default values for dislodgeable fraction when 'wipe test' results are not available would be 15.0% for considering the short-term exposure scenario and 2.0% for the long-term scenario. As a refinement, a 'wipe test' study is submitted where the highest amount dislodged was 5.0% and in the following 28 days the mean TWA of the amount dislodged was 0.5%.

Establishing TRVs

Data indicate oral absorption (bioavailability) of the pharmacologically active substance to be 80% and dermal absorption to be 1% (using an aqueous solution). A dermal absorption study using the final product formulation, which included penetration enhancers, indicated that 2% of the administered dose was absorbed into the systemic circulation. The conversion of an oral NO(A)EL into a dermal NO(A)EL is calculated by adjusting for differences in absorption between routes and species, i.e.

$$\text{Adjusted dermal NO(A)EL} = \text{Oral NO(A)EL} \times \frac{Abs_{oral}}{Abs_{derm}}$$

References submitted indicated the following TRVs for the active substance for the different exposure scenarios:

- Short-term dermal: No relevant dermal study with the final product formulation was available for the substance of concern, the dermal TRV is calculated from the oral TRV adjusted for oral/dermal absorption. The Abs_{derm} of 2% as derived for the final product formulation has to be used.

$$\text{Adjusted dermal NO(A)EL} = 0.9 \text{ mg/kg bw} \times \frac{0.8}{0.02} = 36 \text{ mg/kg bw}$$

- Short-term oral: 0.9 mg/kg bw derived from a 28-day repeated dose toxicity study in the rat.
- Long-term dermal: No relevant dermal study was available for the substance, the dermal TRV is calculated from the oral TRV adjusted for oral/dermal absorption; for the long-term exposure scenario the Abs_{derm} of 1% is acceptable (as penetration enhancers are not considered to play a significant role for the long-term exposure scenario).

$$\text{Adjusted dermal NO(A)EL} = 0.33 \text{ mg/kg bw} \times \frac{0.8}{0.01} = 26.4 \text{ mg/kg bw}$$

- Long-term oral: 0.33 mg/kg bw based on 13 week oral (diet) study in rats

Estimating exposure

1) Contact to the product (see section 4.3.2 of this guideline)

Pre-application phase

Accidental oral exposure of a child if an opened pipette is left out on a surface whilst an adult is restraining an animal or if the product is accessible by a child. As the product is not in a child-resistant packaging, the child can be exposed up to 10% orally. Exposure would then be:

Oral (Direct)
$D = \frac{\mathrm{AR} * \mathrm{FA}}{\mathrm{BW}} = \frac{700 * 0.1}{12.5}$
= 5.6 mg/kg bw

Application phase

Dermal and oral exposure of an adult if the product comes into contact with the user's skin during administration and then is subsequently transferred to the mouth

Dermal	**Oral (Hand-to-mouth)**
$D = \frac{\mathrm{AR} * \mathrm{FA}}{\mathrm{BW}} = \frac{700 * 0.1}{60}$	$D = \frac{\mathrm{AR} * \mathrm{FA}}{\mathrm{BW}} = \frac{700 * 0.01}{60}$
= 1.2 mg/kg bw	= 0.12 mg/kg bw

2) Contact to the treated animal (see section 4.3.3 of this guideline)

Post-application phase – Short-term exposure

Dermal exposure of children after contact with the animal

Using 'wipe test' results	**Using default values**
$TR = \frac{\mathrm{AR} * \mathrm{F}_{AR}}{SA_{animal}}$	
AR = Application Rate = 134 mg F_{AR} = Fraction of the Application Rate available as transferable residue = 0.05 SA_{animal} = Surface Area of the animal = 7000 cm^2	AR = 134 mg F_{AR} = 0.15 (default) SA_{animal} = 7000 cm^2
$TR = \frac{134 * 0.05}{7000}$	$TR = \frac{134 * 0.15}{7000}$
TR = 0.00096 mg/cm²	**TR = 0.0029 mg/cm²**
$\mathrm{DE}_{bw-corr} = \frac{\mathrm{TR} * \mathrm{SA}_{contact}}{\mathrm{BW}}$	
TR = 0.00096 mg/cm^2 $SA_{contact}$ = the surface area of a child in contact	TR = 0.0029 mg/cm^2 $SA_{contact}$ = 1790 cm^2 (default)

with the animal per day = 1790 cm^2 (default) BW = Body Weight of a child = 12.5 kg (default)	BW = 12.5 kg (default)
$\mathrm{DE}_{bw-corr} = \frac{0.00096 * 1790}{12.5}$	$\mathrm{DE}_{bw-corr} = \frac{0.0029 * 1790}{12.5}$
$DE_{bw-corr}$ = 0.137 mg/kg bw	**$DE_{bw-corr}$ = 0.411 mg/kg bw**

Oral exposure of children due to hand-to-mouth contact

Using 'wipe test' results	**Using default values**
$\mathrm{HR} = \frac{\mathrm{DE} * \mathrm{F}_h}{SA_h}$	
HR = Hand Residue loading (mg/cm^2) DE = Dermal exposure not corrected for bw = (0.00096*1790) = 1.7133 mg F_h = Fraction of total dermal exposure expected to be on both hands = 0.15 (default) SA_h: Surface Area of both hands of a child = 270 cm^2 (default)	HR = Hand Residue loading (mg/cm^2) DE = (0.0029*1790) = 5.140 mg F_h = 0.15 (default) SA_h = 270 cm^2 (default)
$\mathrm{HR} = \frac{1.7133 * 0.15}{270}$	$\mathrm{HR} = \frac{5.140 * 0.15}{270}$
HR = 0.000952mg/cm^2	**HR = 0.00286 mg/cm^2**
$\mathrm{OE} = \frac{\mathrm{HR} * \mathrm{SA}_m * \mathrm{HTM} * \mathrm{HIM}}{\mathrm{BW}}$	
OE = Oral exposure due to hand-to-mouth contact (mg/kg bw/day) HR = 0.000952 mg/cm^2 SA_m =Surface Area mouthed = 7 cm^2 (default) HTM = Hand-to-Mouth contacts per day = 20 (default) HIM = Hand-into-Mouth contact = 0.4 (default) BW = Body Weight of a child = 12.5 kg (default)	OE = Oral exposure due to hand-to-mouth contact (mg/kg bw/day) HR = 0.00286 mg/cm^2 SA_m = 7 cm^2 (default) HTM = 20 (default) HIM = 0.4 (default) BW = 12.5 kg (default)
$\mathrm{OE} = \frac{0.000952 * 7 * 20 * 0.4}{12.5}$	$\mathrm{OE} = \frac{0.00286 * 7 * 20 * 0.4}{12.5}$
OE = 0.00426 mg/kg	**OE = 0.0128 mg/kg**

Combined exposure: dermal exposure + oral exposure due to hand-to-mouth contact

Using 'wipe test' results	**Using default values**

	External dose	Internal dose*	External dose	Internal dose*
Dermal exp	0.137	0.00274	0.411	0.00824
Oral exp	0.00426	0.00341	0.0128	0.0102
Total exp		0.00615		0.01844

*To calculate the internal dose an F_{oral} of 80% and F_{dermal} of 2% is used.

Post-application phase – Long-term exposure

Dermal exposure of children after contact with the animal – Long-term exposure

Using 'wipe test' results	**Using default values**
$TR = \frac{AR * F_{AR}}{SA_{animal}}$	
AR = Application Rate = 134 mg F_{AR} = Fraction of the Application Rate available as transferable residue = 0.005 SA_{animal} = Surface Area of the animal = 7000 cm^2	AR = 134 mg F_{AR} = 0.02 (default) SA_{animal} = 7000 cm^2
$TR = \frac{134 * 0.005}{7000}$	$TR = \frac{134 * 0.02}{7000}$
TR = 0.000096 mg/cm²	**TR = 0.00038 mg/cm²**
$DE = \frac{TR * SA_{contact}}{BW}$	
TR = 0.000096 mg/cm^2 $SA_{contact}$ = the surface area of a child in contact with the animal per day = 1790 cm^2 (default) BW = Body Weight of a child = 12.5 kg (default)	TR = 0.00038 mg/cm^2 $SA_{contact}$ = 1790 cm^2 (default) BW = 12.5 kg (default)
$DE_{bw-corr} = \frac{0.000096 * 1790}{12.5}$	$DE_{bw-corr} = \frac{0.00038 * 1790}{12.5}$
$DE_{bw-corr}$ = 0.0137 mg/kg bw	**$DE_{bw-corr}$ = 0.0548 mg/kg bw**

Oral exposure of children due to hand-to-mouth contact – Long-term exposure

Using 'wipe test' results	**Using default values**
$HR = \frac{DE * F_h}{SA_h}$	
HR = Hand Residue loading (mg/cm^2) DE = Dermal exposure not corrected for bw = (0.000096*1790) = 0.1713 mg F_h = Fraction of total dermal exposure expected	HR = Hand Residue loading (mg/cm^2) DE = (0.00038*1790) = 0.6853 mg F_h = 0.15 (default)

to be on both hands = 0.15 (default) SA_h: Surface Area of both hands of a child = 270 cm^2 (default)	SA_h = 270 cm^2 (default)
$HR = \frac{0.1713 * 0.15}{270}$	$HR = \frac{0.6853 * 0.15}{270}$
HR = 0.000095 mg/cm²	**HR = 0.000381 mg/cm²**
$OE = \frac{HR * SA_m * HTM * HIM}{BW}$	
OE = Oral exposure due to hand-to-mouth contact (mg/kg bw/day) HR = 0.000095 mg/cm^2 SA_m =Surface Area mouthed = 7 cm^2 (default) HTM = Hand-to-Mouth contacts per day = 20 (default) HIM = Hand-into-Mouth contact = 0.4 (default) BW = Body Weight of a child = 12.5 kg (default)	OE = Oral exposure due to hand-to-mouth contact (mg/kg bw/day) HR = 0.000381 mg/cm^2 SA_m = 7 cm^2 (default) HTM = 20 (default) HIM = 0.4 (default) BW = 12.5 kg (default)
$OE = \frac{0.000095 * 7 * 20 * 0.4}{12.5}$	$OE = \frac{0.000381 * 7 * 20 * 0.4}{12.5}$
OE = 0.00043 mg/kg	**OE = 0.00171 mg/kg**

Combined exposure: dermal exposure + oral exposure due to hand-to-mouth contact

Using 'wipe test' results			**Using default values**	
	External dose	Internal dose*	External dose	Internal dose*
Dermal exp	0.0137	0.000137	0.0548	0.00055
Oral exp	0.00043	0.000341	0.00171	0.00136
Total exp**		0.000478		0.00191

*To calculate the internal dose an F_{oral} of 80% and F_{dermal} of 1% is used (as no penetration enhancers were present after 12 hours).

**It is acknowledged that dermal exposure is slightly overestimated in this calculation, as once the product is orally absorbed it cannot contribute to dermal exposure as well. The overestimation, i.e. a mouthed surface area of 7 x 20 x 0.4= 56 cm^2 when compared to the default surface area in contact with the animal of 1790 cm^2 is considered minimal.

Calculation of MOEs

Pre-application phase (Child)

Exposure Route	Relevant NO(A)EL	Estimated Exposure	MOE
Direct oral	0.9 mg/kg bw/day	5.6 mg/kg bw/day	0.16

Application phase (Adult)

Exposure Route	Relevant NO(A)EL	Estimated Exposure	MOE
Oral	0.9 mg/kg bw/day	0.12 mg/kg bw/day	7.5
Dermal	36 mg/kg bw/day	1.2 mg/kg bw/day	30

Post-application phase – Short-term exposure

Exposure Route	Relevant NO(A)EL	Estimated Exposure	MOE
Using default values			
Oral	0.9 mg/kg bw/day	0.0128 mg/kg bw/day	70
Dermal	36 mg/kg bw/day	0.411 mg/kg bw/day	88
Oral + dermal	0.72 mg/kg bw/day*	0.01844 mg/kg bw/day**	39
Using 'wipe test' results			
Oral	0.9 mg/kg bw/day	0.00426 mg/kg bw/day	211
Dermal	36 mg/kg bw/day	0.137 mg/kg bw/day	263
Oral + dermal	0.72 mg/kg bw/day*	0.00615 mg/kg bw/day**	117

*Internal NO(A)EL: oral NO(A)EL of 0.9 mg/kg bw/day adjusted for oral absorption (80%)

**Internal exposure

Post-application phase – Long-term exposure

Exposure Route	Relevant NO(A)EL	Estimated Exposure	MOE
Using default values			
Oral	0.33 mg/kg bw/day	0.00171 mg/kg bw/day	193
Dermal	26.4 mg/kg bw/day	0.0548 mg/kg bw/day	482
Oral + dermal	0.264 mg/kg bw/day*	0.00191 mg/kg bw/day**	138
Using 'wipe test' results			
Oral	0.33 mg/kg bw/day	0.00043 mg/kg bw/day	767
Dermal	26.4 mg/kg bw/day	0.0137 mg/kg bw/day	1927
Oral + dermal	0.264 mg/kg bw/day*	0.000478 mg/kg bw/day**	552

* Internal NO(A)EL: oral NO(A)EL of 0.33 mg/kg bw/day adjusted for oral absorption (80%)

**Internal exposure

Risk mitigation measures

When considering the MOEs calculated above, it is clear that children should not have access to the product in the pre-application phase. In order to protect children, the following risk mitigation measures could be appropriate:

- The product should be kept in child resistant packaging;

In addition, the following user warnings could be appropriate:

- Avoid contact of the product with skin, eyes or mouth.
- Do not eat, drink or smoke while handling the product.
- Wash hands thoroughly after use.
- In case of accidental spillage on skin, wash off immediately with soap and water.
- If the product is accidentally swallowed, seek medical advice immediately and show the package leaflet to the physician.
- Keep stored pipettes in the original packaging until ready to use. In order to prevent children from getting access to used pipettes, dispose of used pipettes immediately in a proper way.

The above also encompass appropriate warnings for adults in case of accidental exposure during treatment. It is noted that in the application phase the MOE when considering dermal contact including subsequent oral exposure is <100. The need for risk mitigation measures following an MOE of less than 100 will need to be considered on a case by case basis. In this example, the calculated MOE following dermal exposure may suggest the need for protective gloves. However, in this case it was not considered necessary to recommend the wearing of gloves because the NO(A)EL was based on a repeated dose toxicity study (with no acute effects) whereas exposure during application is considered a single exposure. In light of this the above measures are considered sufficient for this product.

In the post-application phase, there are two scenarios presented. Using the default values for the amount dislodged, the product fails in the acute phase (short-term exposure) as the MOE <100. In such a situation, results from a wipe test will be required and appropriate risk mitigation measures such as the following would be required for safe use of the product (provided that safe use can be demonstrated for the 12 hour time point, and all subsequent time points):

- Treated animals should not be handled or played with for at least 12-hours after treatment. Animals should be treated in the evening in order to minimise contact with the treated animal. On the day of treatment, treated animals should not be permitted to sleep with their owner, especially children.

A modified warning would be required for the product that submitted a 'wipe test' study even though the MOE >100, as a general warning for topically applied products. Hence, the following warning would be included:

- Animals should be treated in the evening in order to minimise contact with the treated animal. On the day of treatment, treated animals should not be permitted to sleep with their owner, especially children.

No additional warnings are required for the long-term exposure post-application of the product. However, there may be a need for additional formulation specific warnings following the evaluation of skin/eye irritation and skin sensitisation studies using the final product formulation.