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4 Guideline on user safety of topically administered 5 veterinary medicinal products

6 Draft

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8 This guideline will supplement the existing "Guideline on user safety for pharmaceutical veterinary
9 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 must provide 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 product. This new guideline provides additional guidance and advice on user safety of topically administered products and on conducting user safety risk assessments for such 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. The CVMP published a concept paper early in 2014 outlining the need for a supplementary guideline to provide stakeholders with guidance on how risk to users can be assessed for topically administered products. This guideline uses, as its starting point, existing guidance in the form of a US EPA SOP (2012) as well as guidance developed by some individual EU member states.

2. Scope

This guideline focuses specifically on how user safety for topically administered products can be addressed and should be read in conjunction with the CVMP revised general Guideline on user safety for pharmaceutical veterinary medicinal products.

Exposure to topically administered products may occur via direct exposure to the product from the container (accidental spillage), or when owners or other household members including children come into contact with the animals after administration of a topical product. Exposure can be divided into the acute phase and the chronic phase. 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. In particular, the amount of residue dislodged from a treated animal onto the user is often investigated by means of the so called 'wipe test'. This guideline will provide recommendations for the conduct of a wipe test.

The principles of exposure estimation from the skin/fur of animals are similar for most types of topically applied products. These types of products include spot-ons, collars, pour-ons, sprays, topically applied powders and transdermal products.

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.

3. Legal basis

Requirements for safety testing for a marketing authorisation application are laid down in Article 12 of Directive 2001/82/EC of the European Parliament and of the Council, as amended by Directive 2004/28/EC and Directive 2009/9/EC.

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 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 SOP 2012 guidance as the basis for the estimation of both dermal and oral exposure of users. However, the algorithms have been modified alongside some of the default values included in this guideline. In doing this the CVMP utilised data and information available from Rijksinstituut voor volksgezondheid en milieu (RIVM) in the Netherlands.

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, 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 exposure from the scenarios;
- 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) in order to define TRVs with respect to the identified exposure scenarios.

This process should be based on the assessment of all available experimental animal scientific data that should be 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 the exposure and any identified gaps in the dataset. If appropriate TRVs cannot be established, new studies should be performed to generate them.

The studies used to define TRVs should be carried out in accordance with VICH/OECD guidelines and current methodology or may be from a reputable published source. These studies should provide sufficient data for the assessment of the toxicity of the active substance for acute, sub-chronic and chronic exposure scenarios and to consider effects including those on 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 acute/accidental risk assessment should be based on acute, sub-acute or sub-chronic NO(A)ELs, the latter representing a worst case approach. For chronic risk assessment, the use of a sub-chronic NO(A)EL or other chronic TRVs can be considered acceptable. Available human data can also be considered if these studies are relevant from a scientific point of view (i.e. not using therapeutic doses), although the ethical acceptance of these human data is an issue that the competent authorities undertaking the user safety assessment will need to consider.

Toxicity data on any (photo)degradation products of the active substance, of the excipients or of the final formulation should also be taken into consideration, if the toxicological impact of these substances appears also important. The approach taken should be fully justified.

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 most cases, data from animal studies allows a quantitative dose-response analysis (quantitative evaluation of the nature of the adverse effects associated with the exposure to the substance) to be made. Use of the benchmark dose 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.

Some TRVs (e.g., the acceptable daily intake, ADI) already include an uncertainty factor (see section 4.5) and are developed according to a highly structured and demanding approach that involves collective assessments. If available, and considered as appropriate in the assessment, these TRVs can be used. If not, NO(A)EL values should be retained as the TRV.

In every case, TRVs are established for all relevant critical effects, and are specific to a substance, duration of exposure (acute, sub-chronic or chronic) and a route of exposure (oral, dermal etc.). If more than one TRV is available for a given exposure scenario, the choice of TRV should be fully justified. In the context of a risk assessment, these values should be compared to exposure levels of the active substance(s) 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 adequate absorption factors (see section 4.3 "Identifying exposure scenarios and estimating corresponding exposure levels", below). Even if the NO(A)EL is based on the most sensitive effect, other effects could also be taken into consideration (i.e. reproductive effects) in order to focus the user safety risk assessment on specific scenarios or users and to lead to potential additional risk mitigation measures.

In summary, the establishment of TRVs should include relevant toxicological end points that relate to the different exposure scenarios. For topical sprays and powders, inhalational exposure should be considered. Therefore, TRVs for both acute and chronic exposure scenarios should be included as follows:

A.	Acute dermal	→	Accidental contact during administration or general contact with the product → Contact with the treated animal in the acute phase	TRV (NOAEL, ARfD...) to be based on short term dermal toxicity study or, if not available, to be based on long term dermal toxicity study. The final formulation should be used to derive the dermal TRV. In the absence of dermal toxicity study using the formulation, TRV will be based on short or long term oral toxicity study corrected for dermal/oral absorption (see dermal penetration enhancers section below).
B.	Acute oral	→	Accidental ingestion of the product → Hand-to-mouth exposure following contact with the treated animal in the acute phase	TRV (NOAEL, ARfD...) to be based on acute oral toxicity study or, if not available, to be based on sub-acute, sub-chronic or chronic oral toxicity study
C.	Chronic dermal	→	Post 12-hour repeated contact with treated animal	TRV (NOAEL, ADI...) to be based on longer term (ideally linked to the expected total duration of exposure) dermal toxicity study or, if not available, to be based on longer term oral toxicity study corrected for dermal/oral absorption
D.	Chronic oral	→	Repeated hand to mouth exposure after contact with treated animal (post 12-hours)	TRV (NOAEL, ADI...) to be based on longer term oral toxicity study

Use of dermal penetration enhancers

When assessing the acute dermal user exposure from topically administered products, the effect of the formulation and in particular penetration enhancers should be considered. Topically administered products may be formulated in such a way that dermal absorption is affected. Unless the final formulation is used to derive the dermal TRV, it is difficult to determine the role of the formulation (which may include penetration enhancers) in producing the effects observed. In instances where no formulation specific dermal TRVs are available a number of options are available:

- an oral TRV using the active can be used for assessing acute dermal exposure. However, in instances where the dermal absorption is greater than oral absorption, use of an oral TRV would not be acceptable
- use a corrected oral TRV adjusted with a route to route extrapolation using oral bioavailability data with a dermal absorption study using the final formulation
- A dermal TRV could be used, but data would be required comparing the absorption of the formulation used in the TRV study with that of the final product formulation.

In the absence of formulation specific dermal absorption data, dermal absorption is assumed to 100%. The use of a penetration enhancer in the formulation is not considered to play a role for the chronic exposure scenario (beyond 12 hours).

4.3. Identifying exposure scenarios and estimating corresponding exposure levels

Direct accidental oral exposure to the product must be considered as well as indirect oral exposure where dermal exposure to the product occurs and this dermal loading might be transferred to the mouth before, during or immediately after administration of the product. In identifying and estimating the exposure scenarios, the risk to adults who will be handling and/or administering the product should be considered as well as the risk to children who may come into contact with the product. This document will concentrate more on the risk to children as the risk to children is generally greater. However, applicants should always consider the risk to adults who may be administering the product or stroking the animals. 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.

Ocular exposure is also possible and the ocular irritancy of the product should be addressed.

Additionally, oral exposure due to hand-to-mouth contact post-application needs to be considered for collars and topically applied products, such as spot-on products, that may result in residues on the fur that can be transferred to the mouth as a result of stroking the pet. However, this aspect will not be considered here but as part of the sections on acute/chronic dermal/oral risk.

The following need to be considered in relation to particular product types:

Spot-on solution

A spot-on solution provided in a pipette may be regarded as child-resistant packaging, only if it has been demonstrated to be so in accordance with the European Standard EN14375. However, an opened pipette might be left out on a surface whilst an adult is restraining a pet. It is considered unlikely that the entire contents could be swallowed by a child if it had access to the opened pipette. Considering the viscosity of the material and the difficulty a child is likely to have in extracting the contents, a reasonable worst case estimate of the amount that may be accidentally ingested is considered to be 10% of the total amount contained in the pipette.

Shampoo

Shampoos may be available in different pack sizes and if left open while preparing the animal or left in a place accessible to children, it is possible that children would become exposed dermally and even orally. However, it is likely that if a small child were to pour shampoo into his/her mouth, most would be spat out as shampoo is likely to be unpalatable.

Collar

A collar is usually provided in different sizes to fit different size pets. It is not possible to orally ingest an entire collar. However, a child could swallow any cut off excess length or be exposed to the product dermally when handling the product or stroking the animal wearing a collar. Although unlikely due to physical difficulty and possible bitter taste of collar, a child could also chew on any part of a collar. However, oral exposure to the collar whilst it is attached to a pet is considered negligible.

Pour-on

Pour-on products are generally available for farm animals and these products may not be readily available to children. However, the risk of exposure to children cannot be automatically disregarded. Accidental dermal exposure for the person administering the product as well as dermal and oral exposure to children should be considered as outlined in the CVMP Guideline on user safety for pharmaceutical veterinary medicinal products.

Powder/Spray

For powder/spray formulations, the main risk of exposure is likely to be through the generation of dust/vapour and inhalation. Adults as well as children may also be exposed dermally when handling animals that have been treated with a topical powder. Both dermal and oral exposure resulting from stroking of the animals would need to be considered and the approach outlined in this document is applicable.

Other product types

The general principles described in this guideline apply for all topically applied product types including, for example, transdermal products. If appropriate, considerations relevant to the specific product type should be highlighted and addressed.

In practice, for all product types, exposure will be influenced by product-specific factors such as physicochemical properties, as well as the nature and state of the fur and the vigorousness and time of contact. However, this guideline uses a standardised approach in estimating exposure that is considered to be sufficiently conservative to cover these differences.

4.3.1 Risk assessment for acute dermal and oral exposure scenarios and corresponding exposure levels after contact with the product

Pre-application phase

A. Accidental oral exposure by a child (bodyweight 12.5 kg) should be considered. This is possible if a child is able to gain access to the product. For example, if an opened pipette is left out on a surface whilst an adult is restraining a pet or if the product is easily accessible by a child (i.e. if the product is not in a child-resistant packaging). Oral exposure is considered to represent the worst case scenario 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. On the other hand, if child-resistant packaging is required in order to mitigate against oral exposure, this will also mitigate against dermal exposure.

Application phase

B. Accidental dermal and 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.

Post-application phase

C. Accidental oral exposure of a child is possible if any remaining unwanted product e.g., residual contents of a used pipette, is not disposed of immediately and safely and the child places this remaining product directly or indirectly (ie via hand to mouth) into the mouth. Oral exposure is considered to represent the worst case scenario as for the pre-application phase.

As a reasonable worst case, it is suggested that:

- Direct oral exposure to active substance will be to a maximum of 10% of a spot-on pipette, 10% of a collar or 10% of shampoo contents (for scenarios A and C above).
- Direct dermal exposure to active substance 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.
- Indirect oral exposure might occur following dermal exposure of product and subsequent hand-to-mouth transfer of this dermal loading to the mouth. However for the purposes of assessing the acute oral risk, it is suggested that as a reasonable worst case, oral exposure to active substance will be to a maximum of 1% of collar, spot-on pipette or shampoo contents (i.e. 10% dermal exposure and then 10% of this dermal loading transferred to the mouth (for scenario B above).

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 user is exposed (mg/kg)

AR = Amount administered (the amount applied to animal (mg) in collar, largest pipette or shampoo dose applied to animal).

FA = Fraction available for exposure by the relevant route.

Pre-application (direct oral exposure) for spot-on, collar or shampoo, FA = 0.1

During application (direct dermal exposure), FA = 0.1

During application and post-application (indirect oral exposure), FA = 0.01

BW = 12.5 kg child or 60 kg adult

4.3.2 Risk assessment for post application dermal and oral exposure scenarios and corresponding exposure levels 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 then 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 not considered necessary. As a result the following two scenarios have to be considered:

A. dermal exposure of children after contact with the treated animal

B. oral exposure of children due to hand to mouth contact

Both scenarios should be considered for acute exposure and chronic exposure to a treated animal. Acute 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. Chronic exposure reflects daily exposure to the average residue levels during the period of claimed efficacy but beyond the first 12 hours. For risk assessment of chronic exposure, the potential that the product may be used repeatedly would inform the decision on which TRV to use for the risk assessment.

4.3.2.1 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 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 to animals treated with a variety of liquid formulations, including spot-ons. A one-to-one relationship between dislodgeable residue on the animal (spread over its surface area) and the surface area in contact with the user is assumed.

The following equations should be used to calculate dermal exposure of a child in contact with a treated animal:

$$DE = \frac{\mathrm{TR} * SA_{contact}}{\mathrm{BW}}$$

Where:

DE = Dermal Exposure (mg/kg bw/day);

TR = Transferable Residue, which is the concentration of the active substance per surface area of the treated pet 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. The value corresponds to the 25th percentile of the Dutch population (considered to be representative for the European 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 may occur. Finally, the approach assumes that the product will evenly distribute over the whole body surface of an animal which is considered to underestimate the amount of substance present on those areas of the animal that are most often in contact with users (see SA_{animal} below);

BW = Body Weight of a child. The default body weight is set to 12.5 kg. This value is considered to represent a realistic worst case scenario, representing a child of 2 to <3 year old which is active in exploring their environment. The value corresponds to the 25th percentile of the Dutch population; 12.4 kg (RIVM report 090013003/2014) rounded up to 12.5 kg;

It is assumed that one animal is contacted. If more animals are present, it is expected that total contact activity remains the same.

$$TR = \frac{\mathrm{AR} * \mathrm{F}_{AR}}{SA_{animal}}$$

Where:

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

AR = Application Rate, the amount of active substance applied to the animal (mg). Generally the pipette size used to treat a medium sized animal (10 to 20 kg for a dog or <6 kg for a cat) 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 acute exposure and 0.02 (2%) for chronic exposure. These defaults are considered worst case based on review of company-submitted data. Refinements can be made by deriving actual data on the formulation by performing wipe tests (see 4.5);

SA_{animal} = Surface Area of the animal (cm^2). The surface area is considered to be 7000 cm^2 for a medium sized dog (10 to 20 kg) and 2500 cm^2 for a cat (small dog surface area is 3000 cm^2 ; large dog surface area is 11000 cm^2 and large cat surface area is 4000 cm^2). The surface area of animal that gives worst case active dose to surface area ratio is generally that of a medium dog (7000 cm^2) and medium cat (2500 cm^2). By using this surface area, it is assumed that the active substance will evenly distribute over the animals whole body surface. It is noted however, 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.

4.3.2.2 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 to 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% of the total dermal exposure, simply based on surface area (270/1790 cm^2).

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;

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

BW = Body weight of a child. Default: 12.5 kg.

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 expected that hands are loaded every time hand-into-mouth contact occurs.

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

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).

4.3.2.3 Combined exposure by different routes.

If more than one route of exposure is involved in a single situation (i.e. within one scenario), 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 pet when the active substance is present on a collar being worn or is present on the animal's skin or fur. This measure can be derived from a suitable product specific exposure study (pet wipe test). However, while the methodology of the wipe test will have a large influence on the results obtained, even for identical products, at the time of writing there does not appear to be any 'standard' wipe test protocol. It is not the intention of this guideline to state a recommended protocol for a wipe test but a number of recommendations are made in order to reduce the variability inherent in methods that might be employed in wipe studies, which are then used to assess the risks to those in contact with treated animals. For products intended for use in both dogs and cats, a 'wipe test' study is only required in dogs.

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

Test Substance

This should be adequately described, tested and stored. The product under consideration should be used.

Experimental design

This should be adequately described including the animal selection criteria. Animals should be in good general health and not have been exposed to the test substance for 90 days prior to inclusion in the study. Animals should not be bathed after application of test material (unless required by product information) and arrangements should ensure no cross contamination of residues occurs between animals.

The number of animals (at least 8), breed, approximate age, sex, hair length and weight should be documented. The animals should be housed individually.

Application of product

Animals should be treated on day 0 in accordance with the product information.

For spot-on products, the pipette that gives the highest active substance to surface area ratio should be used. The animals should have weights in the lower 10% weight range specified in the product information.

Sample Collection and Handling

Careful consideration needs to be given to sampling time points, as these data may lead to 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 acute exposure scenario and time points beyond 12 hours would cover the chronic exposure scenario. However, for certain product types (e.g., flea collars) the highest exposure may occur later. An acute exposure estimation should be undertaken using the single highest value observed at any time point measured.

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 acute and chronic exposure scenarios.

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 pet. 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 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

Analyses of residues (parent and/or relevant degradation products) must be adequately validated. The amount of residue on the whole gloves should be determined. If samples were stored prior to analysis, storage stability under the conditions should be demonstrated.

Presentation of results

The amounts (mg) of active substance applied to each animal should be recorded as well as the amount of residue dislodged (collected on the gloves) at each time point as well as animal weight, breed and hair type.

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, maximum and minimum values for each animal.

For acute exposure scenarios, the single highest value found should be used. The resulting "high-end" exposure will account for the potentially greater health impact of experimental uncertainties in the acute phase.

For chronic exposure scenarios, the mean time weighted average (TWA) should be used. It is recommended to calculate a time weighted average for eachindividual animal from the results of the wipe test and then take the mean of these values. 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). However, where data show a MOE <100 in the acute phase, thereby requiring risk mitigation measures limiting exposure in the acute phase (i.e. 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. 4 or 12 hours), since the risk mitigation measure(s) should reduce the likelihood of exposure during the acute phase.

4.5. Margins 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-quantitative risks a qualitative risk characterisation should be conducted.

As detailed in the Guideline on user safety for pharmaceutical veterinary medicinal products, where the exposure estimate is less than the NOAEL, the magnitude by which the NOAEL 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;
- 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.

These parameters are used to establish an uncertainty factor, which the MOE will then be compared to. It is generally recognised that the default uncertainty factor (UF) is 100 i.e. a MOE of 100 or higher would be considered acceptable. This value of 100 is the product of two factors of 10, one for inter-species extrapolation and the other for intra-species (inter-individual) variability. The interspecies uncertainty factor converts the animal derived TRV into a TRV for an average healthy individual. The interindividual factor takes into account susceptible human subpopulations.

For some TRVs (e.g. ADI) the level of uncertainty has already been taken into account in its calculation. The uncertainty factor used in establishing these TRVs can be compared with the MOE, where the same type of exposure is being assessed. For example, if the estimated oral exposure is less than the ADI, the risk for the user is considered to be acceptable.

Where reliable data are available there may be a case for accepting an uncertainty factor other than 100, for example, if there is a case for accepting that the standard values for inter- and intraspecies variation do not apply. Similarly, the nature of the studies used to determine the TRV will also influence the uncertainty factor. For example, if the TRV is based on a NOAEL derived from a human study then a MOE of 10 could be accepted. Or if the TRV is a LOAEL then an additional factor of 2 - 10 would be required.

Other factors that need to be considered are the severity of the effect likely to arise from exposure to the product. The magnitude of the uncertainty factor can be increased with effects such as non-genotoxic carcinogenicity, neurotoxicity or teratogenicity. Severe effects such as these may require an additional factor of between 2 and 10. It should be noted that in order to compensate for deficiencies in toxicity data, additional factors may be required, increasing the acceptable MOE above the default factor of 100.

Correction factors relating to extrapolation between routes of exposure and the effect of formulation on deriving a dermal TRV are considered earlier in this document, in the establishing TRVs section.

With multiple factors influencing the magnitude of the acceptable MOE, adequate justification for each parameter should be provided. The acceptability of the MOE and thus risk to the user will require expert judgement. In the case of a potential risk to the user, risk management options should be proposed and evaluated

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 companion animal veterinary medicinal products, the examples are not intended to be exhaustive. For further guidance on how to approach risk communication see the Guideline on user safety for pharmaceutical veterinary medicinal products (section 5.3.3).

In all cases the concerned risk should first be 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 situations where exposure can occur include storing or accessing the product or preparing it for use and this will depend on container design. 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 need for child-proof packaging in accordance with ISO 14375. Examples of mitigation measures that can reduce the risk include:

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

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 the risk include:

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

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

Post-application

The post-application phase consists of both acute and chronic oral and dermal exposure. The handling of animals following treatment or contact with a medicinal collar poses potential exposure risks. Consideration should also be given to children accessing 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 proposed. 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 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, e.g. sleeping with a pet wearing a collar.

Examples of impracticable measures would be the washing of hands each time after stroking or handling pets, 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 12-hours (i.e. overnight) is not 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 the use where these vulnerable users are present needs to be considered.

In all cases the applicant should demonstrate that the proposed risk mitigation measures are feasible and reduce exposure to an acceptable level.

The communication of user warnings and risk mitigation measures (RMMs) is important. For many topical products, repeat treatments are required and separate package leaflets can easily get lost. For such products, it is necessary that user safety information is available to the user at each time of use. Therefore, if the product is for general sale to the public, without professional point of sale advice, then the full safety information should be additionally permanently attached to the packaging, preferably printed on the immediate container or outer package with instruction to keep the product in the original packaging until ready to use (though a permanently attached concertina leaflet would be acceptable).

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, ARfD etc.).

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.

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 touching the skin or eyes. Exposure may be short-term (acute exposure), of intermediate duration, or long-term (chronic exposure).

Acute exposure: Contact with a substance that occurs once or for only a short time. In the context of this guideline, the acute exposure covers from the time of treatment until the timepoint at which the highest exposure occurs. This is likely to be up to 12 hours but could be longer.

Chronic exposure: Contact with a substance that occurs over a longer period. In the context of this guideline, the chronic exposure covers a period of time beyond 12 hours.

Acute toxicity study The test substance is administered once daily in graduated doses to several groups of experimental animals for a period of no more than 7 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.

Time weighted average (TWA): Exposure concentration per individual animal averaged over the time until claimed length of efficacy with setting measurements below LOQ to LOQ.

If t1, t2, …, tn are the time points of the stroke tests, and c1, c2, …, cn the corresponding concentrations, 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

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 dogs contains 134 mg active substance while the largest pipette (5 ml) contains 700 mg of active substance. The default values for dislodgeable fraction when 'wipe test' results are not available would be 15.0% for considering acute exposure scenario and 2.0% for the chronic 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

Published data indicate oral absorption of the active substance to be 80% and dermal absorption to be 1% (using an aqueous solution). *In vitro* dermal absorption study using the final 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 correcting for differences in absorption between routes and species, i.e.

$$\text{Corrected dermal NO(A)EL} = \text{Oral NO(A)EL} \times \frac{ABS_{oral-}}{ABS_{derm}}$$

References submitted indicated the following TRVs for the active substance:

- Acute dermal: No relevant final formulation dermal study was available for the substance, the acute dermal TRV is calculated from the oral TRV corrected for oral/dermal absorption. The ABS_{derm} of 2% as derived for the formulation has to be used.

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

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

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

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

Estimating exposure

Pre-application phase

Accidental oral exposure by a child if an opened pipette is left out on a surface whilst an adult is restraining a pet or if the product is easily 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

Accidental 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

Post-application phase - Acute phase

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 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**
$DE = \frac{\mathrm{TR} * SA_{contact}}{\mathrm{BW}}$	
TR = 0.00096 mg/cm^2 $SA_{contact}$ = the surface area of a child in contact with the animal per day = 1790 cm^2 BW = Body Weight of a child = 12.5 kg	TR = 0.0029 mg/cm^2 $SA_{contact}$ = 1790 cm^2 BW = 12.5 kg

$DE = \frac{0.00096 * 1790}{12.5}$	$DE = \frac{0.0029 * 1790}{12.5}$
DE = 0.137 mg/kg	**DE = 0.411 mg/kg**

673

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

Using 'wipe test' results	**Using default values**
$HR = \frac{\mathrm{DE} * F_h}{SA_h}$	
HR = Hand Residue loading (mg/cm^2) DE = Dermal exposure not adjusted for bw = (0.00096*1790) = 1.7133 mg F_h = Fraction of total dermal exposure expected to be on the 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)
$HR = \frac{1.7133 * 0.15}{270}$	$HR = \frac{5.140 * 0.15}{270}$
HR = 0.000952mg/cm^2	**HR = 0.00286 mg/cm^2**
$OE = \frac{HR * SA_m * HTM * HIM}{BW}$	
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 (def.) HTM = Hand-to-Mouth contacts per day = 20 (default) HIM = Hand-into-Mouth contact = 0.4 (def.) BW = Body Weight of a child = 12.5 kg	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
$OE = \frac{0.000952 * 7 * 20 * 0.4}{12.5}$	$OE = \frac{0.00286 * 7 * 20 * 0.4}{12.5}$
OE = 0.00426 mg/kg	**OE = 0.0128 mg/kg**

675

676 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

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

678

679 **Post-application phase - Chronic phase**

680 Dermal exposure of children after contact with the animal – Chronic phase (> 12 hours)

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 = 0.005 SA_{animal} = Surface Area of the animal = 7000 cm^2	AR = 134 mg F_{AR} = 0.02 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**
$DE = \frac{\mathrm{TR} * SA_{contact}}{\mathrm{BW}}$	
TR = 0.000096 mg/cm^2 $SA_{contact}$ = the surface area of a child in contact with the animal per day = 1790 cm^2 BW = Body Weight of a child = 12.5 kg	TR = 0.00038 mg/cm^2 $SA_{contact}$ = 1790 cm^2 BW = 12.5 kg
$DE = \frac{0.000096 * 1790}{12.5}$	$DE = \frac{0.00038 * 1790}{12.5}$
DE = 0.0137 mg/kg	**DE = 0.0548 mg/kg**

681

682 Oral exposure of children due to hand-to-mouth contact – Chronic phase

Using 'wipe test' results	**Using default values**
$HR = \frac{\mathrm{DE} * F_h}{SA_h}$	
HR = Hand Residue loading (mg/cm^2) DE = Dermal exposure not adjusted for bw = (0.000096*1790) = 0.1713 mg F_h = Fraction of total dermal exposure expected to be on the hands = 0.15 (default) SA_h: Surface Area of both hands of a child = 270	HR = Hand Residue loading (mg/cm^2) DE = (0.00038*1790) = 0.6853 mg F_h = 0.15 (default) SA_h = 270 cm^2 (default)

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/cm² SA_m =Surface Area mouthed = 7 cm² (def.) HTM = Hand-to-Mouth contacts per day = 20 (default) HIM = Hand-into-Mouth contact = 0.4 (def.) BW = Body Weight of a child = 12.5 kg	OE = Oral exposure due to hand-to-mouth contact (mg/kg bw/day) HR = 0.000381 mg/cm² SA_m = 7 cm² (default) HTM = 20 (default) HIM = 0.4 (default) BW = 12.5 kg
$OE = \frac{0.000095 * 7 * 20 * 0.4}{12.5}$	$OE = \frac{0.000381 * 7 * 20 * 0.4}{12.5}$
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 Foral of 80% and Fdermal 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 surface area of 7 x 20 x 0.4= 56 cm2 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 - Acute phase

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 NOAEL: oral NOAEL of 0.9 mg/kg bw/day corrected for oral absorption (80%)

**Internal exposure

Post-application phase - Chronic phase

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 NOAEL: oral NOAEL of 0.33 mg/kg bw/day corrected 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 NOAEL was based on a repeated dose toxicity study (with no acute effects) whereas accidental exposure 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 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 chronic phase 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 formulation.