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Guideline on user safety of topically administered veterinary medicinal products

Draft

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This guideline supplements the existing 'Guideline on user safety for pharmaceutical veterinary medicinal products' (EMEA/CVMP/543/03-Rev.2).

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
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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 veterinary medicinal products (VMPs) has been developed to provide specific guidance and advice on how user risk assessments should be conducted for such products. The guideline initially came into effect in 2018 and has been revised in 2025. This guideline should be used in conjunction with the 'Guideline on user safety for pharmaceutical veterinary medicinal products' (EMA/CVMP/SWP/42923/2005-Rev.2). Approaches common to all pharmaceutical veterinary medicinal products, if initially described in this guideline, have been transferred to the 'Guideline on user safety for pharmaceutical veterinary medicinal products' during the revision. This guideline has been further revised to reference current legislation (EU)2019/6 and its Annex II. Additional guidance has also been included on appropriate toxicological reference values to be used in the risk characterisation including the use of dermal absorption factors. Moreover, more guidance is provided on the assessment relevant for pregnant women, Situations for which wipe tests are required are further reviewed including reconsidering the appropriate defaults. In the end the adequacy of the risk mitigation measures has been reconsidered.

1. Introduction (background)

Marketing authorisations for veterinary medicinal products (VMPs) in the European Union are granted in accordance with Regulation (EU) 2019/6. This legislation requires that applications for VMPs contain safety documentation. Annex II of Regulation (EU) 2019/6 states that "*the safety documentation shall be adequate for assessment of (b) 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*". Furthermore, it provides that, with regard to user safety "*This section shall include an assessment of the effects found in Part II.3A to II.3A4* (or Part IIIa.3A to IIIa.3A4) *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.*"

The legislation does not provide specific guidance on data requirements and assessment methods to be used to identify the risks, or on 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 VMPs including topically administered VMPs. This complementary guideline presents additional guidance and advice on how risk to users can be assessed for topically administered VMPs.

The increase in the number of applications for topically administered VMPs in recent years has highlighted the need for a coherent and harmonised approach to the assessment of exposure to such products.

Exposure to topically administered VMPs may occur via direct exposure to the product (accidental ingestion or accidental spillage including hand-to-mouth contact (HTM) and hand-to-eye contact (HTE)), or through contact with treated animals by pet owners, other household members or any other person, including children following administration of a topical VMP. 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 estimates 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 and/or fur is to be 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-)administration phase, may also be applicable to VMPs for food producing animals or other topical VMPs that do not spread over the animal's body, and for which user risk assessments are also required.

This guideline can in principle be used for all types of authorisation procedures for VMPs including post-authorisation changes, generic or hybrid VMPs where relevant. General information with respect to the assessment of user safety, as well as specific remarks on post-authorisation changes, and generic and hybrid VMPs can be found in the CVMP general 'Guideline on user safety for pharmaceutical veterinary medicinal products'. Specifically, for topically administered VMPs it is feasible that differences (qualitative and quantitative) in excipients may result in differences in exposure of the user (e.g. pet owner), e.g. when the VMP is spilled or when the treated animal is handled (e.g. stroked), due to potential changes in dermal absorption and/or the amount of VMP removed from the animal's fur ~~when stroked~~. In such cases the outcome of the risk assessment and subsequent risk mitigation measures may be different from those of the reference product.

In accordance with the CVMP 'Guideline on user safety for pharmaceutical veterinary medicinal products', occupational safety during the manufacture of veterinary medicinal products is not addressed.

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

3. Legal basis

Requirements for safety testing for a marketing authorisation application are laid down in Regulation (EU) 2019/6 of the European Parliament and of the Council.

This guideline outlines how the requirements of Annex II to Regulation (EU) 2019/6, as set out in Part 3 of Section II (for VMPs other than biological VMPs) and Section IIIa (for biological VMPs other than immunological VMPs), "User safety" are to be applied: "This (the user safety) section shall include an assessment of the effects found in Part II.3A to II.3A4 (or Part IIIa.3A to IIIa.3A4) 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." Moreover, "User safety shall be addressed in accordance with Committee for Medicinal Products for Veterinary Use (CVMP) guidelines."

All animal experiments should be conducted taking into account section I.1.7 of Annex II of Regulation (EU) 2019/6 and the 3Rs principles (replacement, reduction and refinement), notwithstanding the place of conduct of the experiments. Alternatives to *in vivo* test methods should be employed whenever possible.

4. Principles of the assessment

In the development of this 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.

The main aspects involved in the user risk assessment for topically administered VMPs are similar to those outlined in the original CVMP 'Guideline on user safety for pharmaceutical veterinary medicinal

products'. A risk analysis presented for the VMP, covering those handling and administering it or those exposed via contact with a treated animal, should be provided, incorporating the following aspects:

- hazard identification and characterisation. An appraisal of the inherent toxicity of the VMP and the identification of the most relevant toxicological reference values (TRVs);
- exposure assessment. An appraisal of how and when the user may be exposed to the VMP – identification of user groups, relevant exposure scenarios and estimation of the user exposure for each scenario;
- risk characterisation. The assessment of the level of risk by establishing margins of exposure (MOEs) through comparison of the exposure levels with the toxicological reference values, and the assessment of local effects;
- risk management and communication. The proposal of appropriate and practical risk mitigation measures, where relevant.

5. User risk assessment

5.1. Hazard identification and characterisation

The first step of the user safety assessment corresponds to the hazard identification and characterisation of each active substance(s) and relevant 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 presented in the safety part of a marketing authorisation (MA) dossier (Part 3A Safety Documentation). The overall assessment of the data allows a conclusion to be drawn on whether available data are sufficient for use in the risk assessment. The potential need for additional studies depends on any identified data gaps. New studies should only be performed where necessary to generate an appropriate TRV for a particular route of exposure, if an identified risk cannot be adequately mitigated using existing data and further refinement is required. These new studies may be *in vivo* or based on scientifically valid alternative methods, however, a stepwise approach should be employed, with animal testing used only where absolutely necessary. General information with respect to establishing toxicological reference values can be found in the CVMP general 'Guideline on user safety for pharmaceutical veterinary medicinal products'.

For topically administered VMPs, dermal exposure of the user is an important exposure route. Although dermal studies with the formulation would be ideal for the risk characterisation of dermal exposure, in general the available data primarily comprise oral studies or, occasionally, dermal studies with the active substance. In those situations, existing TRVs would need to be corrected for differences in bioavailability between different exposure routes or between different formulations. This is addressed in section 5.1.3. TRVs are established for all relevant toxicological endpoints (i.e. most sensitive critical effect), and are specific to a substance, duration of exposure (acute, sub-chronic or chronic) and route of exposure (oral, dermal, inhalation; the latter in the case of topical sprays, aerosols and powders). Even if the TRV is based on the most sensitive critical effect, other effects may also be taken into consideration (e.g. reproductive or developmental effects) in order to focus the user risk assessment on specific user groups. For instance, any possible adverse effect on the pregnant female and the development of the embryo should be assessed using an appropriate TRV, if developmental effects have been identified during the hazard identification and if significant user exposure may be expected. In the case of topically administered VMPs, it is expected that significant (external) user exposure may occur due to the formulation of these products, for example when handling the product or touching a treated animal. For the evaluation of user safety, data on developmental toxicity are therefore required

for such VMPs. Adverse effects on male/female fertility may also need to be addressed for certain substances. The establishment of TRVs should be related to the different exposure scenarios, and the choice of the TRV should be justified. In the context of a risk assessment, the TRVs should be compared to the exposure levels of the substance(s) of concern that correspond to similar durations and routes of exposure. 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 should be considered, using route-to-route extrapolation with appropriate adjustments to address differences in bioavailability. For topically administered VMPs, the following exposure scenarios and appropriate TRVs for both short-term and long-term exposure are considered relevant. Again, it is emphasized that the approach described in section 5.1.3, implementing the 3Rs principles, should be taken into account when selecting the appropriate TRV:

A.	Short-term dermal	→	Contact during administration or other direct contact with the VMP Contact with the treated animal in the acute phase	TRV based on acute effects in toxicity studies. In most cases, only oral toxicity studies are available. In that case, generally no new dermal toxicity studies are required. In the absence of dermal toxicity studies, the TRV will be based on acute effects in oral toxicity studies, with or without adjustment for differences in dermal-to-oral bioavailability (see section 5.1.3.).
B.	Short-term oral	→	Accidental ingestion of the VMP Hand-to-mouth exposure following contact with the treated animal in the acute phase	TRV based on acute effects in oral toxicity studies.
C.	Long-term dermal	→	Repeated contact with treated animal	TRV based on sub-chronic or chronic toxicity studies. In most cases, only oral toxicity studies are available. In that case, generally no new dermal toxicity studies are required. In the absence of dermal toxicity studies, the TRV will be based on effects in oral toxicity studies, with or without adjustment for differences in dermal-to-oral bioavailability (see section 5.1.3.).
D.	Long-term oral	→	Repeated hand to mouth exposure after contact with treated animal	TRV based on sub-chronic or chronic oral toxicity study (depending on the longest duration of user exposure)

The duration of the study from which the TRV is derived should preferably reflect the duration of user exposure. The risk assessment of short-term exposure should be based on acute TRVs or, if not available, on sub-acute or sub-chronic TRVs, the latter generally representing a worst-case approach. In addition, the TRV may be based on information from long-term studies if no other data are available, or if acute effects have been observed on the first day(s) of dosing in these studies. For the risk assessment of long-term exposure, the use of a sub-chronic or chronic TRV can be considered acceptable, depending on the longest duration of user exposure, including exposure due to repeated treatment of the target animal.

5.1.1. Factors that influence dermal absorption

Topically administered VMPs may be formulated in such a way that dermal absorption of the active substances and other excipients is affected, e.g. by the use of penetration enhancers (mostly organic solvents). For this reason, it is important to address the impact of the formulation on the risk assessment of VMPs. VMPs may fall into different formulation categories, which depend on the phase in

which the active substance is incorporated, dissolved, emulsified or suspended (see table 1). These categories are, i) solid VMPs that might be for example tablets, collars or powders, ii) water-based VMPs that might be for example shampoos, or iii) organic solvent-based VMPs that might be for example spot-ons. Solutions, suspensions and sprays can be water-based as well as organic solvent-based. Solid and water-based formulations are not expected to contain high amounts of penetration enhancers, while organic-solvent based VMPs may enhance penetration of active substances. Therefore, it can be assumed that solid and water-based formulations will have a significantly lower dermal absorption potential than organic-solvent based VMPs.

5.1.2. Estimation of dermal absorption

Although dermal studies with the formulation would be appropriate for the risk characterisation of dermal exposure, in general the available data primarily comprise oral studies or dermal studies with the active substance. In those situations, TRVs would need to be corrected for differences in bioavailability between different exposure routes or between different formulations. In such cases, information on dermal absorption is required.

Data on dermal absorption should preferably have been generated according to internationally agreed guidelines, e.g. according to OECD Test Guideline No. 428 or 427. In line with 3Rs principles new data should be generated using the *in vitro* methods.

Recommendations for performing and interpreting dermal absorption studies are included in the "Guidance on dermal absorption" (EFSA, 2017) and in the OECD Series on Testing and Assessment No. 156 "Guidance notes on dermal absorption". While the above guidance documents were originally developed to advise for setting of dermal absorption values to be used in the risk assessment of active substances of Plant Protection Products (PPPs) they are also considered applicable for active substances of VMPs when assessing user safety.

If no study derived data on dermal absorption are available, default values can be used as a surrogate. The "Guidance on dermal absorption" (EFSA, 2017) describes default values that were originally developed based on data for active substances in PPPs. However, these default values are also considered to be applicable to active substances in VMPs (Table 1).

From this table, it can be derived that dermal absorption is significantly impacted by the concentration status and formulation category of a product. In this context, the "Guidance on dermal absorption" (EFSA, 2017) defines a "concentrate" to contain > 5% active substance and a "dilution" to contain ≤ 5% active substance, respectively. Furthermore, formulation categories depend on the phase in which the active substance is incorporated, dissolved or emulsified/suspended in. The "Guidance on dermal absorption" (EFSA, 2017) differentiates these formulation categories as solid, water-based/dispersed or organic solvent- or other solvent-based.

Table 1: **Default values to be used in the absence of dermal absorption data**

Default values derived from "Guidance on dermal absorption" (EFSA, 2017). Formulation type depends on the phase in which the active substance is incorporated, dissolved or emulsified/suspended. The concentration of active substance is either a 'concentrate' (> 5%) or a 'dilution' (≤ 5%).

Formulation category	Concentration of active substance in final VMP formulation	Default value for dermal absorption
Organic solvent-based or other*	> 5% active substance	25%
	≤ 5% active substance	70%
Water-based/dispersed or solid	> 5% active substance	10%
	≤ 5% active substance	50%

*Formulation types that do not fit into the categories organic solvent-based, water-based/dispersed or solid

5.1.3. Approach for derivation of dermal TRVs

The major exposure route for topically administered VMPs is dermal exposure. Therefore, risk characterisation requires the derivation of dermal TRVs. From a scientific point of view, dermal toxicity studies using the formulation would provide the most relevant data for user risk assessment. However, in line with the 3Rs principles, the conduct of new animal studies should be avoided wherever possible. To this end, animal data already available (existing data) shall be submitted and employed for risk assessment.

Such existing data mostly comprises studies for the oral route of exposure, in which the active substance is administered, or dermal studies in which the active substance, rather than the formulation, is administered. Consequently, route-to-route extrapolation, and where relevant extrapolation between different formulations, will need to be applied in order to derive dermal TRVs from such studies.

In order to provide guidance on how existing data can be employed for the derivation of dermal TRVs, approaches for both short-term and long-term exposure are presented in this section.

Depending on the characteristics of available toxicity studies and on supplementary (existing) data the most suitable approach should be selected for derivation of dermal TRVs.

Importantly, new *in vivo* dermal toxicity studies should only be conducted where additional information is considered necessary, i.e., where quantitative user risk assessment based on existing data indicates an unacceptable risk to the user that cannot be mitigated, or where a data gap needs to be addressed as no data are available or non-animal methods would not be sufficient.

When relevant dermal TRVs may also need to be derived for excipients (e.g. an excipient which is known to be harmful).

Short-term exposure

The following approaches can be employed for the derivation of dermal TRVs for **short-term exposure**. They are also applicable for long-term exposure if penetration enhancing excipients remain present after administration, i.e. if it cannot be demonstrated that penetration enhancing excipients have evaporated from the site of administration. For example, evaporation can be demonstrated by a high volatility of excipients (vapour pressure ≥ 10^{-2} Pa at 20 °C is considered to demonstrate high volatility (ECHA, 2013; EFSA, 2022; European Commission, 2003)). Depending on the available data the approaches are:

Dermal toxicity studies

i. a NOAEL/BMDL derived from a relevant dermal toxicity study using the VMP formulation.

ii. a NOAEL/BMDL derived from a relevant dermal toxicity study using the active substance, together with dermal absorption studies comparing the preparation of the active substance used in the dermal toxicity study with that in the VMP formulation.

The dermal NOAEL/BMDL should be adjusted for differences in dermal absorption between the active substance used in the dermal toxicity study and the active substance in the VMP formulation (the latter is expected to have higher dermal absorption if penetration enhancers are present).

Oral toxicity studies employing route-to-route extrapolation

Note that route-to-route extrapolation is only accepted when toxicity following oral administration is related to systemic exposure rather than to effects at the site(s) of contact. Furthermore, detoxification in the gastrointestinal tract (e.g. due to acidic conditions, or first-pass metabolism), which might result in an underestimation of potential toxicity following dermal exposure compared with oral exposure, needs to be considered.

iii. a NOAEL/BMDL derived from a relevant oral toxicity study using the active substance, together with data on dermal absorption of the active substance in the VMP formulation and on oral bioavailability of the active substance.

The oral NOAEL/BMDL should be adjusted for differences in oral bioavailability of the active substance and dermal absorption of the active substance in the VMP formulation.

If no data on dermal absorption of the active substance in the VMP formulation are available, default dermal absorption values can be used (see table 1).

iv. a NOAEL/BMDL derived from a relevant oral toxicity study using the active substance.

In exceptional cases where no information on oral bioavailability of the active substance is available, the oral NOAEL/BMDL can be used without correction for bioavailability if it can reasonably be assumed that dermal absorption of the active substance is lower than (or similar to) its oral bioavailability. This would normally be the case, for example, if the final formulation of the VMP is water-based/dispersed or a solid formulation (powder).

The use of this approach is only accepted provided that there is no significant detoxification of the active substance, i.e. due to acidic conditions in the gastrointestinal tract, or first-pass metabolism. These conditions could result in a low oral systemic bioavailability (and a 'high' TRV) and subsequently in an underestimation of the dermal TRV if this oral NOAEL/BMDL would be used as a surrogate.

v. a NOAEL/BMDL derived from a relevant oral toxicity study using the active substance, together with an additional uncertainty factor.

Under section iv., conditions are described that preclude the direct use of an oral NOAEL/BMDL to derive a dermal TRV. This normally applies, for example, to diluted organic solvent-based formulations (≤5% active substance) where no oral bioavailability data are available for the active substance. It might also apply in cases where there is significant detoxification of the active substance, for example, due to acidic conditions in the gastrointestinal tract, or significant first-pass metabolism, which might result in an underestimation of the dermal TRV.

In these cases, it cannot be assumed that dermal bioavailability is lower than (or similar to) oral bioavailability.

However, the NOAEL/BMDL of the relevant oral toxicity study may still be employed in these cases to derive a dermal TRV, by applying an additional uncertainty factor of 2-10 in order to address potential route-dependent differences in ADME of the active substance. The choice of the uncertainty factor should be justified.

Long-term exposure

The following approaches can be employed for **long-term exposure if** it can be justified that **excipients have evaporated** from the site of administration, for example, by demonstrating high volatility of the excipients (vapour pressure ≥ 10^{-2} Pa at 20 °C is considered indicative of high volatility (ECHA, 2013; EFSA, 2022; European Commission, 2003)). Depending on the available data, the approaches are:

Dermal toxicity studies

i. a NOAEL/BMDL derived from a relevant dermal toxicity study using the active substance (or the VMP formulation).

Excipients are not expected to influence dermal bioavailability for the user in this scenario, provided it is demonstrated that they have evaporated. Therefore, a dermal toxicity study with the active substance would be sufficient.

Oral toxicity studies employing route-to-route extrapolation

Note that the conditions for the acceptability of route-to-route extrapolation from oral to dermal are the same for long-term and short-term exposure (see above).

ii. a NOAEL/BMDL derived from a relevant oral toxicity study using the active substance, together with data on dermal absorption of the active substance and on oral bioavailability of the active substance.

To derive the dermal TRV, the oral NOAEL/BMDL should be adjusted for differences in oral bioavailability of the active substance and dermal absorption of the active substance.

Dermal absorption values may be derived from a dermal absorption study with the active substance or the VMP formulation. If no data on dermal absorption are available, default dermal absorption values can be used (see table 1).

iii. a NOAEL/BMDL derived from a relevant oral toxicity study using the active substance.

If no data on oral bioavailability of the active substance are available, the oral NOAEL/BMDL can be used without correction for oral and dermal bioavailability if it can be assumed that, for the active substance, dermal bioavailability is lower than (or similar to) oral bioavailability. This would be the case if it is assumed that penetration enhancers are not present or have evaporated.

In general, the use of this approach is only accepted provided that there is no significant detoxification of the active substance, for example due to acidic conditions in the gastrointestinal tract or significant first-pass metabolism. This could result in low oral bioavailability (and a 'high' TRV) and subsequently in an underestimation of the dermal TRV if this oral NOAEL/BMDL would be used as a surrogate.

iv. a NOAEL/BMDL derived from a relevant oral toxicity study using the active substance, together with an additional uncertainty factor.

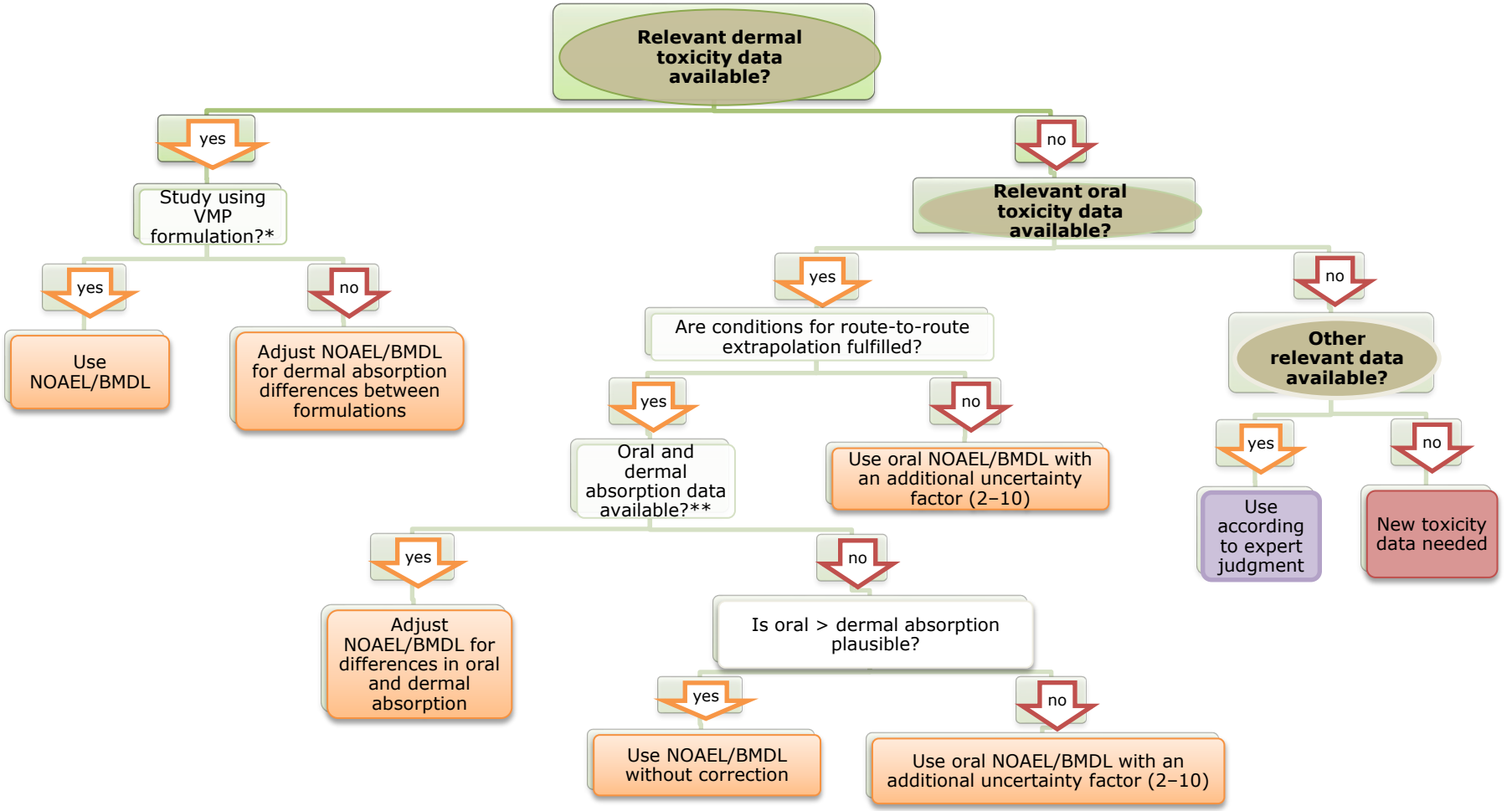
If there is significant detoxification of the active substance, for example due to acidic conditions in the gastrointestinal tract or significant first-pass metabolism, resulting in low oral bioavailability (and a 'high' TRV), the oral NOAEL/BMDL cannot be used directly and an additional uncertainty factor of 2-10

should be applied in order to address potential route-dependent differences in ADME of the active substance. The choice of the uncertainty factor should be justified.

If neither relevant dermal nor oral toxicity studies are available, other relevant data might exist that could be used to derive a dermal TRV, for example, studies with other routes of exposure. Only where no adequate data are available to perform a quantitative risk characterisation should new toxicity data be generated.

The decision tree below (Fig. 1) provides guidance on how to use existing data for derivation of dermal TRVs.

Fig. 1: Decision tree for use of data for derivation of dermal TRVs



*For long-term exposure, if evaporation of potentially penetration-enhancing excipients can be demonstrated (e.g., vapour pressure ≥ 10^{-2} Pa at 20 °C), the NOAEL/BMDL of dermal toxicity studies can be directly employed for TRV derivation regardless of whether studies were conducted using the VMP formulation, the active substance only or other formulations.

** If no data on dermal absorption of the active substance in the VMP formulation are available, default dermal absorption values can be used.

5.2. Exposure assessment

5.2.1. 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 VMP.

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

Phases	User	Details	Routes of exposure	Component of exposure	Duration/frequency of exposure
Contact with the VMP (further detailed in paragraph 5.2.2)					
Pre-administration phase	Child	Accidental access to VMP when stored	Oral and dermal	Whole formulation	Accidental Once
Administration phase	Adult including pregnant women	Opening / administration of VMP	dermal including HTM	Whole formulation	Once or short-term
	Child	Not relevant since the product is to be applied by an adult.			
Post-administration phase	Child	Accidental access to residual product	Oral and dermal	Whole formulation	Accidental Once
		Exposure during the pre-administration phase for children is considered to be worst-case. Additional calculation for post-administration exposure is therefore not necessary.			
Contact with the treated animal (further detailed in paragraph 5.2.3)					
Post-administration phase (short-term)	Child	Handling/stroking of the treated animal	dermal including HTM	Whole formulation	Once or short-term
Post-administration phase (long-term)	Child	Handling/stroking of the treated animal	dermal including HTM	Residues	Long-term Repeated
Post-administration phase (short-	Adult including	Exposure assessment during the post-administration phase for children is considered to be worst-case due to their lower bodyweight. Additional calculations for adults are therefore not necessary, except			

term and long-term)	pregnant women	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 are 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, for example, sprays, aerosols and powders, exposure by inhalation may be relevant and needs to be taken into consideration. No guidance is provided in this guideline on the assessment of risks via the inhalation route of exposure, which should be addressed on a case-by-case basis.

5.2.2. Exposure assessment for short-term dermal and oral exposure scenarios after direct contact with the VMP

The following paragraphs focus on the most sensitive population, i.e. children, because of their lower body weight, 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, as identified in the hazard assessment. Then, for example, the risk for pregnant women and women of childbearing age, or effects on male/female fertility should also be assessed. For the administration phase only, an adult is considered to administer the VMP to the animal. 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 obviate the need to routinely assume that more than one animal will be treated.

The exposure assessment focusses on active substances, though may also be relevant for excipients (e.g. an excipient which is known to be harmful).

5.2.2.1. Phases:

A. Pre-administration phase

Accidental oral exposure due to unintended access to the VMP by a child (body weight 12.5 kg) should be considered. This might occur if the VMP is left out on a surface whilst an adult is restraining an animal or if the product is accessible to a child (i.e. if the product is not properly stored or the packaging is not child-resistant). Collars are usually provided in different sizes to fit animals of different sizes. 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 unlikely. Oral exposure is considered to represent the worst-case scenario for children during pre-administration 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. Likewise, if child-resistant packaging is used in order to mitigate oral exposure, this will also mitigate against dermal exposure during the pre-administration phase.

The following assumptions are made as a conservative approach:

- For child exposure, direct oral exposure to the product (i.e. the final product formulation) is assumed to 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 (assumed to correspond to

a maximum swallow volume). Where appropriately justified, refinements can be made to these default values.

B. Administration phase

Accidental dermal and indirect oral exposure of adults, including pregnant women (bodyweight 60 kg), is possible if the product comes into contact with the user's skin during administration, including opening the product, mixing/diluting, loading administration devices and administering it to the animal, and is subsequently transferred to the mouth. It is considered that the VMP will be administered by an adult only.

1) Direct dermal exposure to the final product formulation during administration is assumed to be 10% of the administered dose as a default. A refinement of this value may be accepted where justified by the type of product and packaging. Additionally, actual measurements on transferability of the substance of concern during product handling can be used for refinement.

2) Indirect oral exposure might occur following dermal exposure to the product and subsequent hand-to-mouth transfer of this dermal loading to the mouth. For the purposes of assessing acute oral risk, it is suggested that, as a reasonable worst-case assumption, oral exposure to the final product formulation will be to a maximum of 10% of the dermal loading transferred to the mouth, i.e. 1% of the administered dose.

C. Post-administration phase

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

5.2.2.2. Calculations:

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

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

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

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

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

Pre-administration (direct oral exposure) for spot-on, collar or shampoo, FA = 0.1 (taking into account the default maximum volume of 5 ml for liquids and a length of 2 cm for collars).

During administration (direct dermal exposure), FA = 0.1

During administration (indirect oral exposure), FA = 0.01

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

BW = Body weight
For children: 12.5 kg (default value considered to represent a child aged of 2 to <3 years who is actively exploring their environment. This value is derived from a study in the Dutch population (considered to be representative of the European population) and corresponds to the 25th percentile; 12.4 kg (RIVM report 090013003/2014) rounded up to 12.5 kg).
For adults: 60 kg (default value used by the CVMP).

5.2.3. Exposure assessment for post administration exposure scenarios after contact with the treated animal

It is assumed that residues on the animal are transferred to the skin of the user who comes into contact with the treated animal during stroking. Additionally, users may become orally exposed via hand-to-mouth contact. Exposure in children is considered to represent the worst-case scenario, due to their low body weight. Therefore, additional calculations for adult exposure are normally not necessary, except when the substance may pose a risk for specific populations, as identified in the hazard assessment. In such cases, a risk assessment for both child and adult should be performed. Consequently, the following scenarios should be considered:

1) **dermal exposure of children (or specific populations, e.g. pregnant women) following contact with the treated animal**

2) **oral exposure of children (or specific populations, e.g. pregnant women) due to hand-to-mouth contact**

Both scenarios should be considered for short-term and long-term exposure to a treated animal. Short term exposure reflects exposure to the highest residue levels observed, which are generally those immediately after administration of the product and during the first 12 hours after treatment, but may occur later. Long-term exposure reflects daily exposure to the average residue levels during at least the period of claimed efficacy. For risk assessment of long-term exposure, the potential for repeated use of the product should be taken into account when selecting the appropriate TRV.

5.2.3.1 Dermal exposure of children (or specific populations, e.g. pregnant women) following 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 the use of the child's surface area in contact with the treated animal provides a more direct estimate of dermal exposure. Accordingly, it is assumed that the dislodgeable residue equals the transferable residue. Furthermore, a one-to-one relationship between dislodgeable/transferable residue on the animal (distributed over its surface area) and the surface area in contact with the user is assumed, such that the concentration of residues per cm^2 on the animal surface equals the concentration per cm^2 on the human skin surface.

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

Dermal exposure of a child following 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, defined as the concentration of the active substance per unit surface area of the treated animal that may be transferred 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 the neck of a 2 to <3-year-old child. This value is derived from a study in the Dutch population (considered to be representative of 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, although in practice multiple events per day with smaller contact surface areas may occur.

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

When there might be a risk for pregnant women or women of childbearing age, as to be concluded from the hazard assessment, the following defaults can be used in the exposure assessment. BW: 60 kg (default body weight used by the CVMP, which is also considered relevant for pregnant women, as exposure may occur at the early stage of pregnancy). SA*contact* of 3200 cm^2. This value represents the surface relevant for dermal exposure, i.e. the surface area of both hands and both arms of the woman (RIVM report 090013003/2014). The transferable residue is calculated as follows. It is assumed that one animal is contacted. If more animals are present, it is expected that the total contact activity remains unchanged.

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

Where:

TR = Transferable Residue, defined as the concentration of the active substance per unit surface area of the treated animal that may be transfered to the user (child) (mg/cm^2);

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

F_{AR} = Fraction of the Administration Rate available as transferable residue.
The nominal defaults are set to respectively 0.30 (30%)* for short-term exposure and 0.02 (2%) for long-term exposure. These defaults are considered sufficiently conservative based on a 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);

*In the initial guideline, it was considered that a default value of 15% was conservative based on the available data. However, experience gained over recent years, based on company-submitted data, has demonstrated that this value is not sufficiently conservative for short-term exposure and has been exceeded in several cases. A re-evaluation of all available studies revealed that a value of 30% is appropriate as the default value.

SA_{animal} = Surface Area of the animal (cm^2).
The surface area of animal that gives worst-case active substance-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 entire body surface[1] of the animal.

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

5.2.3.2 Oral exposure of children (or specific populations, e.g. pregnant women) due to hand-to-mouth contact

This scenario assumes that part of the total residues to which a child (or pregnant woman) is dermally exposed will be present on the hands and may subsequently be ingested due to hand-to-mouth contact. The oral exposure is calculated 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 hands 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 on 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; representing the surface area of both hands of a child divided by the surface area of the unprotected body parts of a child). For a pregnant woman, a value of 25% (800/3200 cm^2) is assumed, representing the surface area of both hands divided by the surface area relevant for dermal exposure for an adult.

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

The following equations are used to calculate the oral exposure of a child following contact with 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);

[1] 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.

HR = Hand Residue loading (mg/cm^2), defined as the amount of residues on the hands per unit surface area (cm^2).
See below;

SA_m = Surface Area in contact with the mouth.
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 in contact with the mouth (RIVM report 320005004/2007).

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 the calculation the mouthed area is assumed to be fully loaded each 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).

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 the hands are loaded each time hand-into-mouth contact occurs.

When there might be a risk for pregnant women or women of childbearing age, as identified in the hazard assessment, other defaults for SA_m, HTM, HIM need to be taken into account. While it is acknowledged that oral ingestion due to HTM may result in significant exposure for adults, actual data on mouthing behaviour and the surface area in contact with the mouth are lacking. As a reasonable worst-case assumption, and as no actual data are available for adults, data from the age group 6 to <11-year-old children are recommended for use in this scenario (RIVM report 320005004/2007). SA_m: 15 cm^2, HTM: 10, HIM: 0.3).

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

Where:

HR = Hand Residue loading (mg/cm^2), defined as the amount of residues on the hand per unit surface area (cm^2);

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

F_h = Fraction of the total dermal exposure expected to be present on the hands.
Default: 0.15 (15%) for a child or 0.25 (25%) for a pregnant woman based on surface area comparison (see above);

SA_h = Surface Area of both hands. 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 of the European population) (RIVM report 090013003/2014). For a pregnant woman, a value of 800 cm^2 is used, corresponding to the surface area of both hands.

5.2.3.3 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 (i.e. the sum of exposures from all routes) should be calculated.

5.3 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 contact with a collar when stroking). As a first step, estimations of transferable residue can be calculated on the basis of default values (see section 5.2.3.1). However, in the case of identified risks using default values, calculations must be refined based on data derived from a suitable product-specific *in vivo* exposure study, i.e. a pet animal wipe test. A flow diagram to decide when it is necessary to perform a wipe test and how to act on the outcome is shown in Annex 1.

When using the defaults of 30% and 2% and no risk is identified, it is assumed that the highest dislodgeable fraction (at any time point), i.e. the transferable residue from the animal's fur, will not be >30% and the average dislodgeable fraction will not be >2%. In cases where, when using the default values, a risk is identified for acute/short term exposure, but not for long-term exposure, it will not be sufficient to add a standard statement < *treated animals must not be handled for at least 12 hours after administration of the product* >. This is because it is not known at what time point the acute risk becomes acceptable. A wipe test still needs to be performed in order to monitor the depletion of the residues from the fur and determine the time point at which there is no acute risk.

It should 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 conducting a transferable residue study that is acceptable to the competent authority, to 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 performed using the final product formulation, administered to the test animals in accordance with the proposed Summary of Product Characteristics (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 could be sufficient as this will be considered worst-case where the same dose is applied. This is due to the fact that cats are expected to have a more intense grooming pattern which will lower the dislodgeable residues. The derived data may then also be used for cats. The applicant must justify the chosen species.

Experimental design

Animals should not be bathed after administration of the 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 should 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 the 3Rs principles, but as long as necessary in order to ensure the scientific validity of the study. In any case, this should be justified by the applicant.

Administration 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 dose-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 5.2.3.1.). This dose should be applied to the test animals, which are in general medium sized animals (with the dose corrected for differences in body weight). To obtain the highest active substance dose-to-surface area ratio, 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 2 ml pipette is recommended for a medium sized animal of 10 to 20 kg body weight, the highest active substance dose-to-surface area ratio will be 2 ml applied to 10 kg animals. In case the test animals in the wipe test weigh 20 kg, a dose of 4 ml 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 are considered to 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 of the final product formulation and/or the active substance(s) can be taken into account when selecting 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 spot-on products. The highest residues are expected at later time points when the active substance 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 designed 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, applying uniform, moderate pressure using motions which run with the lay of the hair coat. One petting simulation 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 site(s) of administration for spot-on products and the collar for medicated collars (not only the fur adjacent to the collar).

The cotton and impermeable glove should be removed carefully by turning each glove inside out and placing them in separate containers for storage and 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 are 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, together with animal body weight, breed and hair length. During the petting procedure, if there is any visible wetness on the site of administration and/or on the cotton glove, covering the hand, it should be recorded in the raw data. This will provide information on the time period until the site of administration has fully dried, although this does not automatically relate to the absence of dislodgeable residues, i.e. even if the site of administration has fully dried, dislodgeable residues may still be present.

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 the applied dose.

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

To compensate for the fact that only a limited number of animals are included in the wipe test, an 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 at any time point.

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 for 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 handling 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.

5.4 Risk characterisation

The procedure for the quantitative risk assessment consists of comparing the exposure levels to which the user is or is likely to be exposed with the TRVs (exposure levels at which no adverse effects are expected to occur), i.e. calculating the margin of exposure (MOE).

The procedure for the quantitative risk assessment should follow that detailed in the 'Guideline on user safety for pharmaceutical veterinary medicinal products'. The parameters to be taken into account when determining an acceptable MOE, such as intra- and interspecies variation, the nature and severity of effects, and so on, are further specified in that guideline. Where the MOE is deemed acceptable based on these parameters, the risk to the user is also considered acceptable. If this is not the case, appropriate risk mitigation measures should be considered.

For non-quantifiable risks, such as irritation of skin and/or eyes and hypersensitivity reaction, a qualitative risk characterisation should be conducted.

5.5 Risk Management and Communication

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 RMMs should reduce exposure to an acceptable level and that the measures are 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.

The relevant risks should be communicated following the A, B, C, D format presented in section 5.5. of the 'Guideline on user safety for pharmaceutical veterinary medicinal products', i.e. A. the concerned risk, B. what exposure must be avoided to minimise the concerned risk, C. how to avoid that exposure and D. what to do in the event of exposure.

Pre-administration

Pre-administration situations where exposure can occur include storing or accessing the product. The potential for, and the nature of, exposure will depend on, for example, packaging design, storage, or the skills of the user. The type of exposure of concern is acute dermal and/or oral. The primary concern is exposure of children 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 the sachet with the <collar><pipette> in the <outer carton><original packaging> until use.
- Keep pipettes in the original packaging until use.

- Dispose of any surplus collar immediately.
- In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician.

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

Administration

Situations where exposure can occur include opening the product and administering the VMP to the animal. The type of exposure of concern is primarily acute dermal, oral (due to hand-to-mouth contact), inhalation, as well as ocular exposure, 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 the skin, eye and mouth, including hand-to-mouth and hand-to-eye contact. Do not smoke, drink or eat during administration. Wash hands after use. In case of contact with the skin or eyes, rinse immediately with water.
- Spray animals in the open air or in a well-ventilated area.
- Pregnant women or women trying to conceive should handle or administer the veterinary medicinal product with caution.
- Personal protective equipment consisting of impervious gloves should be worn by pregnant women or women trying to conceive when handling the veterinary medicinal product.

Personal protective equipment

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

Post-administration

The post-administration phase consists of both short-term and long-term dermal and oral exposure due to hand-to-mouth contact. The handling of animals following treatment, including contact with the medicated 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.
- 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:

- Treated animals should not be handled, especially by children, <for at least X hours after administration of the veterinary medicinal product>. It is recommended to administer the product

in the evening. Recently treated animals should not be allowed to sleep in the same bed as their owner(s), especially children.

- Treated animals should not be handled, especially by children, for at least 1 hour after administration of the veterinary medicinal product. It is recommended to apply the product in the evening. Recently treated animals should not be allowed to sleep in the same bed as their owner(s), especially children.

The latter phrase is considered a precautionary phrase, to be used when no acute risk is identified (see also flow diagram in Annex 1). The recommendation to avoid exposure during the first hour after administration is supported by the fact that the wipe tests generally start at the 1-hour time point. In addition, the default value for the dislodgeable fraction of 30% is based on observations ≥1 hour. At earlier time points, higher dislodgeable fractions have been observed in wipe tests.

If an RMM is proposed, it should be justified. For example, the warning <Children should not be allowed to play with treated dogs/cats until the site of administration is dry> should be justified by actual measurement of transferable residue (i.e. wipe test) to prove that no risk is identified when the site of administration is dry. It is, however, preferred to specify the time period instead of using this sentence.

A particular risk arises where the treated animal is in regular contact with the user, for example, topical products for companion animals are likely to present a prolonged post-administration 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 washing 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 an overnight period of 12-hours is also not generally considered practical.

In the event that an acute risk is identified beyond 12 hours, or a chronic risk is identified, even when refining with a wipe test, the applicant could try to refine the TRV, if possible, or to refine data on dermal absorption where assumptions have been made or default values have been used.

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 in order to avoid exposure of vulnerable users, such as pregnant women, should 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 proposed RMMs will be considered in the context of the overall benefit/risk assessment of the VMP.

The communication of user warnings and 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.

In order to illustrate the principles and approaches described in this guideline, a worked example is provided in Annex 2.

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, BMDL).

NO(A)EL: The highest administered dose in a study at which no (adverse) effect is observed.

LO(A)EL: The lowest administered dose in a study at which (adverse) effect(s) are observed.

Exposure: Contact with a substance by oral, dermal, parenteral, ocular and/or inhalation routes. 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 the period of time of treatment until the time point at which the highest exposure occurs. This is likely to be up to 12 hours, but may 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, though it should be taken into account that animals may be treated frequently.

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 more than 90 days.

Uncertainty factor (UF): A numerical factor applied to a toxicological (pharmacological/microbiological) endpoint to allow for uncertainties in risk assessment such as intraspecies (extrapolating animal data to humans) and interindividual (variation in sensitivity among humans) variations, the quality of the data, the severity of the response. The factor may be a default value used in the absence of specific information on a substance or may be modified in the light of specific information.

Margin of exposure (MOE): The ratio of the TRV to an estimated exposure level.

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, k = 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 the claimed period of efficacy or until two subsequent measurements are below the LOQ, with measurements below the LOQ set to half the 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

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

References

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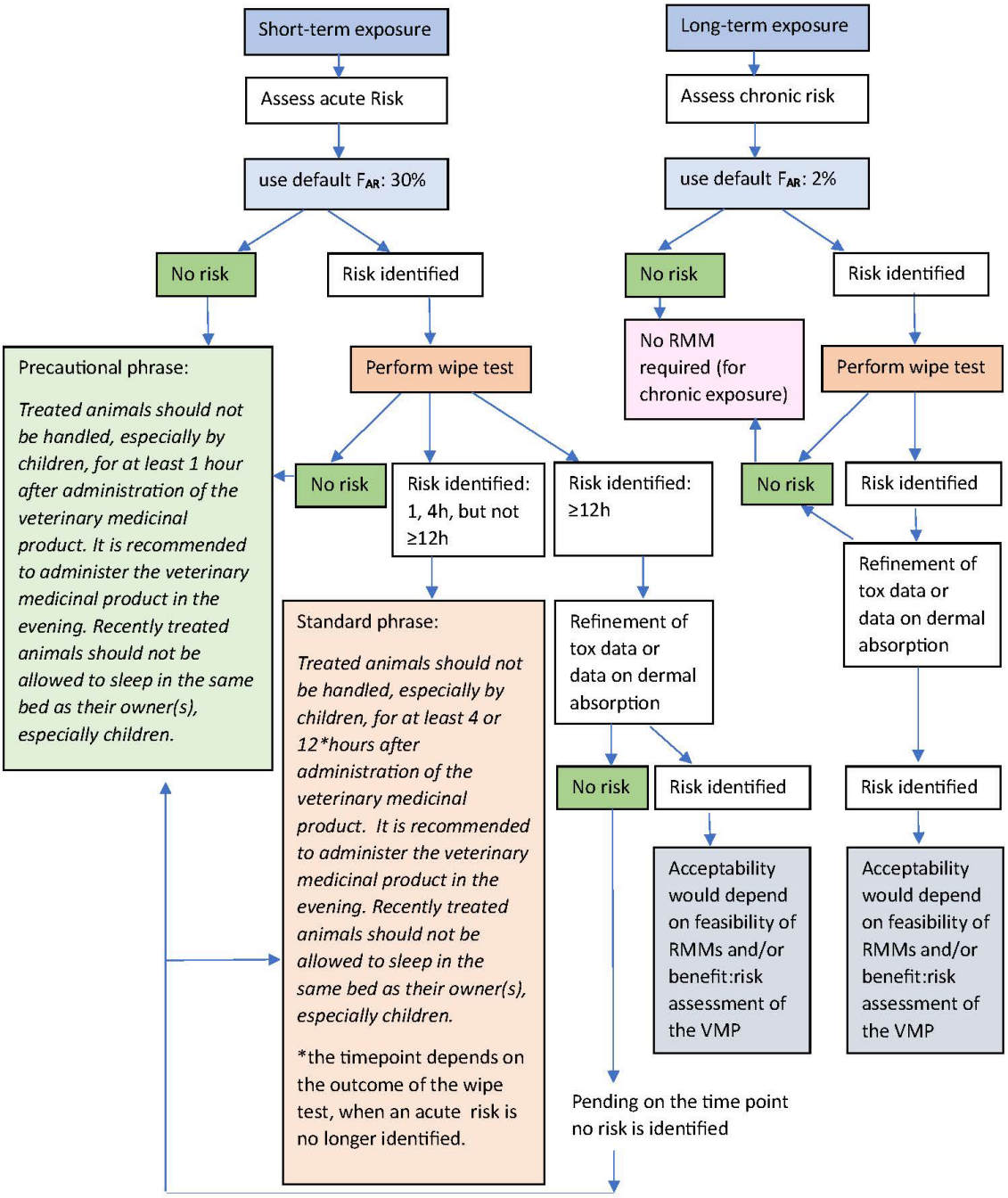
Annex 1

Risk assessment for post administration exposure scenarios after contact with the treated animal, following the scenarios and equations described in section 5.3.



Annex 2

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' results are fictional.

A spot on pipette intended for medium sized dogs contains 134 mg of active substance, while the largest pipette (5 ml) contains 700 mg of active substance. The highest active substance 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 30.0% for the short-term exposure scenario and 2.0% for the long-term scenario. As a refinement, a 'wipe test' study is submitted in which the highest amount dislodged was 5.0% and over the following 28 days the mean TWA of the amount dislodged was 0.5%. For this (fictional) VMP, the risk for pregnant women did not need to be characterised, as the active substance was not associated with embryotoxicity.

Establishing TRVs

Data indicate that the oral absorption (bioavailability) of the pharmacologically active substance is 80% and dermal absorption is 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.:

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

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, therefore, the dermal TRV is calculated from the oral TRV adjusted for oral/dermal absorption. The Abs_{dermal} of 2% as derived for the final product formulation should 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 body weight derived from a 28-day repeated dose toxicity study in the rat.

- Long-term dermal: No relevant dermal study was available for the substance, therefore, the dermal TRV is calculated from the oral TRV adjusted for oral/dermal absorption. For the long-term exposure scenario, the Abs_{dermal} of 1% is acceptable (as penetration enhancers were 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 body weight based on 13-week oral (diet) study in rats.

Estimating exposure

1) Contact to the VMP (see section 5.2.2 of this guideline)

Pre-administration phase

Accidental oral exposure of a child may occur if an opened pipette is left out on a surface whilst an adult is restraining an animal or if the VMP is accessible by a child. As the product is not in 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

Administration phase

Dermal and oral exposure of an adult may occur if the VMP comes into contact with the user's skin during administration and 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 5.2.3 of this guideline)

Post-administration 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 = Administration Rate = 134 mg F_{AR} = Fraction of the Administration Rate available as transferable residue = 0.05 SA_{animal} = Surface Area of the animal = 7000 cm^2	AR = 134 mg F_{AR} = 0.30 (default) SA_{animal} = 7000 cm^2
$TR = \frac{134 * 0.05}{7000}$	$TR = \frac{134 * 0.30}{7000}$
TR = 0.00096 mg/cm^2	**TR = 0.0057 mg/cm^2**
$\mathrm{DE}_{bw-corr} = \frac{\mathrm{TR} * \mathrm{SA}_{contact}}{\mathrm{BW}}$	
TR = 0.00096 mg/cm^2 $SA_{contact}$ = the surface area of a child in contact with the animal per day = 1790 cm^2 (default) BW = Body Weight of a child = 12.5 kg (default)	TR = 0.0057 mg/cm^2 $SA_{contact}$ = 1790 cm^2 (default) BW = 12.5 kg (default)
$\mathrm{DE}_{bw-corr} = \frac{0.00096 * 1790}{12.5}$	$\mathrm{DE}_{bw-corr} = \frac{0.0057 * 1790}{12.5}$
$DE_{bw-corr}$ = 0.137 mg/kg bw	**$DE_{bw-corr}$ = 0.822mg/kg bw**

978 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 = (0.0057*1790) = 10.280 mg F_h = 0.15 (default) SA_h = 270 cm^2 (default)
$\mathrm{HR} = \frac{1.7133 * 0.15}{270}$	$\mathrm{HR} = \frac{10.280 * 0.15}{270}$
HR = 0.000952mg/cm^2	**HR = 0.00571 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 = 0.00571 mg/cm^2 SA_m = 7 cm^2 (default) HTM = 20 (default) HIM = 0.4 (default) BW = 12.5 kg (default)
$\mathrm{OE} = \frac{0.000952 * 7 * 20 * 0.4}{12.5}$	$\mathrm{OE} = \frac{0.00571 * 7 * 20 * 0.4}{12.5}$
OE = 0.00426 mg/kg	**OE = 0.0256 mg/kg**

979 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	0.822	0.0164
Oral exp	0.00426	0.00341	0.0256	0.0204
Total exp		0.00615		0.0369

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

981 **Post-administration phase – Long-term exposure**

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

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

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

Using 'wipe test' results	Using default values
$\mathrm{HR} = \frac{\mathrm{DE} * \mathrm{F}_h}{\mathrm{SA}_\mathrm{h}}$	
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 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 = (0.00038*1790) = 0.6853 mg F_h = 0.15 (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**
$\mathrm{OE} = \frac{\mathrm{HR} * \mathrm{SA}_m * \mathrm{HTM} * \mathrm{HIM}}{\mathrm{BW}}$	
OE = Oral exposure due to hand-to-mouth contact (mg/kg bw/day)	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)	HR = 0.000381 mg/cm^2 SA_m = 7 cm^2 (default) HTM = 20 (default) HIM = 0.4 (default) BW = 12.5 kg (default)
$\mathrm{OE} = \frac{0.000095 * 7 * 20 * 0.4}{12.5}$	$\mathrm{OE} = \frac{0.000381 * 7 * 20 * 0.4}{12.5}$
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 also contribute to dermal exposure. 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-administration 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

Administration 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-administration phase – Short-term exposure

Exposure Route	Relevant NO(A)EL	Estimated Exposure	MOE
Using default values			
Oral	0.9 mg/kg bw/day	0.0256 mg/kg bw/day	35
Dermal	36 mg/kg bw/day	0.822 mg/kg bw/day	44
Oral + dermal	0.72 mg/kg bw/day*	0.0369 mg/kg bw/day**	20
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-administration 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 VMP in the pre-administration phase.

The following user warnings may be appropriate:

- This veterinary medicinal product may cause adverse effects *[the type of adverse effects should be described].*
- Avoid contact of the veterinary medicinal product with skin, eyes or mouth.
- Do not eat, drink or smoke while handling the veterinary medicinal product.
- Wash hands thoroughly after use. Keep pipettes in the original packaging until use. To prevent children from getting access to used pipettes, dispose of them immediately.
- In case of accidental spillage on skin, wash off immediately with soap and water.
- Wash hands thoroughly after use.
- In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician.

The above also encompasses appropriate warnings for adults in case of accidental exposure during treatment. It is noted that in the administration 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 should 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 administration is considered a single exposure. In light of this, the above measures are considered sufficient for this VMP.

In the post-administration phase, there are two scenarios presented. Using the default values for the amount dislodged, the VMP does not meet the acceptable risk threshold in the acute phase (short-term exposure), as the MOE <100. In such a situation, results from a wipe test are required. Using the wipe test, no risk was identified for the example VMP. The precautionary phrase is then applicable:

- Treated animals should not be handled, especially by children, for at least 1 hour after administration of the veterinary medicinal product. It is recommended to administer the product in the evening. Recently treated animals should not be allowed to sleep in the same bed as their owner(s), especially children.

No additional warnings are required for the long-term exposure following administration of the product, as the MOE of >100 is acceptable. However, there may be a need for additional formulation-specific warnings following the evaluation of skin/eye irritation and skin sensitisation studies.