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GUIDELINE ON USER SAFETY

FOR PHARMACEUTICAL VETERINARY MEDICINAL PRODUCTS

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Guideline on User Safety
for Pharmaceutical Veterinary Medicinal Products

Table of contents

1 INTRODUCTION 3

2 SCOPE 3

3 PRINCIPLES OF THE ASSESSMENT 3

4 EXPOSURE ASSESSMENT 4

5 HAZARD IDENTIFICATION AND CHARACTERISATION 7

6 RISK CHARACTERISATION 8

7 RISK MANAGEMENT 9

8 RISK COMMUNICATION 10

9 ABBREVIATIONS 11

10 GLOSSARY OF TERMS 11

11 REFERENCES 14

APPENDIX I - EXAMPLES 15

APPENDIX II – EXPOSURE FACTORS 17

1 Introduction

Applications for marketing authorisations of veterinary medicinal products in the European Union are issued in accordance with Directive 2001/82/EC of the European Parliament and of the Council dated 6 November 2001. This legislation requires for pharmaceutical veterinary medicinal products that the applicant provides safety documentation, which shows the potential risks that may result from the exposure of human beings to the medicinal product, for example during its administration to the animal. For medicinal products that imply such risks, the legislation allows for the definition of special precautions to be taken by the person administering the medicinal product to animals, in order to reduce the risks to an acceptable level. Those precautions are to be stated in the Summary of Product Characteristics (SPC) and package insert.

The legislation does not give specific guidance on exact data requirements and assessment methods to be used to identify the risks, or on the measures for risk reduction. This guideline is presented to provide this guidance.

2 Scope

This guideline applies to all new applications for Marketing Authorisation for pharmaceutical veterinary medicinal products. This guideline shall not apply to Marketing Authorisations granted in accordance with Article 13 (1) (a) (i) and (iii) of Directive 2001/82/EC, but will apply to those in accordance with Article 13 (1) (a) (ii).

For the assessment of user safety, the user is defined as any person that may come into contact with the veterinary medicinal product or components of the product before its application to the animal (e.g. during storage or preparation), during its application, and after its application (e.g. through contact with the treated animals). This implies that the user can be for example a veterinarian, a farmer, a bystander, a breeder, a pet-owner or person living in the same building, a canine beautician, a miller incorporating a medicated premix into a finished feed or a sheepshearer. The guideline does not cover occupational safety during the production of veterinary medicinal products.

The assessment of the user safety of a product should address only the exposure situations resulting from the normal conditions of use and from the foreseeable accidents (including accidental ingestion by children and accidental self-injection). It does not include exposure situations resulting from deliberate misuse, except in the case of particularly dangerous drugs where suitable storage conditions may be imposed to prevent access by unauthorised people.

3 Principles of the assessment

The assessment of the user safety will comprise the following steps:

Exposure assessment → hazard identification and characterisation → risk characterisation → risk management

All relevant exposure scenarios should be considered. To allow the characterisation of risks for each scenario, the hazards should be identified and characterised on the basis of appropriate toxicity tests regarding relevant endpoints for local and systemic toxicity, taking into account the route, duration, and frequency of anticipated exposure. This also means that the route of exposure will determine the required effect studies (e.g. if only dermal exposure is anticipated, no information regarding inhalation toxicity is deemed necessary).

In essence, the procedure for the risk characterisation consists of comparing the exposure levels to which the user is exposed or is likely to be exposed with the exposure levels at which no adverse effects are expected to occur.

When there is a predicted risk for the user, appropriate measures for risk reduction should be proposed and evaluated.

3.1 Professional and non-professional users

It is important to make a clear distinction between the situation in which professional or non-professional users can be exposed. Professional users (e.g. veterinarians, professional farmers) are expected to have the knowledge, the experience, and the skills to handle a veterinary product as intended, whereas non-professional users (e.g. pet owners, hobby farmers) may not necessarily have these qualities.

Professional users are also expected to read the package insert, whereas non-professional users may or may not do this. Hence, the incidence of incorrect use should be lower for professional users compared to non-professional users. On the other hand, non-professional users are expected to have less frequent contact with veterinary products. Another difference is that professional users are generally healthy adults, whereas non-professional users (or people in the same residential environment) can be any person in the general population (including children, the elderly and persons with a diminished level of responsibility). Hence the inter-individual variation (e.g. in susceptibility) could be different for professional users and non-professional users. In addition, professional users generally have access to personal protective equipment (PPE) and other control measures, and have the skills to use it, whereas non-professional users may only have access to a limited choice of PPE (e.g. gardening or kitchen gloves).

4 Exposure assessment

4.1 Description of the product

The first step in the exposure assessment is a description of the product of concern. This description should cover the following items:

- the pharmaceutical form,
- the presentation (quantity available to the user, packaging),
- the method of use, including the route of administration and any dosing equipment to be used,
- relevant physico-chemical characteristics.

4.2 The tasks and situations that lead to exposure

The next step in the exposure assessment is to identify the tasks and/or situations that may lead to exposure of humans. Different phases before, during and after administration of the product to the animal(s) should be considered. It is also important to distinguish between the situations where professional and non-professional users are exposed.

Table 1 illustrates some different tasks and situations that may be relevant for a veterinary product. It should be noted that these are just examples, other situations may be considered when appropriate.

Table 1. Some examples of tasks and situations that may lead to exposure

	Pre-application phase	Application phase	Post-application phase
Professional user	• Storage • Opening or accessing the product • Mixing and/or diluting of concentrates • Loading in application apparatus or system	• Administration to the animal(s)	• Cleaning equipment • Disposal activities • Stroking or otherwise handling the coat of treated animals
Non-professional user	• Storage • Mixing with feed • Taking the product from its container e.g. blister pack or collar	• Administration to the animal(s)	• Disposal activities • Stroking or otherwise handling the coat of treated animals

Some specific examples of tasks and situation that may lead to exposure for certain types of products are given in Appendix I.

4.3 Exposure scenarios

Once the tasks and situations that lead to exposure are identified, the exposure for each task/situation should be further characterised. For each relevant situation one representative exposure scenario has to be defined. An exposure scenario should comprise the following elements:

- the type of user,
- the routes of exposure,
- the components of a product to which the user is exposed,
- the likelihood of exposure,
- the rate, extent, duration, interval, and frequency of exposure.

For one product, these five elements may be different for the different phases and for the professional and non-professional user. The elements are further explained below.

4.3.1 The type of user

It has to be indicated if the product is intended for use by professionals or non-professionals. Because different professionals may have different levels of expertise, it should be explained what persons are involved in an exposure scenario. Examples of persons that can be involved are: a veterinarian, a farmer, a breeder, a pet-owner, a child, etc. (see also 2. Scope).

4.3.2 The routes of exposure

The route(s) of exposure have to be specified for each exposure scenario. The routes of exposure will generally depend on the type of the product, the pharmaceutical form, and the dosing equipment (if any). The routes are generally limited to dermal, inhalation, ocular, and parenteral (self-injection). Oral ingestion is normally considered negligible when elementary personal hygiene is maintained. However, oral exposure should be considered in the following situations:

- Oral exposure due to hand-to-mouth contact needs to be considered with certain scenarios, e.g. after stroking a pet when there are residues on the fur.

- The non-respirable fraction of an inhalation exposure is considered to be swallowed.

The observation of the warning "keep out of reach of children" on the label and insert of products should normally prevent accidental ingestion by children. However, non-professional users may not read or obey such warnings and therefore the risks of oral ingestion should be considered for all consumer products. If the toxicity data suggest that there may be a concern, minimising exposure to children should be addressed, such as considering child resistant packaging.

4.3.3 The components of a product to which the user is exposed

Users can be exposed to:

- the whole product (e.g. a powder, a concentrate), including its active and inactive ingredients;
- to certain components of the product (e.g. an active ingredient released from a collar);
- to solutions or dilutions of a product (e.g. medicated drinking water).

For each exposure scenario, it should be specified to what (e.g. whole product, components, dilution) the user is exposed.

4.3.4 The likelihood of exposure

Although all sorts of situations that lead to exposure can be considered, it will not mean that each of these situations will occur every time the product is used. For example: accidental self-injection will be considered as an exposure situation, but it is clear that there is a low probability that this event will actually happen when the product is used.

Any available data on the incidence of events that lead to exposure related to the use of the (type of) product should be submitted.

4.3.5 The rate, extent, duration, interval and frequency of exposure

The rate, extent, duration, interval, and frequency of exposure determine the quantitative part of an exposure scenario.

Duration, interval, and frequency of exposure are to be estimated by the applicant on the basis of experience with the product or comparable types of products, taking into account the use of the product by professionals and non-professionals, and taking into account the pattern of use (variation in season or region).

The rate and extent of exposure are often determined by parameters like (total) dose, concentration (e.g. in solutions or in air), release rate (e.g. from a collar or from a spray apparatus), release height, vapour pressure, particle size, and droplet size. From these data the external dose is estimated. To estimate the internal dose, the pharmacokinetic properties (in particular data on absorption and bioavailability) of the relevant compounds have to be taken into account. The estimation of the exposure levels may include measured data as well as model calculations. Adequately measured and representative exposure data are preferred to model calculations. Any assumptions made in the exposure assessment should be clearly indicated and justification should be given. When exposure models are used, it is recommended to use (where possible and applicable) the models already commonly employed in the EU for the assessment of substances (see e.g. Technical Guidance Document (TGD) in support of Directive 93/67/EEC). In any case, the input data or default values used for the calculations should be documented. Exposure factors (e.g. standards for bodyweights of adults and children, surface areas of body parts etc.) that can be used are referred to in Appendix II.

Irrespective of the method used, the prediction of the exposure levels should describe a reasonable worst case situation. As a default, the 95^{th} percentile of the distribution represents the reasonable worst case, but expert judgement is needed to check the realism of the exposure value derived from a model, in particular when default values have been used.

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. In some cases, the same compound or product is to be used to treat an animal and its environment (e.g. a flea powder). When it is foreseeable that animal beddings, premises etc. will be treated as well, an assessment of aggregate exposure from both uses should be made.

5 Hazard identification and characterisation

The type and amount of toxicity studies needed for the hazard identification and characterisation as part of the user safety assessment of a product depends on the outcome of the exposure assessment. Generally, most of the toxicity studies are already part of a product dossier (part IIIA). The need for any additional studies depends on the exposure, as reflected in table 2. In some cases the nature of the substances indicate the need to focus on specific end-points of toxicity or pharmacology.

As a general rule, the toxicity data should provide information on the possible adverse health effects after human exposure as described by the exposure scenarios. Therefore, the following should be considered:

- Both local and systemic effects should be considered. Whenever possible, dose-response relationships have to be identified in order to derive the no observed adverse effect level (NOAEL), or, if this is not possible, the lowest observed adverse effect level (LOAEL).
- The systemic effects have to be assessed for the active ingredients only. However, when there is a specific concern with regard to the systemic effects of one or more of the excipients, it may be necessary to assess the systemic toxicity of these excipients or the formulated product.
- Toxicity studies should employ the same routes of exposure as described in the exposure scenarios. Alternatively, route-to-route extrapolation may be considered when appropriate. It should be noted that for route-to-route extrapolation, data on absorption and (if relevant) route-dependent metabolism and/or bioavailability following the concerned routes are needed.
- For studies on local toxicity, the test article(s) should preferably be the same as described in the exposure scenarios (whole product (active ingredients plus excipients) or components/solutions/dilutions thereof). As an alternative, the potential effects of a product can be deduced from data of the single ingredients of the product.
- The duration of the toxicity studies should represent an adequate reflection of the duration/frequency of exposure as described in the exposure scenarios.

The information which is thought to be relevant for certain routes of exposure is given in the following table, and is considered to be the minimum required information, unless the applicant can adequately justify the lack of such information.

Table 2. Minimal required information for different routes of exposure

Relevant route of exposure	Minimal required information regarding:	
	for active ingredients	*for the whole product (active ingredients plus excipients) or components/solutions/dilutions thereof*
Oral	All relevant toxicity data and human data (when available) in accordance with the requirements for dossier parts III.A.1 through III.A.4	-
Dermal	All relevant toxicity data and human data (when available) in accordance with the requirements for dossier parts III.A.1 through III.A.4	Skin irritation Skin sensitisation
Parenteral (i.e. self-injection)	All relevant toxicity data and human data (when available) in accordance with the requirements for dossier parts III.A.1 through III.A.4	Acute parenteral toxicity (local/systemic)
Ocular	Eye irritation[1]	Eye irritation[1]
Inhalation	All relevant toxicity data and human data (when available) in accordance with the requirements for dossier parts III.A.1 through III.A.4	Respiratory irritation Respiratory sensitisation

[1] If the test article is irritating to the skin, it is assumed that it is also irritating to the eyes. Therefore no eye-irritation test has to be performed for skin irritating test articles.

The toxicity tests should be carried out according to current methods (e.g. EC, OECD, or EPA) and be appropriately reported. Other methods may be considered as well, provided that their choice is adequately justified by the applicant in terms of scientific reliability and relevance.

It is noted that for some end-points standardised methods are currently not available, in particular for parenteral toxicity and respiratory sensitisation. For parenteral toxicity, target animal safety studies may provide adequate information on local and systemic effects following this route of exposure. Data on skin sensitisation may serve as a surrogate for respiratory sensitisation, until appropriate methods for the determination of respiratory sensitisation have been established.

6 Risk characterisation

6.1 Qualitative risk characterisation

For a number of toxicological end-points, the methods for testing provide qualitative, non-stochastic, results. This is in particular the case for certain local effects (e.g. sensitisation, skin irritation). For these effects no information on dose response relationship will be available and hence thresholds remain unknown. Consequently, no quantitative risk assessment can be made for the anticipated exposure levels. Instead, only a hazard identification can be made. The hazards with regard to these end-points are to be identified using the classification according to EU-criteria (see Directive 93/21/EEC). Although a quantitative risk characterisation cannot be made, the risk may be (qualitatively) characterised taking into account the likelihood that such effect will occur on the basis

of exposure information. Whenever possible, available information on the severity of an effect at the anticipated exposure levels should be taken into account as well. If such information is not available, it must be assumed that the effects will occur at any exposure level.

In addition, physical risks related to the physico-chemical properties should be identified.

6.2 Quantitative risk characterisation

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

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

Where the exposure estimate is less than the 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);
- the dose-response relationship observed;
- the overall confidence in the database.

To account for uncertainty related to interspecies variation (i.e. extrapolation from animals to humans) a standard factor of 10 is used unless there is reliable data to deviate from this.

To account for uncertainty related to intraspecies variation (i.e. differences in human susceptibility) a standard factor of 10 is used unless there is reliable data to deviate from this.

When alternative factors are proposed, consideration must be given to the guidance document published by the WHO (WHO, 2001).

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

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

7 Risk management

7.1 Non-professional users

Non-professional users may or may not read the product label or package insert. There is an expectation – but little guarantee – that non-professionals comply with the instructions for use of a product. They may have limited access to PPE and might not maintain the PPE properly. Therefore, for this group of users, the use of a product must be acceptably safe, or have an acceptable risk with limited protection.

7.2 Professional users

Where the risk characterisation predicts an unacceptably high risk for the unprotected professional user in one or more of the exposure scenarios, measures to reduce the risk to an acceptable level should be proposed and evaluated.

7.3 Risk control options

In general, the following options for risk control may be used:

- restriction of the distribution, e.g. as prescription only medicine;
- excluding groups at risk, e.g. sensitised people, pregnant women;
- restriction of application methods, e.g. pour-on instead of spraying or use of closed delivery systems;
- restriction of the field of use, e.g. outdoor use only;
- modification of the formulation, e.g. ready-to-use rather than concentrate, replacement of substances of concern with less dangerous ones, etc.;
- modification of packaging, e.g. reduced pack size;
- modification of labelling;
- modification of measures for the protection of users, e.g. general controls like ventilation or PPE like protective gloves, masks or goggles.

The proposed risk reduction measures should be evaluated with the following criteria:

1. the extent to which the exposure is reduced by a measure, alone or in combination with other measures, should be large enough to reduce the risk to an acceptable level;
2. the measure should be practicable, e.g. PPE must be readily available to the user, and measures should not hamper the use of the product too much.

ad 1.: The appropriateness, i.e. the inherent efficiency, of measures should be discussed. For example, the choice of materials should be justified (it is well known that certain substances are able to permeate or penetrate through certain materials, e.g. solvents through latex gloves).

ad 2.: When the proposed measures are not practicable, they are not expected to be followed in practice. Therefore, only practicable measures should be prescribed.

8 Risk communication

The warnings and safety measures in the SPC and package insert should inform the user at least about the following:

A. The concerned risk.

B. What exposure must be avoided to minimise the concerned risk.

C. How to avoid that exposure.

D. What to do in the event of exposure.

Example:

- This product can cause eye-irritation (A).
- Avoid contact with the eyes (B).
- Wear protective glasses (C).
- When the product comes into contact with the eyes, rinse immediately with plenty of water (D).

9 Abbreviations

ADI	Acceptable Daily Intake
AOEL	Acceptable Occupational Exposure Limit
EC	European Commission
EPA	Environmental Protection Agency
EU	European Union
IPCS	International Program on Chemical Safety
LOAEL	Lowest Observed Adverse Effect Level
MOE	Margin of Exposure
NOAEL	No Observed Adverse Effect Level
OECD	Organisation for Economic Co-operation and Development
PPE	Personal Protective Equipment
RfD	Reference Dose
RPE	Respiratory Protective Equipment
SPC	Summary of Product Characteristics
TGD	Technical Guidance Document
WHO	World Health Organisation

10 Glossary of terms

Partly adapted from IPCS (2001)

Acceptable daily intake (ADI)	An estimate of the amount of a substance in food that can be ingested daily over lifetime by humans without appreciable health risk.
Active ingredient	The chemical with pharmacological activity as defined in the Directive.
Aggregate exposure	The sum of exposures to one or more agents with a common mechanism of toxicity from multiple sources of exposure.
Application phase	The administration of the (prepared) veterinary medicinal product to the animal(s), including application by hand or any other dosing equipment. This phase can lead to exposure of the person administrating the product as well of other people who are present during the product application.
Bellows effect	Movement of the body that causes air to be pumped through openings of e.g. sleeves, jackets, etc. This effect causes enhanced penetration of protective clothing.
Exposure	Contact between an agent and a target. Contact takes place at an exposure point or exposure surface over an exposure interval. For inhalation and ingestion routes, exposure is expressed as a function of exposure concentration; for the dermal route, exposure is expressed as a function of exposure loading.

Exposure assessment	The process of estimating or measuring the intensity, frequency, and duration of exposure to an agent. Ideally, it describes the sources, pathways, routes, magnitude, duration, and pattern of exposure; the characteristics of the populations exposed; and the uncertainties in the assessment.
Exposure concentration	The amount of agent present in the contact volume divided by the contact volume. For example, the amount of agent collected in a personal air monitor divided by the volume sampled.
Exposure duration	The total time period over which contacts occur between an agent and a target. For example, if an individual is in contact with an agent for 10 minutes a day, for 300 days over a one year time period, the exposure duration is one year.
Exposure frequency	The number of exposure intervals in an exposure duration.
Exposure Interval	A period of continuous contact between an agent and a target.
Exposure loading	The amount of agent present in the contact volume divided by the exposure surface area. For example, a dermal exposure measurement based on a skin wipe sample, expressed as a mass of residue per skin surface area, is an exposure loading.
Exposure model	A conceptual or mathematical representation of exposure.
Exposure route	The way an agent enters a human or animal after contact (e.g. by ingestion, inhalation, or dermal absorption).
Exposure scenario	A set of facts, assumptions, and inferences about how exposure takes place. Scenarios are often created to aid exposure assessors in estimating exposure.
Exposure surface	A surface on a target where an agent is present. Examples of locations of exposure surfaces include the lining of the stomach wall, the lung surface, the exterior of an eyeball, the skin surface, and a conceptual surface over the open mouth. Exposure surfaces can be absorptive or non-absorptive.
Foreseeable accidents	The use of veterinary medicinal products not in line with the instructions for use or without the consideration of some or all common and specific technical, operational and personal protective measures (e.g. the over-dosing or inadequate dilution of a veterinary medicinal product, common spillage scenarios, use without or with non-proper PPE).
Likelihood of exposure	The expression of probability that exposure will occur at all.
Margin of exposure	The ratio of the No Observed (Adverse) Effect Level (NO(A)EL) to an estimated exposure level.
Non-professional users	The general public – consumers – who may or may not read a product label. There is an expectation – but little guarantee – that non-professionals comply with the instructions for use of a product. They have limited access to PPE.

Non-respirable fraction	The part of an inhalation exposure that will settle in the nasopharyngeal region and not in the tracheobronchial or pulmonary regions. As a rough guide, particles with aerodynamic diameters below 100 µm have the potential to be inhaled. Particles with aerodynamic diameters of above 1-5 µm have the greatest probability of settling in the nasopharyngeal region whereas particles with aerodynamic diameters below 1-5 µm are most likely to settle in the tracheobronchial or pulmonary regions.
Penetration of PPE	The proportion of a veterinary medicinal product that by-passes the PPE, e.g. by soaking through seams and zips, being drawn in at neck, cuffs and ankles by the "bellows effect", that gets inside protective gloves by them being donned with contaminated hands.
Permeation of PPE	The migration of the veterinary medicinal product through the PPE barrier, e.g. a solvent-based product through latex gloves.
Personal protective equipment (PPE)	PPE includes head, eye, respiratory (RPE), body, hand, and foot protection that is designed to protect the wearer from exposure. PPE is sometimes also referred to as Individual Protective Equipment (IPE).
Professional user	Persons for whom the administration of veterinary medicinal product is part of their professions (e.g. veterinarians, farmers, breeders), or persons who may come into contact with residues of veterinary medicinal products as a result of carrying out their professions (e.g. sheepshearers). They are trained and skilled in the main objectives of their occupation and may have some experience and skill in the use of the personal protective equipment (PPE) if that is necessary for their normal work.
Stochastic	Being or having a random variable.
Uncertainty factors	Factors used to adjust for multiple sources of uncertainty encountered in using experimental animal data for predicting effects on humans, such as intraspecies variation and interspecies variation.

11 References

Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products. Official Journal of the European Communities L 311/1.

IPCS (2001) Glossary of key exposure assessment terms.

WHO (2001) Guidance document for the use of data in development of chemical-specific adjustment factors (CSAFs) for interspecies differences and human variability in dose/concentration response assessment. Report WHO/PCS/01.4.

Appendix I - Examples

Some examples of defined tasks and situations that may lead to exposure are given below, based on the type of product. These examples have no binding force. The use of different products of the same type may cause different exposures. Therefore, the exposure situations (and corresponding exposure scenarios) must be established for each single application for marketing authorisation.

Example 1: Flea collar

	Pre-application phase	Application phase	Post-application phase
Professional user	None	1. Fitting the collar around the neck of the animal	2. Removing the collar from the animal and disposal of the collar 3. Contact with the fur of animals wearing a collar
Non-professional user	None	4. Fitting the collar around the neck of the animal	5. Removing the collar from the animal and disposal of the collar 6. Stroking the fur of the animal

In this example you see that only the tasks are identified. For each numbered item (task) under "application phase" and "post-application phase" an exposure scenario has to be described. Note that the tasks and situations for professionals and non-professionals are similar, but that the exposure scenarios can be different in terms of type of user, interval, frequency, etc. For example: Situation number 3 involves a veterinarian or a breeder who has contact with different treated animals during working hours. Only dermal exposure to residues on the fur is anticipated. Situation number 6 involves contact of a pet-owner and persons living in the same building (including children) with one or more treated pets during the whole day. Dermal exposure to residues on the fur is anticipated, but in the case of children a part of the dermal exposure is taken up orally due to hand-to-mouth contact.

Example 2: Powder for administration through drinking water

	Pre-application phase	Application phase	Post-application phase
Professional user	1. Storage	2. Opening bags 3. Shake the bags out in a small container with water 4. Stirring/mixing to dissolve the powder 5. Pour out the solution into the main tank of the drinking water system	6. Disposal of bags and unused material
Non-professional user	None	None	None

Also in this example it is shown that the tasks are identified. Based on each task, exposure scenarios have to be established as described in paragraphs 4.3.1 through 4.3.5 of this guideline. Note that with one task, different routes of exposure can be involved, for example task number 3 may lead to dermal, ocular, and inhalation exposure of the powder (and possibly also oral exposure to the non-respirable fraction of the powder). Note also that with different tasks users can be exposed to different components of the product: the powder (tasks 2, 3, 6), a concentrated solution (tasks 3, 4, 5), or the final solution (task 5).

Appendix II – Exposure factors

To calculate the concentrations and/or amounts of a substance or a formulation for the quantitative exposure assessment, exposure factors are to be considered. Examples of exposure factors are:

- bodyweights (adults/children),
- body (parts) surface areas (adults/children),
- respiratory rates / volumes,
- percentage of a dermal exposure loading that is ingested as result of hand-to-mouth contact,
- size and volume of a room,
- size and volume of a stable (cattle/pig/broiler/laying hens),
- ventilation rates of rooms and stables,
- dip tank volume.

This guideline does not provide standard values for such exposure factors.

Values for exposure factors can be found in e.g.:

Appendix II of part I of the second edition Technical Guidance Document in support of Commission Directive 93/67/EEC on Risk Assessment for new notified substances, Commission Regulation (EC) No 1488/94 on Risk Assessment for existing substances and Directive 98/8/EC of the European Parliament and of the Council concerning the placing of biocidal products on the market.

(available on http://ecb.jrc.it)

- the Exposure Factors Handbook of the EPA (http://www.epa.gov/ncea/pdfs/efh/front.pdf)
- Exposure Factors Sourcebook for European Populations (with Focus on UK Data) from Ecetoc (can be ordered at http://www.ecetoc.org)

The values for exposure factors given in the references above can be used for the exposure assessment, but have no binding force: it is possible to deviate from these values provided that alternative choices are adequately justified.