Joint FAO/WHO Expert Committee on Food Additives (JECFA)

Guidance document for the establishment of Acute Reference Dose (ARfD) for veterinary drug residues in food

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1. Introduction

This document provides guidance on when it is necessary and how to establish an oral acute reference dose (ARfD) for residues of veterinary drugs.

The safety of veterinary drug residues in human food is typically assessed based on results from studies in laboratory animals. Human data, when available, and results from *in vitro* and *in-silico* studies are also considered in this safety assessment. Because humans can be exposed chronically to veterinary drug residues through consumption of food, and because chronic exposures often have a lower threshold for toxic response than infrequent or acute exposures, residues of veterinary drugs in food are routinely evaluated for effects following chronic exposures, and a corresponding acceptable daily intake (ADI) is established. The ADI provides a human health-based guidance value (HBGV) for chronic or long-term exposures to residues in food, and is most often established from a point of departure (POD, e.g., no-observed-adverse-effect level (NOAEL)) identified from repeated-dose exposure study(ies) in experimental animals.

In some instances, there is a potential for veterinary drug residues to cause adverse effects in humans following only a single meal**.** A historical example of this was the acute intoxication by clenbuterol shortly following consumption of veal liver or lamb and bovine meat in Europe (Pulce et al., 1991; Salleras et al., 1995; Sporano et al., 1998; Barbosa et al., 2005). For a product that is given by injection to food producing animals, acute manifestations of toxicity resulting from the ingestion of the entire injection site that contains high residues in a single meal is another possibility (Sanquer et al. a&b, 2006). A further possibility is that people on a special occasion/event or a subpopulation may consume a large portion of food derived from an edible tissue where the veterinary drug residues may be more concentrated. In such cases, the ADI, though protective, may not be the most appropriate value for quantifying the level above which a single exposure (after a single meal or during one day[1]) can produce adverse effects. Establishment of a HBGV based on acute effects, the ARfD, provides an appropriate approach to address this concern.

The ARfD approach has been developed to provide a HBGV for chemicals, when their toxicological profile is such that they have the potential to cause adverse effects following acute or short-term exposures in humans consuming food containing residues. There are a number of existing guidelines and publications describing the derivation of an ARfD; however, they are neither specific in addressing veterinary drug residues (EHC 240, 2009; Solecki et al., 2005; JMPR, 2004; EU, 2001; OECD, 2010), nor provide guidance regarding when there is a need to and how to determine an ARfD for veterinary drug residues (VICH GL #54, 2016).

This guidance document is developed based on existing ARfD guidance (Solecki et al., 2005; EHC 240, 2009; VICH GL #54, 2016) and in consideration of features of veterinary drugs that are different from pesticides or other chemicals (microbiological effects and specific exposure scenarios). Some veterinary drugs, unlike pesticides, are designed to specifically target mammalian pharmacology, and the intended effect of the drug in the target animal species may be regarded as an unwanted/adverse effect in human consumers. A number of veterinary drugs are derived from or started as human drugs and, in such cases, in addition to toxicity data from laboratory animals, information on pharmacology and human clinical data (oral or non-oral routes) is available. Some veterinary drugs are derived from or started as pesticides and, therefore, an ARfD may already exist for such compounds, and can be used in the acute risk assessment for its use as a veterinary drug. For antimicrobial drugs, microbiological assessment of potential adverse effect(s) on the human gastrointestinal microbiota is also needed.

[1] "during one day" still refers to a single exposure but is worded like this to be consistent with how the consumption data were collected.

The document below discusses in Section 2, when an ARfD is necessary, Section 3, how to establish an ARfD, Section 4, exposure considerations, and Section 5, how to apply the ARfD in risk assessment and when recommending maximum residue limits (MRLs).

2. When an ARfD is Necessary

JECFA WHO experts should routinely evaluate both the acute and chronic effects of veterinary drugs that could give rise to residues in food. The results of this evaluation and consideration of specific end-points of toxicity, pharmacology and antimicrobial activity are the initial key determinants in deciding whether it is necessary to establish an ARfD. While focused on pesticide residues, considerations on when it is appropriate to establish an ARfD are well discussed in EHC 240 (2009), Section 5.2.9, Setting acute reference doses (ARfDs).

Similar to pesticides (Solecki et al., 2005), the decision in determining the necessity for establishing an ARfD for residues of a veterinary drug should be based mainly on the hazard profile of the veterinary drug under assessment, with consideration of the following:

- Whether an effect(s) relevant or potentially relevant for acute (a single oral dose) exposure is identified.
- Whether substance-related mortalities are observed at doses up to 1000 mg/kg bw. If mortality is the only effect, can the cause of death be shown to be relevant to human exposure?
- When no substance-related mortalities are observed, has there been exposure up to at least 1000 mg/kg bw after oral administration?

In addition, on a case-by-case basis, unique conditions of use that may result in high acute exposure to residues (e.g. injection site residues) should be considered.

It is noted that misuse or off-label use of compounds is not within the scope of considerations for establishing an ARfD, just as they are not for establishing an ADI for chronic risk assessment.

2.1 Cut-Off for the ARfD for Toxicological and Pharmacological Effects

It makes little sense to spend the time and effort to establish an ARfD when the acute toxicity is so low (i.e., the threshold or POD of the acute toxicological endpoint is so high) that it would not give rise to any concern even at the upper limit of human consumption. Similarly, as the ARfD will never be lower than the ADI (see Section 3.6 below, and EHC 240 (2009), Section 5.2.9.2), there is no concern when high exposure does not exceed the ADI. Therefore, a conservative cut-off value for the ARfD could be determined based on practical considerations on high percentile human consumption and maximum residue levels in food.

The JMPR has proposed a cut-off of 5 mg/kg bw for acute toxicity of pesticides in humans, above which an ARfD would not be necessary. This equates to a POD of 500 mg/kg bw in animal studies with the application of a default uncertainty factor of 100 (See EHC 240 (2009), p. 5-45 and Solecki et al. (2005), p. 1573-1574).

The JMPR proposed this cut-off taking into account the range of established MRLs for pesticides, consumption of a large portion of food from plant origin, the relatively high consumption of food by children in relation to their bodyweight, and the observed unit-to-unit variability in pesticide residue data.

Using the same principles, a corresponding calculation was undertaken for veterinary drugs. This was based on the highest MRLs/tolerances established by Codex, EU and USA

and the 97.5th-percentile highest consumption (consumer only, on one day) for each edible tissue. This resulted in an upper bound exposure estimate of 0.3 mg/kg bw [20 mg/kg (the highest MRL) x 15 g/kg (the 97.5th-percentile highest consumption for kidney tissue)]. It is therefore concluded that, allowing for uncertainty in this estimate, a cut-off value of 1 mg/kg bw would be appropriate for establishing an ARfD for residues of veterinary drugs. Although this is lower than the cut-off value established by the JMPR, in the interest of harmonization because of the dual use of some compounds as both pesticides and veterinary drugs, it is concluded that a cut-off value of 5 mg/kg bw for acute toxicity of residues of veterinary drugs in humans should be used, recognizing that this is very conservative for veterinary drugs. This value should be reconsidered if the JMPR revise their cut-off value.

2.2 Unique Conditions of Exposure

2.2.1 Exposure to residues in injection sites

There is a general agreement among the international regulatory community that injection sites offer a different pattern of exposure to the human consumer than other edible tissues (Reeves, 2007). Injectable drugs are typically administered as one or two injections to the same part of the body of the treated animal (often into low retail value meats, such as the neck). Because injection sites always at least start with a high concentration of veterinary drug residues, and injectable products may be only slowly absorbed, consumers ingesting the injection site muscle are potentially exposed to appreciably higher residues than consumers ingesting other muscle tissue. Hence, while the injection site comprises only a small fraction of the total volume of edible muscle, reducing the likelihood of consuming an injection site in any given meal, it also offers the risk of higher exposure to residues than from other edible tissues. This means that an acute risk assessment based on average dietary patterns may not adequately address this scenario. In this particular case, the residue evaluation would lead to the consideration of the need to establish an ARfD.

2.2.2 Exposure of the intestinal microbiota

There are distinct differences in intestinal microbiota exposure to drug residues following acute intake of microbiologically active drug residues as compared to that following continuous chronic daily ingestion (microbiological ADI) (Cerniglia et al., 2016). The acute intake of microbiologically active drug residue would result in a single exposure wherein the dose is ingested as a one-meal time event and transits down the gastrointestinal tract into the colon, which would contain no other ingested residue of the drug. In the case of chronic exposure to microbiological active drug residue, there is an assumption of ingestion of the drug every day, i.e., each day the ingested meal enters into an intestinal tract that already has drug spanning the intestine due to ingestion from the day before, present at a “steady state” over a lifetime. Thus the exposure of intestinal bacteria to microbiologically active drug concentrations in vivo from an acute dose will be lower than that occurring for chronic ingestion. Therefore, the application of the formula for the microbiological ADI derived from in vitro data specified in VICH GL 36(R) would overestimate the acute effects on the colon microbiota after a single exposure. Available data show that a meal does not transit through the intestinal tract as an intact bolus as is conservatively assumed in microbiological ADI calculations. There is a sequential process of stomach and small intestine loading, transit and emptying, leading to a colonic entry that occurs as a series of small pulsed doses over time (Pišlar et al., 2015). This process of physical and temporal dilution of the ingested meal throughout the gastrointestinal tract is supported by data from Camilleri et al. (1989) in which the movement of radiolabeled pellets and fiber were monitored through the human gastrointestinal tract in healthy volunteers. The study shows that when 10% of the radiolabel is in the colon, ~20% of the radiolabel is in the stomach and ~70% in the small bowel, indicating that the radiolabel is spreading out over the gastrointestinal tract and is not moving as a single bolus dose. Collectively, studies show (Camilleri et al., 1989; Proano et al., 1990; Read et al., 1986) that materials enter the colon in a continuum, not as a single bolus, with

colonic fill starting as early as 1-5 hours of an oral dose leading to roughly 80-90% loading within 12 hours. Excretion also begins within 12 hours with mean total transit times in the order of 24-40 hours (Maurer et.al 2015; Wilson, 2010; Fleming, 1983; Proano, 1990), during which time there will be ingestion of two or more additional (non-residue containing) meals. The above considerations that dietary components contained within a single meal do not enter the colon as a single bolus dose but in a gradient would suggest that the use of a dilution correction factor in the numerator of the formula used in deriving the ARfD for microbiological effects would be necessary. JECFA experts suggested that the inclusion of a dilution correction factor of 3 (i.e., three meals per day) in the numerator of the formula would be appropriate.

3. How to establish an ARfD

The JMPR has established a process for establishing an ARfD for residues of pesticides, as described in detail in EHC 240 (2009) and OECD (2010). A similar procedure should be followed in the case of evaluating residues of a veterinary drug. Much of the text in this section is taken from the above sources, where further details can be obtained.

In general, specific studies of the acute toxicity of veterinary drugs will not be available, though for pharmacological and microbiological effects it is more likely such information is available (see section 3.3 below). Hence, it is often necessary to utilise toxicological information from repeat dose toxicity studies to establish an ARfD. The appropriateness of using the end-point from a short-term or long-term study to establish an ARfD needs to be carefully considered. The biology of the system affected should be reviewed to determine the plausibility that acute exposure could result in the effect observed, or could compromise the ability of the organ to compensate and maintain homeostasis. Particular attention should be paid to observations and investigations at the beginning of repeated dose studies (i.e., after one or a few days). Whilst these may not form the basis of the NOAEL for the study, they could still be considered as the POD for establishing an ARfD. It is important to distinguish between minor or adaptive changes, which may be observed early in a study, and adverse effects. As when establishing an ADI, the toxicological significance of isolated findings showing no specificity or clear relationship to dose should be considered carefully. In the absence of information to the contrary, all toxic effects seen in repeated-dose studies should be evaluated for their relevance in establishing an ARfD (i.e., the likelihood that they could occur after a single dose). The toxicological end-points to which such considerations apply are described in OECD (2010). The POD (e.g. NOAEL) from the most sensitive species should be used, unless there is evidence to demonstrate that it is not appropriate for human risk assessment. The overall process is illustrated in Diagram 1 of the Appendix.

3.1 Stepwise process for establishing an ARfD for toxicological and pharmacological effects

The first step is to consider whether, on the basis of the acute toxicity profile and potency of effects as well as the likelihood of acute exposure, an acute HBGV is necessary. The following stepwise process for establishing an ARfD is suggested:

Step 1. Evaluate the total database on the substance and establish a toxicological and pharmacological profile for the active substance

This should include any information on structure-activity relationships, such as compound class, and the results of non-animal testing that may indicate specificity for a relevant biological target, such as an enzyme or receptor.

Step 2. Consider the principles for when it is not necessary to establish an ARfD

- The substance is not an antimicrobial, or the substance is an antimicrobial, but the answer to steps 1, 2, or 3 of the decision tree described in section 3.2.2.1 is no; and

- No findings indicative of effects elicited, or that might be elicited, by an acute exposure are observed at doses up to 500 mg/kg bw (POD in test animals); and
- No substance-related mortalities are observed at doses of up to 1000 mg/kg bw in a single-dose study after oral administration; If mortality is the only trigger, the cause of death should be confirmed as being relevant to human exposure; and
- Exposure to residues through consumption of an injection site does not exceed 5 mg/kg bw, in accordance with good practice for the use of veterinary drugs (GPVD), that is at the established regulatory withdrawal period according to the approved labeled use.

If the above criteria do not exclude the need to establish an ARfD, then consideration should be given to establishing an ARfD, using the most appropriate end-point. If the establishment of an ARfD is not necessary, the reason must be provided and clearly explained.

Step 3. Select an appropriate end-point for establishing an ARfD

- Identify the toxicological and pharmacological end-points that are (or could be) relevant for a single (day) exposure.
- Select the most relevant study(ies) in which these end-points have been adequately assessed.
- Identify the NOAELs or other PODs for these end-points.
- Select the relevant end-point providing the lowest NOAEL or other POD.
    - Use an end-point from a repeated dose study of toxicity if the critical effect of the compound has not been adequately evaluated in a single-dose study, but effects seen in a repeated dose toxicity study could reasonably have occurred after a single dose. The use of a repeated-dose toxicity study is likely to be a more conservative approach and use of this approach should be stated to provide an indication that refinement may be possible (e.g. in a special single-dose study).
- Where there is high exposure from the injection site, the database should be assessed for potential acute effects at doses above the cut-off value which may necessitate establishing a particularly high ARfD to ensure protection from exposure from injection site residues.
- If, after consideration of all the end-points, it is not necessary to establish an ARfD, this should be justified and clearly explained.

Step 4. Select appropriate uncertainty factors and establish the ARfD
See Sections 3.4 and 3.5.

3.2 Process for deriving the ARfD for microbiological effects

The VICH GL36(R) (2012) provides for a stepwise process to lead to a decision on what microbiological endpoints are needed and provides guidance on how a number of different methodologies and databases can be used to derive a microbiological ADI. The evaluation process has been captured in EHC 240 (2009) but does not reflect the changes provided to the VICH GL36(R) in 2012. While many of the same principles apply in deriving a microbiological ARfD, acute exposure of the intestinal microbiota following acute ingestion of residues is different from that following the chronic daily exposure that the JECFA

evaluates to establish the microbiological ADI as discussed above; the most relevant microbiological end-point for acute exposure would be disruption of the colonization barrier. It is considered that a single exposure to residues of veterinary drugs is unlikely to provide the selective pressure necessary to change the susceptibility of the bacterial population within the microbiome (i.e., antimicrobial resistance).

3.2.1 Derive the microbiological ADI following the EHC 240 process

VICH GL36(R) (2012) states that the guidance provides a "*process for determining if a microbiological ADI is appropriate and discusses test systems that take into account the complexity of the human intestinal flora. These test systems could be used for addressing the effects of antimicrobial drug residues on human intestinal flora for regulatory purposes*" and that: "*it does not limit the choice of studies that may be performed to establish the safety of residues in human food with respect to adverse effects on human intestinal flora. This guidance does not preclude the possibility of alternative approaches that may offer an equivalent assurance of safety, including scientifically based reasons as to why microbiological testing may not be appropriate.*"

For purposes of deriving a microbiological ARfD, the principles outlined in the guidance for deriving the microbiological ADI will also be applicable. However, since the guidance was issued, a number of studies have been published describing new genomic technologies, which can be considered for this purpose (see Ahn et al., 2012a,b,c; Lagier et al., 2012), as the guidance takes into account that the science continues to advance.

The microbiological ADI calculation, based on *in vitro* data, for chronic daily ingestion includes the assumption that the colon volume is 220 ml (mass of colon content of 220 g). This mean value of 220 g used in the formula (EHC 240, 2009) is based on necropsy data of 17 accident victims (Cummings et al., 1990). A summary of the historical source of the 220 g value was provided by Cerniglia and Kotarski (1999 & 2005). More recently, studies using state-of-the-art imaging technology to determine colonic volumes have indicated that the hydrated colon of healthy individuals is larger than the 220 g estimate. For example, Pritchard et al. (2014) showed using 3D abdominal magnetic resonance imaging techniques that the 220 g estimate represents approximately the lower 95th percentile of colon volumes among 75 fasting human volunteers (31 males and 44 females). Pritchard's mean value of 561 ml for the colon volume based on the combined volumes of the ascending colon, transverse colon and descending colon with ranges of 76 to 390, 50 to 541 and 54 to 558 ml, respectively, provides a more robust estimate. This is still a conservatively low estimate of colon volume, because the measured volumes did not take into account the volume of the lower sigmoid colon section as the observations were from fasting individuals. .

A survey of the literature (Khashab et al., 2009; Badley et al., 1993; Linstedt and Schaeffer, 2002; Nilsson, 2015) supports the robustness of the study by Pritchard et al. (2014) and brings into question whether the 220 g value that is currently accepted as a conservative value for deriving a microbiological ADI is an appropriate value to be used. The study by Pritchard et al. (2014) uniquely provides calculations of the volume for segments of the colon in 75 healthy individuals. Based on this recent information, it was concluded that a more appropriate value for the colon volume would be 500 ml (conservatively rounded down from 561 ml). However, it is possible that a higher value would be justified after a thorough evaluation of available literature to confirm or increase this value. It is recommended that the JECFA secretariat organize this review and bring specific recommendations to the next JECFA meeting.

The formulas for the calculation of the microbiological ADI and microbiological ARfD have been modified to reflect this revised estimate of colon volume.

3.2.2 Steps in determining a POD for a microbiological ARfD when necessary

Steps 1-5 in EHC 240 (2009) are applicable to determine whether a microbiological ARfD is needed and are quoted below:

When determining the need for a microbiological ARfD, the following sequence of steps is recommended. The data may be obtained experimentally or from other appropriate sources such as scientific literature. Steps 1-3 are the same as those used for determining the need for establishing a microbiological ADI (VICH GL 36(R)).

Step 1. Are residues of the drug, and (or) its metabolites, microbiologically active against representatives of the human intestinal flora?

Recommended data are MIC data, obtained by standard test methods, from the following relevant genera of intestinal bacteria (*E. coli*, and species of *Bacteroides, Bifidobacterium, Clostridium, Enterococcus, Eubacterium* (*Collinsella*), *Fusobacterium, Lactobacillus, Peptostreptococcus/Peptococcus).*

It is recognized that the understanding of the relative importance of the microbiome to human health and disease is incomplete and that the variability of the intestinal microbiota within and between individuals can change due to environmental conditions. The selection of test organisms should take into account current scientific knowledge.

If no information is available, it is recommended to assume that the compound and (or) its metabolites are microbiologically active.

Step 2. Do residues enter the human colon?

Recommended data are absorption, distribution, metabolism, and excretion (ADME), bioavailability, or similar data that may provide information on the percentage of the ingested residue that enters the colon.

If no information is available in humans, it is recommended to use appropriate animal data. If there is no available information, it is recommended to assume that 100% of the ingested residue enters the colon.

Step 3. Do the residues entering the human colon remain microbiologically active?

Recommended data are data demonstrating loss of microbiological activity from *in vitro* inactivation studies of the drug incubated with feces or data from *in vivo* studies evaluating the drug's microbiological activity in feces or colon content of animals.

If the answer to any of questions in steps 1, 2, or 3 is "no", then the ARfD should not be based on microbiological endpoints and the remaining steps are not necessary.

Step 4: By default, disruption of colonization barrier will be the basis for a microbiological ARfD. The emergence of resistance would not normally be evaluated unless there is an indication that there is a concern following a single exposure.

Step 5. Determine the NOAECs/NOAELs for the endpoint(s) of concern as established in step 4. The most appropriate NOAEC/NOAEL should be used to determine the microbiological ARfD.

3.3 Specific endpoints that should be considered when establishing an ARfD for residues of a veterinary drug

A number of effects could be caused by a single exposure. The relevance of these effects for establishing an ARfD should be considered on a case-by-case basis. The route and method of substance administration should be considered carefully in order to exclude effects not relevant for the intake of residues (e.g. effects induced specifically by gavage or by a specific vehicle or formulation used).

As indicated below, where an effect is observed in a repeated dose study, this should be evaluated carefully to determine whether there is evidence for induction early in the study, such as interim measurements or determination of precursor effects (e.g. clinical chemistry). If not, biological plausibility for the possibility of induction after acute exposure should be considered on a case-by-case basis.

A list of possible target effects following acute exposure is provided below. This is not intended to be an exhaustive list (see Solecki et al., 2005 for detailed guidance).

- Haematoxicity

  The induction of methaemoglobinaemia is regarded as a critical effect in consideration of the acute response to chemical exposure. In the case of haemolytic anaemia, consideration needs to be given as to whether the severity of such an effect after acute exposure is likely to be such that it would be necessary to establish an ARfD.

  Acute haemolytic anaemia
  - Mechanical damage
  - Immune-mediated anaemia
  - Oxidative damage of the red blood cells
  - Non-oxidative damage
  - Effects on circulating cells and precursor cells.

- Immunotoxicity

  Immunotoxicity data derived from repeated dose studies are unlikely to be appropriate for establishing an ARfD for acute adult exposure limits, because immune system cells are constantly replaced and because of inherent redundancy in the system.

- Neurotoxicity

  Any neurotoxicity (including neurobehavioral effects) observed in repeated dose studies could be the result of a single exposure; hence, any evidence of neurotoxicity should be considered relevant to establishing an ARfD, unless it can be demonstrated that the effects are produced only after repeated exposures.

- Hepatotoxicity/nephrotoxicity

  If effects on these organs cannot be shown to be either adaptive or the result of prolonged (repeated) exposure, an ARfD should be established on the basis of such effects. Such an ARfD is likely to be conservative, and it may be possible to subsequently refine it using an appropriately designed single dose study or by additional measurements in a repeated dose study undertaken for another purpose.

- Endocrine/hormonal effects

  In general, adverse effects on the endocrine system observed in routine toxicological testing for regulatory purposes, other than those affecting female reproduction and development of the offspring, are considered unlikely to arise as a consequence of acute exposure. However, exceptions may occur, and a case-by-case assessment is required.

- Reproductive and developmental effects

  Any treatment-related adverse effect on embryos, fetuses or offspring that results from exposure during any phase of development should be considered as potentially appropriate for establishing an ARfD, despite the fact that the treatment period typically consists of repeated dosing, as it could be the result of a single exposure during a critical window of development. Other effects on

reproductive outcomes should be assessed on a case-by-case basis for the plausibility that they could occur after a single exposure.

- Pharmacological effects

  Many veterinary drugs have a specific mode of action that is not relevant for humans (e.g. effects on chitin synthesis by antiparasitic substances). However, other veterinary drugs designed to act on the physiology of target animals (e.g. mammals) are likely to have a mode of action that is also relevant for humans. In addition, the desired effect of the veterinary drug in the target animal may be considered to be an adverse effect for the consumer exposed to residues of veterinary drugs. Therefore, pharmacological effects, i.e., those effects caused by the pharmacological mode of action of the molecule, are relevant for consumer safety and hence, for the establishment of an ARfD.

  Pharmacological effects (i.e., interaction with molecular targets (e.g. receptors) have not been considered in the context of the ARfD by EHC 240 (2009), Solecki (2005), or OECD (2010). Such effects do not automatically raise an acute health concern, but need to be considered for acute and chronic health effects, in the same way as for toxic effects. In practice, this may lead to the same numeric value for the ADI and ARfD. Further guidance on consideration of pharmacological endpoint is given below.

  For the evaluation of pharmacological effects, careful consideration should be given to the mode of action of the veterinary drug. In some cases, the mode of action can involve a number of different effects on physiological systems. For example, catecholamines (acting on the adrenergic system) can have acute effects on airways, blood pressure and heart rate. In those cases, it is recommended that the study be designed with observations at appropriate time points to cover the range of effects arising from the mode of action. The evaluator should pay particular attention to the appropriateness of the observation time(s), as they may not be the same as for other toxicological endpoints. For example, if the plasma levels peak at 2 h after oral administration, then it would make no sense to do the measurements at 24 h after dosing. This is particularly important for direct, reversible, receptor-mediated effects, such as the effects described above for catecholamines.

  Examples of pharmacologically active substances and their pharmacological class, mode of action, and possible pharmacological endpoints are provided in Table 1 below.

Table 1: Examples of pharmacologically active substances

Substance	**Class**	**mode of action**	**Possible pharmacological endpoint**
acetylsalicylic acid	NSAID	• Inhibition of cyclo-oxygenase • Systhesis of prostanoids • Inhibition of thromboxanes synthesis	Inhibition of thromboxane B2-production
Azaperon	Neuroleptic	• Alpha-receptor blocker • Dopamine receptor blocker	Norepinephrine antagonism
beclamethasone dipropionate	Synthetic glucocorticoid	• HPA axis suppression • anti-inflammatory – lipocortin I, p11/calpactin binding protein, secretory leukoprotease inhibitor 1 (SLPI), and Mitogen-activated protein kinase phosphatase (MAPK	Changes in corticosterone concentration

Substance	Class	mode of action	Possible pharmacological endpoint
		phosphatase) • increased gluconeogenesis – glucose-6-phosphatase and tyrosine aminotransferase	
Carazolol	beta-adrenergic blocking agents	• Heart rate reduction • Bronchoconstriction • Blood vessel dilatation	Inhibition of isoxuprine-induced tachycardia in rabbits
Chlormadinon	Synthetic progesterone analogue	• GnRH inhibition • Endometrium proliferation	Endometrium proliferation in oestrogen-pre-treated rabbits (Clauberg-McPhail test)
chlorphenamine	Histamine H_1-receptor antagonist	Inhibition of histamine production	Anaphylactic shock protection in guinea pigs
Clenbuterol	$Beta_2$-sympaticomimetic agent	• Bronchodilatation • Tocolytic action • Tachycardia	Bronchospasmolysis in human volunteers
Furosemide	Diuretic	• Reduced chloride re-absorption in kidneys • Increased PGE2 production	Urine output and sodium/potassium/chloride excretion in dogs

[1]The examples of pharmacological endpoints are based on the MRL evaluations of these substances performed by the European Medicines Agency (EMA), Committee for Medicinal Products for Veterinary Use (CVMP).

- Microbiological effects

  Many of the principles contained within EHC 240 (2009) in the context of determining a microbiological ADI are applicable in addressing the microbiological endpoint due to acute exposure. However, it should be recognized that EHC 240 (2009) chapter 4 does not specifically address derivation of a microbiological ARfD, and there can be differences between the two evaluations for a particular antimicrobial agent, as explained above.

- Other endpoints/findings

  Direct effects on the gastrointestinal tract should be assessed carefully to determine their relevance to human dietary exposure. Considerations would include whether they are due to irritation or a pharmacological effect (which would be relevant to establishing an ARfD) or whether they are related to the method of administration (e.g. only with bolus dosing but not with incorporation into the diet). Similarly, diarrhoea and vomiting in dogs should not be considered as relevant for establishing an ARfD if these effects are related to high concentrations following specific dosing methods (e.g. capsule administration or gavage) and local (irritant) effects. However, if a pharmacological mechanism is involved, this may be relevant.

Other findings, such as clinical signs, changes in body weight/body weight gain, changes in food and/or water intake and mortalities observed after one or several doses in oral repeated dose toxicity studies, may suggest the need to establish an ARfD. When considering whether body weight changes are relevant for establishing an ARfD, consideration should be given to potential problems of palatability of the feed.

Table 2 provides examples of data limitations and options for refinement that would inform the establishment of an ARfD based on observations in repeated dose studies.

Table 2: Effects of potential relevance to establishing an ARfD when observed in repeated dose studies

Endpoint	Relevance for ARfD	Data availability	Data limitations	Options for refinement
Methaemoglobinemia	Very relevant	Routine haematology	Time of sampling	Time of sampling; associated effects
Haemolytic anaemia	Questionable	Routine haematology	Time of sampling	Time of sampling; associated effects; mode of action
Immunotoxicity	Unlikely	Blood cell counts; pathology; possibly specific immune response;	Time of sampling; relevance of data	Time of sampling; specific measures of effect
Neurotoxicity	Probable	Observations; clinical chemistry (ChE); pathology	Time of sampling	Time of sampling; specific measures of effect
Organ toxicity (liver/kidney)	Possible	Clinical chemistry; pathology	Time of sampling	Time of sampling; mode of action
Endocrine/hormonal effects	Unlikely	Blood hormones; pathology; reproductive performance; other functions	Time of sampling; relevance of data; range of hormones measured	Time of sampling; mode of action; measurement of relevant hormones;
Reproductive /developmental effects	Assume developmental effects relevant; other repro effects unlikely	Reproductive and developmental outcomes	Duration of dosing	Mode of action; selective dosing periods
Body weight changes	Possible, but only if some evidence for possible acute effect	Absolute weight and rate of change	Time of measurement	Time of measurement; mode of action

3.4 Uncertainty factors for ARfD

The process for establishing an ARfD is essentially the same as that for establishing an ADI, involving the identification of the most appropriate POD and application of uncertainty factors, usually 100-fold for data from studies in experimental animals or 10-fold for data from studies in humans, respectively. Uncertainty factors are used to extrapolate from animals to the average human and to allow for variation in sensitivity within the human population. The default factor of 10 for extrapolating from laboratory animals to humans can be subdivided into 2.5 for toxicodynamics and 4 for toxicokinetics, whereas the default human variability factor of 10 can be subdivided into identical factors of 3.2 for toxicokinetics and toxicodynamics, as described by IPCS (2005) under the concept of chemical-specific adjustment factors (CSAFs).

As with the ADI, a number of other situations may justify the use of uncertainty factors higher or lower than the default values of 100 or 10 when establishing an ARfD. For

example, data on absorption, excretion and plasma kinetics, together with information on the mode of action, may help to assess whether effects are likely to be related to peak concentration ($C_{max)}$ or plasma concentration integrated over time (area-under-the-curve (AUC)). Human toxicity or pharmacology data are available for some veterinary drugs and these can be used either directly to establish an ARfD or to inform the derivation of CSAFs.

When the effect of concern is due to reversible interaction of the drug with a pharmacological target (e.g. a receptor, ion channel), then the concentration of the substance rather than total exposure usually determines the magnitude of the effect (i.e., C_{max} is likely to be more relevant than the AUC). In such cases, there will be less interspecies and inter-individual variation in plasma kinetics, as absorption varies less than clearance; this might justify a reduction in the respective uncertainty factors. JMPR has used reduced safety factors for both inter-species and inter-individual variability in the plasma kinetics of several carbamate insecticides that inhibit acetylcholinesterase, leading to an overall composite factor of 25 for extrapolation from animal studies (i.e., 5 × 5 instead of 10 x 10 for interspecies and intraspecies factors) and 5 (instead of 10) for human studies. When using categorical factors in this way to establish an ARfD, a full justification for their use must be provided.

Where human data are available but are not sufficient to be used directly in establishing an ARfD, they might nevertheless be of value in determining quantitative differences between experimental animals and humans in the kinetics or dynamics of the compound enabling the calculation of data-derived CSAFs (e.g. data on the production and degradation of a toxic metabolite).

A reduced uncertainty factor might be appropriate if the end-point used to establish the ARfD is of minimal adversity and the critical NOAEL is from a repeated dose study (e.g. increased organ weight with minimal pathological change, or reduced food consumption and body weight gain observed in the first few days of dosing), as the use of such an endpoint to establish an ARfD is very likely to be conservative. Again, any change in the uncertainty factor used must be fully justified.

Situations where additional uncertainty factors might be used are the same as those when establishing an ADI. These include when a NOAEL has not been identified for the most appropriate end-point, and the LOAEL is used as the basis of the ARfD; the severity of the effect; incompleteness of the database. Full details can be found in EHC 240 (2009).

In determining the appropriate uncertainty factors for establishing an ARfD, a stepwise approach is recommended:

- Determine if the data are adequate to support the derivation of CSAFs.
- If CSAFs cannot be derived, consider if there is any other information available that might help assess the magnitude of the uncertainty factor necessary (could this be greater than or less than the default). If not, default factors of 10-fold or 100-fold should be used, as appropriate.
- Whenever an uncertainty factor other than the default is used, a clear justification of the derivation of the factor should be provided, together with the supporting evidence for the choice.

3.5 ARfD calculation (see Diagram 1 of the Appendix)

(1) When a toxicological or pharmacological effect(s) serves as the basis of the POD, the ARfD is determined as follows:

$$ARfD = \frac{POD}{Uncertainty\ Factor}$$

Where:

- **The POD** is the NOAEL, LOAEL, $BMDL_x$, or other appropriate dose parameter;
- **Uncertainty factor** (UF) is the default of 100 when extrapolating from data in experimental animals to humans or 10 when using data from a human study, a CSAF, a categorical or database-derived adjustment factor or some other combination of factors, as justified in the assessment.

(2) When a microbiological effect based on in vitro data (MIC or NOAEC) is used to establish the microbiological ARfD, the following equation is used:

$$microbiological\ ARfD = \frac{(MIC_{calc}\ or\ NOAEC) \times Correction\ Factors\ \times colon\ volume}{Fraction\ of\ oral\ dose\ available\ to\ microorganisms \times 60}$$

Where:

- **MIC_{calc}**, computed the same as in the case of microbiological ADI, represents the lower 90% confidence limit for the mean MIC_{50} of the relevant genera for which the drug is active; the **NOAEC** was determined based on a single acute dosing in an *in vitro* system (e.g. continuous or semi-continuous culture of fecal contents);
- **The colon volume is 500 ml**;
- **The fraction of an oral dose available to colonic microorganisms** is ideally based on in vivo measurements for the drug administered orally. Alternatively, if sufficient data are available, it can be calculated as 1 minus the fraction of an oral dose excreted in urine. Human data are preferable; in their absence, non-ruminant animal data are recommended. In the absence of data to the contrary, it should be assumed that metabolites have antimicrobial activity equal to that of the parent compound. The fraction may be lowered if the applicant provides quantitative in vitro or in vivo data to show that the drug is inactivated during transit through the intestine (see also Appendix D of the VICH GL36(R) document);
- **Correction factors** (where appropriate) take into account considerations not used for the microbiological ADI, but may be appropriate to the microbiological ARfD. This includes a factor of 3 to allow for temporal dilution during gastrointestinal transit and for dilution by consumption of additional meals as explained in Section 2.2.1. Additional factors may be considered, to take into account the inoculum effect on MIC determinations, pH effects on MIC, and possibly other physico-chemical-specific factors of the growth conditions used in testing (e.g. incubation atmosphere, growth substrates/factors that affect growth and metabolism of the tested organisms (Maurer et al., 2015; Cerniglia and Kotarski, 1999 & 2005). For continuous or semi-continuous culture and batch fed culture used in deriving a NOAEC, data from studies of the effects of an acute dose (one-time exposure) of the drug on the intestinal microbiota should be evaluated; however, if this information is not available, then studies of repeated doses or continuous exposure to drug (i.e., after one or a few days of drug added to the test systems) may yield a NOAEC for acute exposure, or may provide sufficient information to derive a correction factor;
- **60** is the standard adult human body weight in kg used by JECFA. This value is necessary so that the colon volume is scaled to body weight, and hence the

mADI is applicable to children, and small and large adults because it is expressed in terms of acceptable daily intake in mg per kg body weight.

(3) When a microbiological endpoint based on a NOAEL from in vivo data is used to establish the microbiological ARfD, the following equation applies:

$$microbiological\ ARfD = \frac{NOAEL}{Uncertainty\ Factor}$$

In establishing an ARfD based on a microbiological endpoint, the following need to be considered and the value adjusted accordingly:

- The VICH GL36(R) recommends uncertainty factors for in vivo studies be assigned as appropriate, taking into consideration the class of compound, the protocol, numbers of donors, and sensitivity of the measured outcome variables. Likewise, such uncertainty factors are applicable in derivation of a microbiological ARfD;
- Were the assumptions and uncertainty factors used in the microbiological ADI applicable for a single exposure? For example, were multiple doses administered to the animals?
- Since microbiological endpoints used in *in vivo* evaluations reflect NOAELs for impacts on the intestinal ecosystem, and not the host species itself, it is not necessary to include an uncertainty factor for interspecies differences, and such an uncertainty factor is not recommended in deriving a microbiological ARfD;
- If the experimental design used repeat dosing to derive a microbiological ADI for chronic exposure, particular attention should be paid to observations and investigations at the beginning of studies (i.e., after one or a few days) as the basis to establish an ARfD, or as the basis for a correction factor.

Where an ARfD established using the approach described above has a numerical value that is lower than the upper bound of the ADI, then the ADI should be reconsidered. In such circumstances, the upper bound of the ADI would normally be established at the same numerical value as the ARfD.

If structure activity considerations, such as compound class, suggest the likelihood of acute effects but adequate data supporting such effects are not available, there are three possible options:

a. Consider using the upper bound of the ADI as a conservative surrogate, based on weight of evidence from the database. Indicate that a conservative value has been used for the ARfD;
b. Advise that it is not possible to establish an ARfD and limit the exposure (through the established MRL) below the upper bound of the ADI;
c. Do not establish an ARfD and do not make a specific recommendation regarding the risk from acute exposure.

In the case of recommendations a and b above, these should be accompanied by an indication of the type of information that would help refine (option a) or establish (options b) the ARfD, as appropriate. For example, this might be possible by conducting an appropriately designed single-dose study. The protocol for a suitable single-dose study of toxicity is outlined as an annex in the detailed OECD guidance document for the derivation of an ARfD (OECD, 2010). However, this should be a last resort, and other approaches, such as read across and non-animal testing methods,

should be explored to the extent possible before embarking on additional studies in experimental animals.

3.6 Establishing an ADI when the critical effect is acute

Given the respective definitions of the ADI and ARfD for residues of a veterinary drug, when the lowest relevant POD is for an acute effect, this should serve as the basis for establishing both a toxicological ADI and a toxicological ARfD, using the procedures described above. Given that in general, GECDE (global estimated chronic dietary exposure) is less than GEADE (global estimated acute dietary exposure**)**, if the GEADE is less than the ARfD, then the GECDE will be less than the ADI (upper bound). Hence, the ARfD and GEADE together should be protective of all exposure durations.

4. Exposure Considerations

Assessing the acute exposure to a veterinary drug implies selecting (1) a relevant high level of consumption which may occur over a single day or a single eating occasion and (2) a relevant high residue concentration. In the absence of a probabilistic model at the international level, the consumption and occurrence levels should be combined in a deterministic way to protect consumers without being overly conservative. The principles for a suitable acute dietary exposure assessment method were described in EHC 240 (2009), and details of the method were proposed in the report of the Joint FAO/WHO Expert Meeting on Dietary Exposure Assessment Methodologies for Residues of Veterinary Drugs held in 2011 (WHO, 2012), which defined GEADE. GEADE should be calculated as follows:

$$GEADE = \frac{97.5^{th}\ percentile\ food\ consumption\ (1\ person) \times high\ residue\ (tissue)}{body\ weight}$$

The relevant food consumption data are collected by FAO and WHO. These figures expressed in grams per kg body weight are available for use by JECFA.

It is noted that the High Residue Level may be the MRL, normally corresponding to the upper one-sided 95% confidence limit over the 95th percentile residue concentration (95/95 upper tolerance limit).

It is noted that the theoretical maximum daily intake (TMDI) is not appropriate for acute dietary exposure assessment. The standard “food basket” amounts used in the TMDI can be lower than the 97.5th percentile food consumption estimates, as stated in EHC 240 (2009). The TMDI calculation is a tool used as a proxy in dietary exposure assessment, in which a standard amount of food is combined with a selected highest residue level.

5. How to Apply the ARfD in Risk Assessment and When Recommending MRLs

MRL recommendations will be such that chronic exposure will not exceed the ADI and are consistent with GPVD. If an ARfD is also established for the compound, an acute exposure assessment (for both the general and specific subpopulations) should be performed based on tissue concentrations at the estimated withdrawal times, and the consequences described in detail. If the ARfD is exceeded in any population, this should be clearly noted in the report and possible refinements of the assessment identified, including options such as the selection of a later time point for the derivation of MRLs to be recommended or refinement of the toxicological endpoint.

Where the ARfD has been established on effects observed in a repeated dose study, refinement of the toxicological endpoint might be possible, for example, by the generation of additional data more relevant to acute exposure.

6. Recommendations

- It is recommended that the JECFA secretariat organize a review of available information on colon volume to confirm or increase the current value of 500 ml, and bring specific recommendations to the next JECFA meeting.
- It is recommended that the JECFA discuss the appropriate risk characterization in situations where both a toxicological and a microbiological HBGV (ADI or ARfD) have been derived. A key issue is the potential impact of the respective residue definition (toxicologically active versus microbiologically active) on the risk characterization.

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8. Glossary of Key Terms

Complete Glossary is available at Environmental Health Criteria 240: Principles and Methods for the Risk Assessment of Chemicals in Food, Annex 1 Glossary of Terms (http://www.inchem.org/documents/ehc/ehc/ehc240_annex1.pdf)

Acceptable daily intake (ADI): ADI is the estimate of the amount of a chemical in food or drinking-water, expressed on a body weight basis, that can be ingested daily over a life-time without appreciable health risk to the consumer. It is derived on the basis of all the known facts at the time of the evaluation. The ADI is expressed in milligrams of the chemical per kilogram of body weight (a standard adult person weighs 60 kg).

Acute exposure: A short-term exposure to a chemical, usually consisting of a single exposure or dose administered for a period of 24 h or less.

Acute reference dose (ARfD): The estimate of the amount of a substance in food or drinking water, expressed on a body weight basis, that can be ingested in a period of 24 h or less without appreciable health risk to the consumer. It is derived on the basis of all the known facts at the time of evaluation. The ARfD is expressed in milligrams of the chemical per kilogram of body weight.

Adverse effect: Change in the morphology, physiology, growth, development, reproduction or lifespan of an organism, system or (sub)population that results in an impairment of functional capacity, an impairment of capacity to compensate for additional stress or an increase in susceptibility to other influences.

Benchmark dose (BMD): A dose of a substance associated with a specified low incidence of risk, generally in the range of 1-10%, of a health effect; the dose associated with a specified measure or change of a biological effect.

Dietary exposure assessment: For residues in veterinary drugs, the qualitative and/or quantitative evaluation of the likely intake of chemicals via food.

Chronic exposure: A continuous or intermittent long-term contact between an agent and a target.

Food consumption: For assessing dietary hazards of residues of veterinary drugs, an estimate of the quantity of a food consumed by a specified population or individual. Food consumption is expressed in grams of food per person per day.

Global estimated acute dietary exposure (GEADE): GEADE is an acute dietary exposure model that provides an explicit estimate of acute exposure. It considers high-level exposure from each relevant food of animal origin individually, that is, the concurrence of the selected high residue concentration in each food to which a consumer might be exposed (e.g. MRL or high residue concentration derived from depletion studies, such as the upper one-sided 95% confidence limit over the 95^{th} percentile residue concentration) combined with a high daily consumption (97.5^{th} percentile) of that food (meat, offal, milk, others).

Global estimated chronic dietary exposure (GECDE): The global estimated chronic dietary exposure (GECDE) to the veterinary drug residue for the population group of interest is the highest exposure calculated using the 97.5th percentile consumption figure for a single food selected from all the foods plus the mean dietary exposure from all the other relevant foods.

Good practice in the use of veterinary drugs (GPVD): The official recommended or authorized usage including withdrawal periods, approved by national authorities, of veterinary drugs under practical conditions.

Health-based guidance value (HBGV): A numerical value derived by dividing a point of departure (a no-observed-adverse-effect level, benchmark dose or benchmark dose lower confidence limit) by a composite uncertainty factor to determine a level that can be ingested over a defined time period (e.g. lifetime or 24 h) without appreciable health risk.

MIC_{50}: The minimum inhibitory concentration for 50% of strains of the most sensitive relevant organism.

Microbiota: The microorganisms that typically inhabit a particular environment, such as the gastrointestinal tract.

Microbiome: The collection of microbes (bacteria, archaea, fungi, viruses and single-cell eucaryotes) that live within and on the human body.

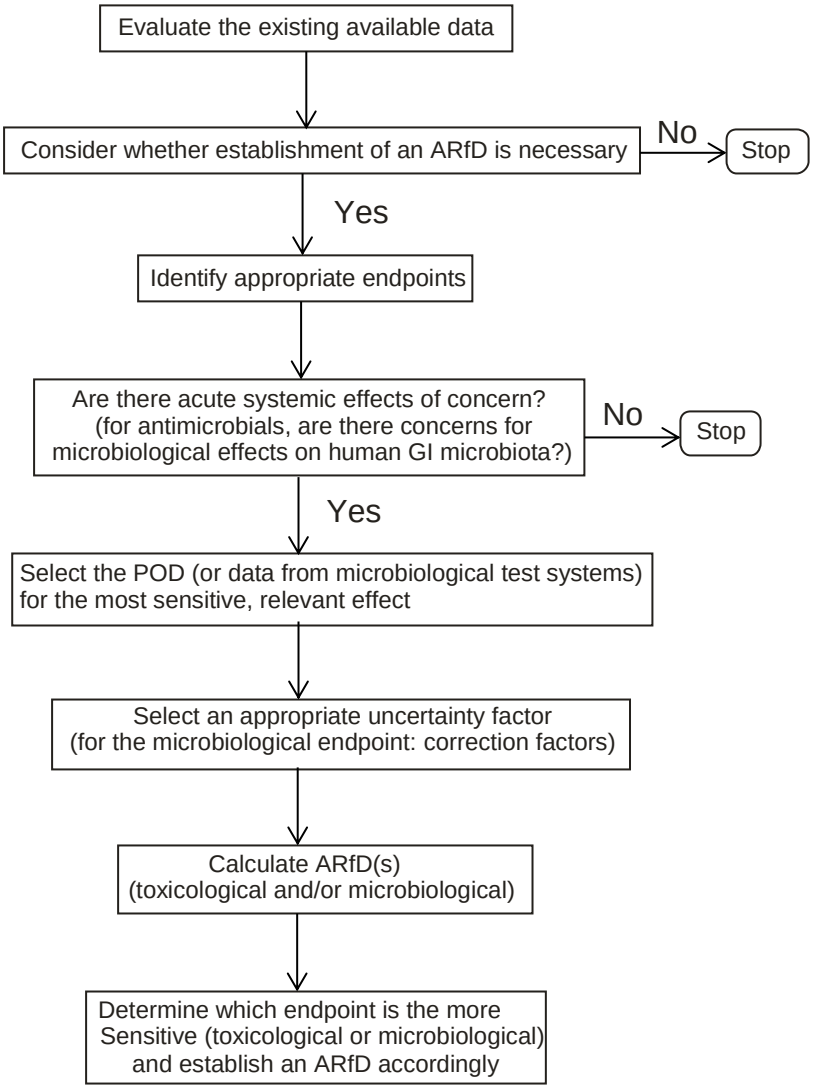
No-observed-adverse-effect level (NOAEL): Greatest concentration or amount of a substance, found by experiment or observation, that causes no adverse alteration of morphology, functional capacity, growth, development or lifespan of the target organism distinguishable from those observed in normal (control) organisms of the same species and strain under the same defined conditions of exposure.

Point of departure (POD): A reference point for hazard characterization, such as a no-observed-adverse-effect level (NOAEL) or a benchmark dose (BMD), which is a dose producing a low but measurable adverse response.

Veterinary drug: Any substance applied or administered to any food-producing animal, such as meat- or milk-producing animals, poultry, fish or bees, whether for therapeutic, prophylactic or diagnostic purposes or for modification of physiological functions or behaviour.

Weight of evidence: A process in which all of the evidence considered relevant to a decision is evaluated and weighed.

9. Appendix I: Diagram illustrating the stepwise approach to establishing an ARfD for residues of a veterinary drug



The diagram shows that the first step is to evaluate the existing available data and to consider whether it is necessary to establish an ARfD. If so, then the next step is to identify the appropriate endpoints of toxicity. If acute systemic effects of concern are identified (for antimicrobials, this could include microbiological effects on human intestinal microbiota), then the next step is to select the appropriate POD or data from microbiological test systems for the most sensitive relevant effect. An appropriate uncertainty factor and correction factors are selected, if applicable. Finally, a determination is made on which endpoint (toxicological or microbiological) is the most appropriate (often chosen based on being the most sensitive) and that endpoint serves as the basis to establish an ARfD.

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