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Development of Guidelines for Elaboration of the Acute Reference Dose for Veterinary Medicinal Products
Concept Paper

January 15, 2009

Introduction:

The Acute Reference Dose (ARfD) is an estimate of the amount a substance in food or drinking water (normally expressed on a body weight basis) that can be ingested in a period of 24 hours or less without appreciable health risks to the consumer on the basis of all known facts at the time of the evaluation.[1] ARfD was developed by the WHO/FAO Joint Meeting on Pesticide Residues (JMPR) in 1995 and has been applied primarily to evaluate the safety of pesticide residues. JMPR has developed guidance on the process of selecting and evaluating appropriate toxicological endpoints for acute guidance values. This JMPR guidance presents a step-wise approach on the derivation of ARfDs and provides specific recommendations on relevant toxicological endpoints, namely hemotoxicity, immunotoxicity, neurotoxicity, liver and kidney toxicity, endocrine effects and developmental effects.

The acute hazard potential of pesticide residues in food has been recognized since the mid-90s and several national and international risk assessment bodies have started setting ARfDs. Current toxicological databases are not usually adapted to characterize acute hazards. Therefore, current practices in setting of ARfDs can vary significantly between expert bodies. JMPR development of guiding principles in this area positions it as a leading international expert body in this area. The JMPR guidance has contributed to international harmonization in the setting of ARfDs, not only for pesticide residues in food, but also for other contaminants in food and drinking water where its use is relevant.

The Joint Expert Committee on Food Additives (JECFA) has recommended that the concept of ARfD be used when a veterinary drug residue that exhibits acute toxicity is being evaluated for safety. JECFA recommended that procedures should be developed to discriminate between Acceptable Daily Intake (ADI) and ARfD for cases where it would be appropriate to estimate short-term (acute) intakes.[2]

ARfD has also been found to be useful by some regulatory agencies in assessing the safety of certain veterinary drug residues in foods that may have acute pharmacological effects in humans. Harmonisation through VICH of data requirements and methodologies for studies to establish an ARfD would provide consensus on the scientific basis for acute exposure risk assessments (i.e. acute single dose intake) undertaken as part of the requirements for licensing of veterinary pharmaceuticals.

[1] FAO/WHO Joint Meeting on Pesticide Residues (2002).
[2] 66th Report of the FAO/WHO Joint Expert Committee on Food Additives (2006)

Problem Statement:

Acute exposure risk assessment of residues varies considerably among global regulatory agencies. Some participating VICH countries (e.g., USA) currently consider acute exposure when assessing risks from residues. Other countries do not consider this type of exposure. Some countries assess these risks by calculating an Acute Single Dose Intake (ASDI). The Australian Pesticide and Veterinary Medicines Authority normally sets an ARfD as part of the registration/approval process for a new animal drug. The FDA has set withdrawal times based on concerns for both acute and chronic effects of residues for some specific products. The ARfD concept has been used previously for the elaboration of MRLs in the EU for penicillins and carazolol. There is a need for harmonization of the data requirements, methods, and study protocols that are used in VICH participating countries and regions.

The evaluation of the ARfD for most pesticides is different from the evaluation of the ARfD for most veterinary drugs. For many veterinary drugs the critical endpoint for the ADI is already associated with acute effects (e.g., pharmacological ADI). In such cases, the ARfD and the ADI are expected to reach identical values if the same safety factors are applied. This is not the case when evaluating most pesticides and therefore the JMPR international consensus on guiding principles, while a good reference point, is not appropriate for providing guidance on evaluating the safety of veterinary drug residues that exhibit acute toxicities.

Impact for Public Health, Animal Health, and Animal Welfare:

Identification of specific scientifically valid methodologies, data requirements, and study protocols that provide the basis for assessing the safety of veterinary drug residues in food benefits the public health by helping to assure that consumers will not be harmed. International consensus on requirements will permit conforming studies to be used in multiple countries or regions in order to license veterinary drug products for which acute toxicities are a concern. Fewer studies will limit the number of research animals required and promote animal welfare.

Anticipated Benefits to Industry, Regulatory Authorities, and Other Interested Parties:

As described above, international consensus will likely result in fewer animal studies. This will conserve industry resources and further industry and government regulatory agency policies to promote animal welfare through reduction in the number of animals used for research purposes. International consensus on ARfD requirements will also help assure that the testing standards and procedures identified result in data and information that will best assure the safety of veterinary drug residues for which acute toxicity is a concern. This result reflects the goals of industry, regulatory agencies, and consumers and thus benefits all interested parties.

Recommendation:

Re-establish the VICH Safety Expert Working Group (Safety EWG) for the purpose of developing guidelines on the study requirements for elaboration of an ARfD.

Mandate, Timetable, and Milestones

The Safety EWG should limit their scientific discussion to the hazard assessment of veterinary substances in relation to setting an ARfD in the pre-approval phase. The Safety EWG should also take into account the work published by JMPR on ARfD for pesticide residues and the comments of JECFA. Furthermore, the method of setting the ARfD recommended by the Safety EWG should be considered by the Metabolism and Residue Kinetics EWG as part of the study designs necessary to enable the risk assessment of residues of veterinary drugs.

As the Safety EWG has developed policies and study requirements for all human food safety issues and the expertise required for the elaboration of ARfD guidelines is similar, the Safety EWG remains the appropriate forum to undertake this new work.

- Steering Committee Meeting—February 2009
- Confirm Safety EWG members by June 1, 2009
- Send introductions/welcome , face to face meeting proposal, and references (citations attached) by July 15, 2009
- Send invitations by November 2009 to the first face-to-face meeting (~3 days duration in Washington, DC) to initiate draft guidance . Meeting to be held in Mid February 2010
- Have follow-up teleconference in 2Q10
- Have 2nd/final face-to-face if necessary (location TBD) during 3Q10

Resources:

It is noted that there are relevant sources of information currently available to the Safety EWG to serve as a starting point in the deliberations. These include:
(1) The advanced drafts of guidelines for the management of acute exposure developed by Australia in the late 1990s.
(2) Guidance from JMPR (Paper 172: 4-8, 2002).
(3) A 2005 publication by Solecki, et. al., entitled Guidance on setting an acute reference dose (ARfD) for pesticides (Food and Chemical Toxicology, 43, 1579).
(4) Draft “Guidance for the setting of an acute reference dose”, European Commission Directorate E1 (Plant Health), 7199/vi/99 rev. 5 05/07/2001.
(5) OECD draft “Guidance for a single dose study for the derivation of an acute reference dose,” Version 5, 30 September 2007.

References:

Sanquer, J. Vet. Pharmacol. Therap., 29, 345, 2006

Sanquer, J. Vet. Pharmacol. Therap., 29, 355, 2006

Solecki, et. al., Guidance on setting an acute reference dose (ARfD) for pesticides. Food and Chemical Toxicology, 43, 1579, 2005