codex alimentarius commission

FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS

WORLD HEALTH ORGANIZATION

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JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX COMMITTEE ON RESIDUES OF VETERINARY DRUGS IN FOODS

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DISCUSSION PAPER ON ROUNDING OF ADIs FOR VETERINARY DRUGS PRIOR TO SETTING OF MRLs

Document prepared by the United States of America

1. BACKGROUND:

In the report of the 36th Joint Expert Committee on Food Additives (JECFA) the committee expressed their procedure for rounding the Acceptable Daily Intake (ADI) for veterinary drugs when the ADI calculated from the No Observed Effect Level (NOEL) using a safety factor has more then one significant figure.

> **"2.7 Expression of ADIs**
>
> When establishing the numerical expression of the ADI, the Committee has decided to express it to only one significant figure. If an ADI is calculated from a no-observed-effect level that has more than one significant figure, the number will therefore be rounded to one significant figure, consistent with acceptable rounding procedures." (Report of the 36th JECFA, page 18)

Though not stated in the 36th JECFA report, rounding of ADIs was established apparently because of inherent uncertainty and imprecision in the NOEL and safety factors and the Committee did not want to give the impression of a precise number. Therefore they decided to express the ADI with only one significant figure and the practice has continued with the calculated ADI rounded to a single significant figure before the setting of the MRLs. When the second significant figure is less than 5, the ADI is rounded down and when the second significant figure is greater than 5, the ADI is rounded up.

There are 25 veterinary drugs for which the current ADI recommended by JECFA is rounded from the ADI calculated from the NOEL and safety factor (Table 1). Of these, 14 ADIs have been rounded down and 11 ADIs have been rounded up. Three times the JECFA have recommended ADIs with two significant figures without rounding. The ADI for most veterinary drugs reviewed by the JECFA have calculated to a single significant figure without rounding.

2. SITUATION:

There are at least two undesirable consequences of rounding the JECFA-recommended ADI for veterinary drugs.

First, when the ADI recommended by JECFA is different from the ADI that has been set without rounding by member governments, it raises questions by developing country governments about the reason for the disparity. The practice and procedure for rounding of ADIs are not mentioned in the *Principles For The Safety Assessment Of Food Additives And Contaminants In Food*, JECFA EH Criteria 70, making it more difficult for the member governments to understand why the JECFA-recommended ADI has been rounded.

A second undesirable consequence of rounding the ADI before the Maximum Residue Levels (MRLs) are recommended occurs when the resulting recommended MRLs are lowered, thus narrowing the gap between the recommended MRLs and actual tissue residues resulting from the good agricultural practice usage of the product. When the first significant figure of the calculated ADI is a small number, rounding of the ADI can have a large impact on the MRLs –approaching a 50% decrease if the first significant figure of the calculated ADI is the number one. A reduction in the recommended MRL can introduce a trade issue where there is no improvement to public health risk.

It is accepted practice that rounding should not be done in an intermediate step of a sequence of calculations. Therefore, accepted practice of rounding would require setting the MRLs from the calculated ADI, rather than a rounded ADI.

A guidance regarding the practice of rounding by JECFA should be selected by the CCRVDF for adoption and forwarding to WHO and FAO. This guidance will be valuable to the ongoing project of WHO and FAO to update the Criteria 70 document, which is to be completed in 2005.

3. OPTIONS FOR A RECOMMENDATION:

Three proposals for updating the JECFA procedure of recommending an ADI and MRLs have been considered and are briefly described:

1) Round all ADIs up to the next significant figure before setting the MRLs.

–Example: Calculated ADI of 0.00134 is rounded up to 0.002 for publication and before setting the MRLs.

The principle of this proposal is that NOELs are imprecise, but the real NOEL is always higher than the estimated one. The magnitude depending on the spacing of the doses in the study used to set the NOEL, there will be a gap between the highest no effect dose and the lowest effect dose, but the real NOEL will be above the highest NOEL of the study. Rounding up the ADI to the next significant figure is moving the ADI in the right direction for approximating the real ADI. Because a large safety factor is used to calculate the ADI from the NOEL, the ADI and resulting MRLs will still be safe from a human health safety standpoint, but disruption of trade over unnecessarily low MRLs will be reduced. Already, JECFA has rounded the ADI up for 11 veterinary drugs by as much as 33% without apparent harm to public health or objection by member governments.

Note: Rounding up should be limited if the resulting ADI is the equivalent of using an “effect dose” in the NOEL study, a precaution that previously may not have been observed.

2) Set the MRLs using the calculated ADI, and afterward round the ADI up or down for publication as JECFA’s recommendation.

–Example: Calculated ADI of 0.00134 is used to set the MRLs, but ADI of 0.001 is published as the JECFA recommended ADI.

This option makes maximum use of the calculated ADI for setting the MRLs, avoiding the disruption of trade over unnecessarily low MRLs. It also avoids the impression of a precise ADI that would result from publishing more than one significant figure in the ADI. The procedure for this process would have to be clear in the drug monographs to avoid confusion when trying to compare the JECFA-recommended MRLs to the JECFA-recommended ADI. I could appear that the MRLs are set excessively high compared to the ADI.

3) Set MRLs using the calculated ADI and publish the calculated ADI as JECFA’s recommendation.

–Example: Calculated ADI of 0.00134 is used to set the MRLs, and ADI of 0.00134 is published as the JECFA recommended ADI.

This option is to not round ADIs at all. It makes maximum use of the calculated ADI for setting the MRLs, avoiding the disruption of trade over unnecessarily low MRLs. It may give the impression of a precise ADI, but it avoids the use of an ADI rounded down and used as though it is a precise number. This option avoids the appearance of mismatched ADI and MRLs, which could be the confusing result of option 2.

4. RECOMMENDATION:

The United States recommends that CCRVDF adopt Option 3, the procedure of setting MRLs using the calculated ADI and publish the calculated ADI as JECFA's recommendation without rounding. When the calculation of the ADI results in a long or repeating decimal, the ADI can be rounded to the nearest third significant number before setting the MRLs and publication. Up to this writing, the calculated ADI for no veterinary drug has had more than three significant numbers. This guidance will be provided to update the document *Principles For The Safety Assessment Of Food Additives And Contaminants In Food*, JECFA EH Criteria 70, a WHO and FAO project which is to be completed in 2005.

Options 1, 2 and 3 adequately protect public health and reduce the potential for trade disputes over unnecessarily low MRLs. The United States judged that option 2 was the least desirable because it is most likely to create confusion when there is disparity between the ADI and MRLs. In a trade dispute, the disparity is likely to complicate the resolution – is the ADI or the MRL more appropriate? The option 3 results in the least potential for objection from individuals untrained in risk management for veterinary products. Therefore option 3 was judged to be the best option.

Table 1. EFFECT OF JECFA ROUNDING OF ADI's (32nd -62nd MEETINGS)

COMPOUND	JECFA Meeting	NOEL mg/kg	Safety Factor	Calculated ADI (mg/kg bw)	Rounded ADI (mg/kg bw)	Rounded Up / Down	% Change
Ronidazole	34	5	200	0.025	0.025	none	0
Sulfadimidine	34	2.2	500	0.0044	0.004	down	-9
Closantel	36	2.5	100	0.025	0.03	up	+20
Fenbendazole	38	5	200	0.025	0.025	none	0
Flubendazole	40	2.5	200	0.0125	0.012	down	-4
Triclabendazole	40	0.27	100	0.0027	0.003	up	+11
Levamisol	42	1.25	200	0.00625	0.006	down	-4
Dexamethasone	42	0.0015	100	0.000015	0.000015	none	0
Dihydrostreptomycin & Streptomycin	43	5	200	0.025	0.03	up	+20
Diclazuril	45	3	200	0.015	0.02	up	+33
Moxidectin	45	0.3	200	0.0015	0.002	up	+33
Abamectin	47	0.12	100	0.0012	0.001	down	-17
α-cypermethrin	47	1.5	100	0.015	0.02	up	+33
Danofloxacin	48	2.4	100	0.024	0.02	down	-17
Enrofloxacin	48	0.0023	1	0.0023	0.002	down	-13
Fluazuron	48	4.3	100	0.043	0.04	down	-7
Azaperone	50	0.63	100	0.0063	0.006	down	-5
Gentamicin	50	0.022	1	0.022	0.02	down	-9
Sarafloxacin	50	0.00033	1	0.00033	0.0003	down	-9
Tetracyclines	50	0.033	1	0.033	0.03	down	-9
Phoxim	52	0.38	100	0.0038	0.004	up	+5
Thiamphenicol	52	0.0046	1	0.0046	0.005	up	+9
Dicyclanil	54	0.71	100	0.0071	0.007	down	-1
Flumequine	54	25	1000	0.025	0.03	up	+20
Lincomycin	54	2.5	100	0.025	0.03	up	+20
Melengestrol Acetate	54	0.005	200	0.000025	0.00003	up	+20
Pirlimycin	62			0.0083	0.008	down	-4
Ractopamine	62	0.067	50	0.00134	0.001	down	-25