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Setting "Dose" Limits without Dosing Information

There are several situations where this may come up. One includes early clinical trial production of drug actives or finished drug products. In that case the dosing has not yet been fully established. Another involves substances, such as cleaning agents, which have no "dose". A third case may involve setting limits for degradation products. In these types of situations, one approach to setting residue acceptance limits is limits based on the Acceptable Daily Intake (ADI) of the target residue. Of course, the question arises on how to determine this information, since rarely is there a reference where you can immediately look up ADI information on a new drug, a cleaning agent, or a degradant.

Fortunately, there are several references that provide factors to convert acute toxicity data to an estimate of an ADI. Such references include:

- D L Conine, B D Naumann, and L H Hecker, Setting Health-Based Residue Limits for Contaminants in Pharmaceuticals and Medical Devices, Quality Assurance: Good Practice, Regulation, and Law, Vol. 1, No. 3, pp. 171-180 (1992).
- H J Kramer, W A van den Ham, W Slob, and M N Pieters, Conversion Factors Estimating Indicative Chronic No-Observed-Adverse-Effect Levels from Short-Term Toxicity Data, Regulatory Toxicology and Pharmacology, vol. 23, pp 249-255 (1996).
- D.B. Layton, B J Mallon, D H Rosenblatt and M J Small, Deriving Allowable Daily Intakes for Systemic Toxicants Lacking Chronic Toxicity Data, Regulatory Toxicology and Pharmacology, Vol. 7, pp. 96-112 (1987).

Each of these papers gives information (including factors) for converting acute (LD_{50}) data into estimates of ADI. The reference I have used the most, since it comes from researchers at a pharmaceutical company, has been the Conine et. al. reference. That reference, for example, states that to convert an animal LD_{50} to an ADI, one uses a safety factor of >1000 with an additional safety factor of 1-10. Being somewhat conservative would suggest a factor of at least 10,000 in converting an animal LD_{50} into an ADI. For example, an ADI would be calculated as:

$$\text{ADI (mg/day)} = \frac{LD_{50}\text{ (mg/kg) X human body weight (kg)}}{\text{Conversion Factor}}$$

Where the conversion factor, in the case of data based on an animal LD_{50} is at least 10,000.

This ADI value is then substituted for the factor "one one-thousandth of a minimum daily dose" of the target residue in the conventional calculation of a residue limit for finished drugs. Note that in using the ADI in place of the dose, the ADI does not replace the minimum daily dose of the target residue; rather it replaces the minimum daily dose reduced by the safety factor. The rationale for this is that that once one achieves an acceptable daily intake, no further safety factors are needed; the safety factors are actually built into the conversion factor in going from the acute toxicity information (LD_{50}) to the ADI. In performing conversions from acute toxicity data to an ADI one should preferably use the same route of administration (that is, use an

oral LD_{50} for an oral ADI value and an IV LD_{50} for IV ADI values). However, in deciding acceptable limits in such cases where information on the daily dose is not available or not applicable, all available safety data should be considered.

The discussion in this Cleaning Memo is not to suggest that this method is the only way to set acceptance limits when a dose is not known. However, it is one possible alternative.