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Issues in Limits for Formulated Cleaning Agents

For formulated cleaning agents (those cleaning agents containing surfactants and other functional aids, perhaps in addition to an alkali or acid), residue limits are generally set based on toxicity of the cleaning agent. Rather than using something like 0.001 of a dose (as is used for actives), the limit of the formulated cleaning agent in the next manufactured product is based on an Acceptable Daily Intake (ADI) value. Note that in this case, 0.001 of a dose of the active is a "safe" level. When using the ADI for calculations, it is not appropriate to use 0.001 times the ADI. The ADI itself is the safe level. (One could conceivably use 0.001 times the ADI for the cleaning agent limit; there is nothing wrong from a compliance viewpoint. However, one might find the limit well below the detection limit of the analytical method for measuring the formulated cleaning agent.)

There are two ways industry has calculated ADI values for formulated cleaning agents. Both involve using a short term toxicity value, such as a LD_{50} ("lethal dose 50%") value. The LD_{50} value is a value (usually in units like mg or mL per kg of body weight) at which half the test animals given the test substance die.

One way that industry converts a LD_{50} value to an ADI value is by first converting the LD_{50} value to a NOEL ("no observable effect level") value. Then, the NOEL value is converted to an ADI value by applying a "safety factor". This approach is perfectly acceptable. However, it is perhaps inappropriate to call the second conversion factor (from the NOEL to the ADI) a "safety factor". But, much like the designation of the conversion factor in limits for actives being called a safety factor, the industry is probably not going to get away from this terminology. Note that I am much more comfortable calling each conversion factor just that – a conversion factor. Each conversion factor has a degree of a "safety" built into it. However, the important thing is not so much what it is called, as what the overall factor is in reducing the LD_{50} value to an ADI value. Examples of values used by industry usually include a factor of 0.001 to convert the LD_{50} to a NOEL and then a safety factor of 0.01 to convert the NOEL to an ADI. Note that in such an approach, and using the example values, the resultant overall factor to convert an LD_{50} to an ADI is 0.00001.

The second way that industry converts a LD_{50} value to an ADI value is by using one factor to convert directly from the LD_{50} to the ADI. For example, an ADI value may be determined by multiplying the LD_{50} value by 0.00001. There is no need for a separate safety factor since a safety factor is included in the conversion factor.

Note that in the two examples cited, the net effect was the same - the ADI was ultimately 0.00001 times the LD_{50} value. Either method may be used to estimate an ADI value from an LD_{50} value. It should also be remembered that the LD_{50} value should be by the same route of administration as the next product manufactured in the cleaned equipment.

Some cleaning agent suppliers provide toxicity information as an LD_0 (a dose at which no test animals die). It is not appropriate to use an LD_0 value as a NOEL value. While a LD_0 value may be a level at which no animals died, there still may be significant effects (short of death) which are reported. Therefore, the LD_0 may be utilized in place of the LD_{50} value for calculation purposes since the LD_0 value is lower and therefore more conservative. However, it is not a substitute for a NOEL value.

The three literature reference used to estimate ADI values from short term toxicity information are listed

below:

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).

Note that the values given for conversion factors above are strictly examples. However, it should generally be the case that the overall conversion factor should be at least 0.00005. Also note in calculating limits that the ADI should be converted from a value of mg (or µg) per kg of body weight to an absolute value (mg or µg) for a certain body weight (based on 60-70 kg for an adult, for example).