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More on Limits for Formulated Cleaning Agents

In last month's Cleaning Memo, I discussed that for formulated cleaning agents (those cleaning agents containing surfactants and other functional aids), residue limits are generally set based on the 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. The ADI is based typically on a fraction (such as 0.00001) of an LD_{50} value for the formulated cleaner. What if such a value for the LD_{50} is not available; is it possible to look at the constituents of the cleaning agent for which there are LD_{50} values, and then estimate the LD_{50} of the complete formulation? This can be done, but this is not the preferred option. If an estimate of the toxicity of formula is made based on the toxicity of the individual components, this should NOT be done by trying the "average" the LD_{50} based on the percentage of each component in the formulation. Let me illustrate this using a formulated cleaning agent composed of 10% sodium hydroxide, 5% EDTA, and 5% sodium lauryl sulfate. Here are several values off the web for LD_{50} values for these components:

Sodium hydroxide	500 mg/kg
EDTA	2000 mg/kg
Sodium lauryl sulfate	1300 mg/kg

If the LD_{50} is to be estimated, it is better to assume that the lowest LD_{50} value of any component is a worst case estimate of the LD_{50} value of the formulation as a whole. In the example cited, a value of 500 mg/kg would be used as the worst case estimate of the cleaning formulation as a whole. No attempt should be made to "weight" the percentages of each component and estimate a higher LD_{50} (remember that a lower LD_{50} results in a lower limit, and therefore is a worse case). The acceptability of this approach will have to be judged by each company. For the most part this approach should be avoided, especially for oral LD_{50} values, because oral LD_{50} tests are relatively inexpensive.

One alternative to actually obtaining a true LD_{50} value is to obtain an LD_0 value. An LD_0 value is a dose (again in mg/kg) at which no animals die. Using a LD_0 value represents a more conservative approach (again because it is a lower value than the LD_{50}). The main reason for using a LD_0 for an ADI calculation is that it is less expensive than obtaining an LD_{50}. Particularly for IV toxicity data, an IV LD_0 is much less expensive than an IV LD_{50}. It should be noted here that, for those people who calculate the ADI from the NOEL value, that the LD_0 is NOT a substitute for a NOEL value. The LD_0 value is that level at which no animals die; there may be (and usually there are, unless the dose is a very low dose) significant effects short of death. Therefore, if the two step calculation is used (as discussed in last month's Cleaning Memo), the LD_0 value is first converted to a NOEL value and then the NOEL value is converted to an ADI.

Another issue for cleaning agents is the issue of a "default" value to be used if the calculated safe value is above that default value. For drug actives for finished drug manufacture, a default value of 10 ppm drug active in the next product is typically used. Is it required to have a similar default value for cleaning agents? It should be remembered that while the practice of having a default value is not a regulatory requirement, it is a very common industry practice. Such a default value prevents cases where the medically safe calculated value is very high (also note that a requirement that the equipment be visually clean also prevents cases where the

medically safe calculated level is very high). It should be noted that a very high "medically safe" level may not be acceptable for other reasons, such as quality specifications and/or stability of the next manufactured product. If a default value, such as 10 ppm in the next product, is selected for formulated cleaning agents, it is preferable that the default value be 10 ppm detergent solids. This makes it more analogous to the 10 ppm drug active default value typically used. Again it is not a requirement that the 10 ppm be based on formulated detergent solids. However, the rationale for this recommendation can be illustrated by the example of two cleaning agents, one called Product ABC containing only 25% sodium lauryl sulfate (SLS) and another called Product XYZ containing only 50% SLS. Does it make logical sense to set a default limit of ABC at 10 ppm (equivalent to 2.5 ppm SLS), while the default limit of XYZ is also 10 ppm (equivalent to 5 ppm SLS)? If the two products were compared on the same solids basis of 10 ppm, the limit for ABC would be set at 40 ppm formulated product and the limit for XYZ would be set at 20 ppm formulated product. Each of these situations would result in setting the default limit at 10 ppm SLS. Here again, it is not a requirement that default values for formulated detergents be set based on detergent solids. However, there is some logic to doing so.

A final issue on limits for formulated cleaning agents is what to do for those cases where the calculation requires an IV LD_{50}, but there is no IV toxicity information available from the formulated detergent supplier. Again, the preferred option is to have the IV toxicity info, perhaps an IV LD_0 value, available. If it is not available, then it may be possible to estimate a worst case IV LD_{50} based on the IV toxicity data of the individual components. However, while oral LD_{50} values for components are widely available, the same cannot be said for IV LD_{50} data for those same components. If the cleaning agent must continue to be used, other techniques, such as analogies to other products, may have to be utilized. If such an approach is used, care must be used so that worst case estimates are utilized and justified.
This Cleaning Memo presents several issues in calculating residue limits for formulated cleaning agents in finished drug manufacture. It should be emphasized that the preferred option is to base calculations on documented LD_{50} values by the same route of administration. However, in the absence of such information, several options are presented for making worst case estimates of toxicity.