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Cleaning Validation for the 21st Century: Acceptance Limits for Cleaning Agents

by Andrew Walsh, MS, Mohammad Ovais, MP, Thomas Altmann, Gr FC, and Edward V. Sargent, PhD

This article presents currently suggested approaches to setting acceptance limits for cleaning agents, some of the difficulties with these approaches, emphasizing the need to move to a health-based approach as was suggested for APIs.

Two previous articles in this series discussed acceptance limits for Active Pharmaceutical ingredients (APIs) and moving to a health-based approach.[1-2] This article will discuss the currently suggested approaches to setting acceptance limits for cleaning agents, some of the difficulties with these approaches, and emphasize the need to move to a health-based approach as was suggested for APIs.

This discussion needs to begin with the origins of the FDA's expectations for cleaning validation regarding detergents as cleaning agents. The assumptions, rationale, and basis and even the thought processes resulting in requirements for setting acceptance limits for cleaning agents will be reviewed. As with the articles on APIs, we need to take a historical approach and go back to the FDA's:

Guide to Inspections: Validation of Cleaning Processes

The original guide[3] was conceived in 1992 by a number of inspectors in the MidAtlantic region during the Barr Laboratories case in part as a reaction to Judge Wolin's criticism of the GMPs for being vague and lacking detail. This Guide was intended to be very detailed and specific and was meant to clarify what their expectations were for cleaning validation.

The guide was updated and adopted for national use in 1993. Toward the end of the Guide under "Other Issues," there is a short section with concerns about detergents. In this section, the guide states:

> *"If a detergent or soap is used for cleaning, determine and consider the difficulty that may arise when attempting to test for residues. A common problem associated with detergent use is its composition. Many detergent suppliers will not provide specific composition, which makes it difficult for the user to evaluate residues. As with product residues, it is important and it is expected that the manufacturer evaluate the efficiency of the cleaning process for the removal of residues."*

The FDA made it clear that they expected companies to test for detergent residues not just API residues, which was a point of contention during the Barr Laboratories case. Judge Wolin agreed with FDA and stated that:

> *"…firms must identify the cleaning agents used in its (sic) cleaning processes. When these agents are known to cause residues, the company must check for the residue."*[4]

Then, after pointing out how difficult it is for companies to

evaluate detergent residues, the FDA went on to state:

> *"However, unlike product residues, it is expected that* ***no***** (or for ultra sensitive analytical test methods –* ***very low****) detergent levels remain after cleaning."*

The FDA had just acknowledged how difficult it was to test for detergent residues and then required that companies demonstrate that no residues (or at least very low) are present. This follow-up statement was, in effect, a "Catch 22" for companies and put them into a difficult situation; most companies at that time had no analytical methods available for detergents and these can be difficult to develop.

And if testing for detergent residues wasn't enough of a challenge, the guide goes one step further and states:

> *"Detergents are not part of the manufacturing process and are only added to facilitate cleaning during the cleaning process."*

This last statement created some confusion. Clearly, the API in Product A is not part of the manufacturing process for Product B, yet the FDA accepts that there can be residues of the API for Product A in the manufacturing equipment during the manufacture of Product B. Why did they not expect "no (or for ultra sensitive analytical test methods – very low)" levels for API residues then? It would seem that drug residues are less of a concern than detergent residues which begs the question: Are detergents really that unsafe?

On the other hand, the regulations (21 CFR 211.67(a)) clearly state that:

> *"Equipment and utensils shall be cleaned,..."*

If this is so, cleaning is a required operation in manufacturing. Cleaning involves the use of cleaning agents (detergents or surfactants). So if the regulations require cleaning and cleaning involves cleaning agents, clearly cleaning agents are a required part of the manufacturing process.

These issues with using detergents also affected the...

Determination of Acceptance Limits for Cleaning Agents

As with APIs, acceptance limits for cleaning agents need to be established to evaluate any swab or rinse samples taken for residues of these cleaning agents. Unlike APIs, where limits have been set based on a fraction of the APIs lowest therapeutic dose, cleaning agents have no therapeutic dose in humans so this approach could not be used.

The Hall Approach

An alternative approach was first proposed by Dr. William Hall in 1999 in an article[5] and is described in more detail in the book "Pharmaceutical Process Validation."[6] This approach was adopted in a modified form by the Parenteral Drug Association in 1999[7] and in a greatly simplified form by CEFIC/APIC also in 1999.[8]

The approach presented by Dr. Hall is:

First, $NOEL = LD_{50} \times 0.0005$

Where: NOEL = No Observable Effect Level
LD_{50} = Lethal Dose required to kill 50% of the test population
0.0005 = "a constant derived from a large toxicology database"*
*(Definition used in Dr. Hall's article)

Second, $ADI = NOEL/SF$

Where: ADI = Acceptable Daily Intake
SF = Safety Factor

So the conversion from acute LD_{50} to an ADI depends on two aspects:

1. Conversion from acute LD_{50} to $NOEL_{chronic}$ by multiplying by 0.0005 (or dividing by 2000) commonly known as the "empirical factor", and
2. Derivation of an ADI value by inclusion of a "route of administration"-based Safety Factor.

The examples in Dr. Hall's article use 100 as a Safety Factor for a product administered by the oral route and 5,000 for a product administered by the intravenous route, but no specific references for the origin of these values was provided. These calculated ADI values are then used in the typical cleaning validation equations for calculating a Maximum Allowable Carryover (MAC or MACO).[1,2]

The combination of the factors used in the two calculations comes to a total factor of 200,000 and 10,000,000 for the oral and intravenous examples respectively to convert from an LD_{50} to an ADI.

Hall states that his approach is based on ideas described in a series of papers published by the Environmental Protection Agency,[9] the Army Bioengineering Research and Development Laboratories,[10] and the Toxicology Department at Abbott Laboratories.[11] Let's examine these papers.

The Dourson and Stara Article

Dourson and Stara[9] published an important review of the origins of safety factors (referred to as uncertainty factors in their article) used for risk assessment.

For the use of uncertainty in the derivation of Acceptable Daily Intakes (ADIs), Dourson and Stara provide the following calculation:

Factor	Suggested Guidelines based on Literature for Use of Factor
10	Used when extrapolating from valid experimental results from studies on long term ingestion by man (this 10 fold factor protects the sensitive members of the human population estimated from data garnered on average healthy individuals).
100	Used when extrapolating from valid results of long term feeding studies on experimental animals with results of studies of human ingestion unavailable or scanty (this represents and additional 10-fold uncertainty factor in extrapolating from the average animal to the average human).
1,000	Used when extrapolating from less than chronic results on experimental animals with no useful long term or acute human data (this represents and additional 10-fold uncertainty factor in extrapolating from less than chronic to chronic exposures).

Table A. Uncertainty factors for converting no effect levels to ADIs.

$$\text{ADI} = \frac{\text{“no effect” level}}{\text{uncertainty factor}}$$

The review discusses an article by Lehman and Fitzhugh of the FDA[12] dating back to 1954 that suggested calculating an ADI by dividing an NOEL or NOAEL (No Observable Adverse Effect Level) by 100. The rationale being that a factor of 100 accounted for uncertainties in differences between animals, variations in sensitivities, size of test populations, etc. They go on to say that the FDA then later recommended an uncertainty factor of 1,000 when only data from sub-chronic studies were available and 2,000 when the data was available from only one species. The authors reviewed the literature and show that uncertainty factors of 10, 100 and 1,000 are suggested when extrapolating an ADI from data under different circumstances. The guidelines provided in their article are shown in Table A.

Basically, the uncertainty factor of 1,000 is derived from a factor of 10 for intraspecies differences, a factor of 10 for Interspecies differences, and a factor of 10 for adjustment from sub-chronic to chronic exposure.

The authors then provide an analysis of intraspecies adjustments, interspecies adjustments and chronic and sub-chronic exposure adjustments to show that each factor of 10 is conservative and that factors of 3 to 5 are sufficient in most cases. They also give an example where an uncertainty factor of 1,000 may be overstated by a multiple of 5 and an uncertainty factor of 200 may be more appropriate.[9]

In summary, Dourson and Stara's article indicates factors from 10 to 1,000 to convert from a "no effect" level to an ADI.

The second paper from the Army Bioengineering Research and Development Laboratories has become known in the Cleaning Validation community as:

The Layton Article

Layton, et. al.,[10] in their article were concerned with estimating Acceptable Daily Intakes (ADIs) of potentially toxic substances encountered at hazardous waste sites. Most chemicals have no human toxicological or chronic toxicity data and this makes it very difficult to determine the health risks due to exposure to such environmental contaminants. Consequently, the authors attempt to derive a method to convert acute animal toxicity data (i.e., LD_{50} values) to human ADIs. This was done by evaluating a database of compounds with known LD_{50}s and NOELs and selecting a conversion factor that corresponded to the 5th cumulative percentile, that is, 95% of the conversion factors from the database were lower. The authors warn that:

> *"This paper focuses specifically on the use of oral LD_{50}s to provide **provisional*** estimates of the acceptable intakes of noncarcinogenic chemicals. These estimates are meant to be conservative; that is, if the ADI could be computed from a NOEL determined in a chronic toxicity study, it would nearly always be higher than the value estimated from the LD_{50}."*
>
> *(Emphasis from the original article)

Layton, et. al., make it clear that the approach in the article may be appropriate for compounds that have very little to no toxicological data available and clearly note that if additional data were used, any calculated ADI would almost inevitably be higher.

A large database of pesticides was used for the evaluation and they note that pesticide studies look at cholinesterase inhibition which typically generate lower ADIs than other toxic effects. After reviewing the database they write:

> *"We suggest values from 5×10^{-6} to 1×10^{-5} day^{-1} for establishing interim ADIs from oral LD_{50} data (in mg kg^{-1}). The use of such factors is meant primarily for situations where there is a need to manage the health risk of exposures to contaminated soils, waters, crops, or other material at a particular site."*

However, in their conclusion, the authors make note that:

> *"We recognize, though, that in some instances it might be desirable to use higher or lower conversion factors. The NOEL/LD_{50} ratios given in this paper can easily be reevaluated to establish different conversion factors."*

In summary, the Layton article indicates factors from 200,000 to 100,000 to convert from an LD_{50} to a *provisional* ADI, while recognizing that these factors were based

Patient Exposure	Dosage	Safety Factor
Short Term Use	LD_{50} animal	>100
Prolonged Use	LD_{50} animal	≥ 1,000
Lifetime Use	LD_{50} animal	≥ 1,000

Table B. Factors for converting LD50s to ADIs from Conine, et. al.

in part on a very conservative endpoint (cholinesterase inhibition) and that the ADI would be higher (i.e., lower Safety Factors used) with additional information.

The Conine Article

The third paper by Conine, et. al.,[11] developed a method for establishing residue limits specifically for pharmaceutical products and medical devices. In particular, this article addressed the different exposures that a patient may experience with products that are administered over a lifetime or on a long term basis (e.g., daily injections of Insulin) vs. products that are administered on a one time or short term basis (e.g., an emergency use of Epinephrine). It seems obvious that limits in these very different circumstances should be different.

These authors proposed that limits be derived for three different categories: for short-term use, for prolonged use, and for lifetime use. Correspondingly, acute data should be used to set short-term limits, subchronic and reproductive effects data should be used for prolonged exposure limits and chronic/lifetime data should be used for lifetime limits. The authors emphasized the importance of using high quality data and that regardless of the limit being set (short-term, prolonged or lifetime) that ***all data should be taken into consideration***. Table B summarizes the factors suggested for converting LD_{50} data into an ADI.

The authors added a footnote to all their tables that acknowledged:

> *"The actual factor may be modified on the basis of the data under evaluation and **the professional judgment of the toxicologist performing the evaluation*** to arrive at the actual safety margin to be applied. In each case an additional modifying factor between 1 and 10 may be applied. In addition, since acute data represent the least acceptable data for calculation of acceptable daily intake values for lifetime exposure, the range of modifying factors based solely upon such data may be expanded."*
>
> *(Emphasis added)

They then provide the following calculation:

$$\text{ADI (mg/day)} = \frac{\text{NOEL, LOEL, etc. (mg/kg/day)} \times \text{human body weight (kg)}}{\text{safety margin}}$$

Where: safety margin = safety factor × modifying factor

In summary, the Conine article indicates factors from 100 to 1,000 to convert from an LD_{50} to an ADI with an additional modifying factor between 1 and 10 in most cases, or possibly more, depending on the data used.

After reviewing the content of the articles by Dourson and Stara, Layton, et. al., and Conine, et. al., it is difficult to determine exactly how Dr. Hall used these references since the authors cannot find any connection between the safety factors proposed by these articles and the ones proposed by Dr. Hall. For example, the origin of the safety factor of 5,000 used to calculate the ADI from the "No Observed Effect Level" in the intravenous example is not found in any of these articles. An important observation to make is that, while the authors of the articles warn that their approaches are very conservative and the Safety Factors should be probably lower in most cases, Dr. Hall chose to use even higher Safety Factors.

The Kramer Article

Another paper by Kramer, et. al.,[13] reviewed conversion factors used to convert short-term toxicity data (LD_{50}s) into NOAELs. Like the Layton article, this article looked at a database of compounds with known LD_{50}s and NOAELs and selected a conversion factor that corresponded to the 95% used by Layton, et. al., but also added in an upper 95% Confidence Interval to adjust for estimation errors in the analysis. In effect, this step makes the results of this approach 95% confident that the Conversion Factor is higher than 95% of the other compounds.

Like the Layton article, Kramer, et. al., points out that these types of approach may be inaccurate:

> *"The (Geometric Mean) of the ratios is the factor that converts a toxicity parameter into the most likely NOAELchronic. This factor may be **highly inaccurate for individual compounds*** because of the large variation between compounds."*
>
> *(Emphasis added)

Also like the Layton article, Kramer, et. al., point out that pesticides made up the majority of the database used in the analysis (approx 50%), followed by solvents (approx 25%) plus some metal containing compounds, phthalates and some other compounds.

This certainly biased the analysis on the high side leading to high values for the conversion factors. For example, the authors point out that the cholinesterase inhibitors as a subgroup of the database has a significantly lower Geometric Mean:

> *"Examination of the LD_{50}/$NOAEL_{chronic}$ ratio of the cholinesterase inhibitors resulted in GM = 197 and GSD*

= 5.8 (n = 28). The GSD was statistically significantly reduced (P < 0.05) compared to the GSD of complete data set…"

Since the cholinesterase inhibitors were included in the overall analysis, the values calculated by Kramer, et. al., are even higher and even more excessively conservative than for Layton, et. al.

While Dr. Hall did not reference the Kramer article, another author, Destin LeBlanc, uses values of 105 and 106 in several of his articles on cleaning agent limits[14-17] and does reference the Kramer article; but he references those of Layton and Conine as well, so it is not clear how they were derived as these values do not match the safety factors from any of the three articles. LeBlanc clearly believes that safety factors should be this high for cleaning agents as in Slide 18 of his 2008 webinar "Are we Setting Limits Correctly?"[17] LeBlanc states that concerning detergents:

"Conversion Factors like 5 × 10^4 are not appropriate; should be 10^5 or 10^6"

What should be clear is that LeBlanc suggests safety factors that are even more conservative than the safety factors found in these articles which their authors admit are overly conservative. A comparison of all these approaches with their point of departures and safety factors used can be seen in Table C.

Source	Dosage Used	Safety Factor
Lehman and Fitzhugh	NOEL or NOAEL	100
Dourson and Stara	"no effect" level	1,000
Layton, et.al.	LD_{50} animal	100,000 to 200,000
Conine, et.al.	LD_{50} animal	>100 (Short Term)
		≥ 1,000 (Prolonged)
		≥ 1,000 (Lifetime)
Kramer, et.al.	LD_{50} animal	1,700,000*
Dr. Hall's approach	LD_{50} animal	200,000 (oral)
		10,000,000 (intravenous)
LeBlanc approach	LD_{50} animal	100,000 to 1,000,000
*Kramer, et. al. indicated a Conversion Factor of 1.7 × 10^4 for an LD_{50} to an NOAEL with a most likely additional factor of 100 to convert to an ADI.		

Table C. Factors suggested for converting no effect levels/LD_{50}s to ADIs.

Industry and Regulatory Guidance

There have been a number of examples of industry guidance documents implementing some form of the toxicology-based approach proposed by Dr. Hall. In 2000, the CEFIC/APIC Guide[18] was greatly updated and presented the following approach:

$$NOEL = \frac{LD_{50}\ (g/kg) \times 70\ (kg\ a\ person)}{2000}$$

From the NOEL number a MACO can then be calculated according to:

$$MACO = \frac{NOEL \times MBS}{SF \times TDD_{next}}$$

Where: MACO = Maximum Allowable Carryover: acceptable transferred amount from the investigated product ("previous")
NOEL = No Observed Effect Level
LD_{50} = Lethal Dose 50 in g/kg animal. The identification of the animal (mouse, rat etc.) and the way of entry (IV, oral etc.) is important.
70 kg = 70 kg is the weight of an average adult
2000 = 2000 is an empirical constant
TDD_{next} = Largest normal daily dose for the next product
MBS = Minimum batch size for the next product(s) (where MACO can end up)
SF = Safety factor

The CEFIC/APIC Guide states that Safety Factor (SF) varies depending on the route of administration" with a factor of 200 for APIs that will be in oral dosage forms. CEFIC/APIC goes on to say that the SF can vary depending on substance/dosage form and lists ranges similar to those listed in PDA's Guide for Therapeutic dose calculations (Topicals: 10-100, Oral products: 100-1000, Parenterals: 1,000-10,000). This leaves the selection of Safety Factors up to the person doing the calculation which is usually the person writing the Cleaning Validation Protocol, but values anywhere from 20,000 to 20,000,000 are possible.

The implementation in the 1999 PDA Technical Report 29[19] was also slightly modified from the Hall approach and shows the following equations:

$$NOEL = LD_{50} \times \text{Emperical (sic) Factor}$$

and

$$ADI = NOEL \times AAW \times SF$$

where: NOEL = No Observed Effect Level
LD_{50} = Lethal Dose for 50% of animal population in study

empirical factor = " derived from animal model developed by Layton, et. al.
ADI = Acceptable Daily Intake
AAW = Average Adult Weight
SF = Safety Factor

The PDA equation did not specify a value for the "empirical factor" and instead refers to an "animal model" from an article by Layton, et. al.,[9] The ADI calculation is further modified to convert to a total dose rather than leaving the ADI in a mg/kg (or µg/kg) form. Although Hall states he used an AAW of 70 kg in his examples, he did not show it in his equations. This again leaves the selection of Safety Factors up to the person doing the calculation.

The PDA recently updated this Technical Report 29[20] and now suggests using the ISPE Risk-MaPP approach which requires a *qualified toxicologist* to determine the Acceptable Daily Exposure (ADE) based on all of the available clinical and toxicological data. However, the updated guide also offers as an alternative the following equation:

$$NOEL = \frac{LD_{50} \times BW}{MF_1}$$

where: NOEL = No Observed Effect Level
LD_{50} = the 50% Lethal Dose of the target residue in an animal, typically in mg/kg of body weight (by the appropriate route of administration)
MF_1 = modifying factor or factors, selected by the toxicologist

The cumulative modifying factors selected are generally no more than 1000. Once the NOEL is estimated, the SDI is determined by:

$$SDI = \frac{NOEL}{MF_2}$$

where: SDI = Safe Daily Intake of the residue
MF_2 = modifying factor or factors, selected by the toxicologist

The cumulative modifying factors selected are generally no more than 1000. Once the SDI is established the ARL is determined:

$$ARL = \frac{SDI}{LDD}$$

where: ARL = acceptable residue level in the next drug product
LDD = largest daily dose of the next drug product to be manufactured in the same equipment

This suggested approach also can lead to a combined safety factor of 1,000,000 which most workers would probably default to and avoid using a qualified toxicologist and sidestep the calculation of an ADE.

The PDA has also issued another guide on cleaning validation for biologics.[21] In this guide, "15.0 Appendix Carryover Calculations" provides an example calculation "based on the toxicity of a *cleaning agent for formulation/fill* manufacturing." Although the guide does not provide an equation per se, based on the example calculation provided it can be seen that the equation would be:

$$ADI = \frac{LD_{50} \times BW}{CF}$$

where: LD_{50} = Lethal Dose for Cleaning Agent
BW = Body Weight of patient taking product B
CF = Conversion Factor

The example goes on to state that the Body Weight used is 60 kg and the Conversion factor is 100,000.

Interestingly, when Health Canada released their Cleaning Validation Guidelines[22] in June of 2000 Section 10.0 "Establishment of Limits" they make no mention of a toxicological approach to setting limits but at the very end added the following note:

> *"Environmental Protection Agency and toxicologists suggest that an acceptable level of a toxic material may be that which is no more than 1/1000 of a toxic dose or 1/100 - 1/1000 of an amount which is not known to show any harmful biological effect in the most sensitive animal system known, e.g., no effect."*

Unfortunately there were no references provided and this passage does not exist on their current website. Health Canada opened their guide to comments in 2012 and currently does not provide the document on their website. Other guidelines such as the PIC/S Guidelines[23] and the WHO Guidelines[24] make no mention of calculating limits based on toxicological data at all.

Relevance of Currently Used Safety/ Conversion Factors

Overall, the pharmaceutical industry has had great difficulties with using the safety factors as suggested by Dr. Hall and LeBlanc. The following are three brief vignettes to underline the difficulties the use of these safety factors has created.

Case Study 1

A pharmaceutical company created a new cleaning validation standard and decided that the safety factor for their

Compound	LD_{50} (mg/kg^{-1})	NOEL (mg/kg/day^{-1})	Factor to Convert LD_{50} to True NOEL
Benzalkonium chloride	400	94	4
Sodium dodecylbenzenesulfonate	1260	150	8
Tergitol 08	5750	290	14
Calcium disodium edetate	7000	375	18

Table D. Factors to convert LD_{50} to true NOEL (data from Layton, et.al.)

cleaning agents was inadequate and should be set higher. The safety factor they decided upon was 10^6 or 1/1,000,000 of the toxic dose (LD_{50}). Immediately, there was an issue with a cleaning agent used to clean one of their products. The new acceptance limits were now below the Method's LOQ and far below the rinse data that was being achieved during the cleaning validation for this product.

What was this cleaning agent? ***Isopropyl alcohol.*** However, Isopropyl alcohol is rated by ICH as a Class 3 solvent with low toxic potential and allowed in pharmaceutical products at levels up to 0.5%. The HERA Report[25] for Isopropyl Alcohol points out that "A substantial amount of toxicological data and information in vivo and in vitro demonstrates that IPA has a low order of acute toxicity." So why should the pharma industry need to apply such low limits for Isopropyl alcohol?

Case Study 2

Another pharmaceutical company was using a parts washer to clean equipment from a packaging line. Limits were calculated using 1/1,000,000 of the toxic dose (LD_{50}) and were below the limits of detection for the method. This company saw that it had two options: convert to disposable parts or stop using the cleaning agent. The company decided to stop using the cleaning agent and to wash with water only.

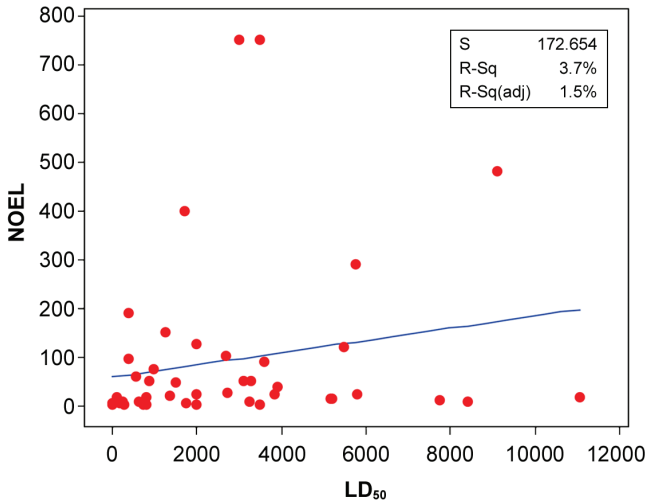

Figure 1. LD50 vs. NOEL Values.*

What was this cleaning agent? ***Sodium Lauryl Sulfate (SLS).*** However, SLS has a long history of use as a pharmaceutical excipient and as a food additive and is a common ingredient in toothpaste used by millions of people everyday. SLS is listed on the Inactive Ingredient Database and can be up to 40% in topicals and in tablets. Sodium Lauryl Sulfate is also on the EAFUS list of substances that the FDA has either approved as food additives or listed or affirmed as GRAS. EPA also has posted on its website "Sodium Lauryl Sulfate; Exemption From the Requirement of a Tolerance"26 that specifically exempts SLS from needing a limit for food. In addition, the FDA already allows SLS to be added to foods up to 1,000 parts per million.[27] Finally, the Organization for Economic Cooperation and Development Screening Information Data Set (OECD SIDS) concluded that "..sodium dodecyl (lauryl) sulfate is of no concern with respect to human health."[28] So why should the pharma industry need to apply such low limits for sodium lauryl sulfate?

Case Study 3

Another pharmaceutical company was manufacturing an injectable product. The Cleaning Validation Acceptance Limit for one of the cleaning agents used in cleaning this product was calculated to be < 10 ppb and could not be met.

What was this cleaning agent? ***Sodium Hydroxide.*** However, NaOH is a common component in the formulation of injectable drug products and in one product has been approved by FDA at 19.27%.[29] NAOH is not considered by the FDA to be unsafe and is on the Generally Recognized as Safe[30] (GRAS) lists and allowed as a food additive. It can be used "quantum satis" in Europe, meaning you can add as much as you need to achieve a specific effect (but not more than that). A common use for Sodium Hydroxide is pretzel manufacturing; the pretzel dough is formed and immersed into a 2-4% NaOH solution before the baking process. This procedure results in the typical brown and smooth pretzel surface.[31] So why should the pharma industry need to apply such low limits for Sodium Hydroxide? (Note: the ECHA review[32] concluded that no valid oral LD_{50} exists for sodium hydroxide. This greatly undermines the argument that the LD_{50} divided by some safety factor is valid for establishing cleaning limits).

At first consideration, it would seem that the recommended safety/conversion factors may be overinflated. Let's look at a few compounds where the LD_{50}s and the NOELs have been determined experimentally. Table D lists a few well known compounds listed in the Layton article that happen

to be used as cleaning agents. As can be seen, the factor needed to convert their LD_{50}s to their true NOEL are much less than the 1,000 to 2,000 suggested by the above articles and guidance. For Benzalkonium chloride, the conversion factor is only 4 which is 500 times lower that those suggested. So the initial assumption of 2,000 is clearly too high in these cases.

Let's examine the relationship between the LD_{50} and the NOEL. Figure 1 shows a plot of LD_{50}s and their known NOELs from the Layton article which shows a clear lack of linearity (R^2 = 1.5%). This clearly indicates that using a single factor to convert all LD_{50}s to their equivalent NOELs will be highly inaccurate.

To examine if the limits derived through the Dr. Hall and Leblanc approaches are overly conservative, ADIs were calculated for the three cleaning agents discussed in the case studies (plus one additional) using both approaches and the results compared to ADEs determined by a highly trained and experienced toxicologist using the approach described in the ISPE Risk-MaPP Guide that considers all the available data on the compounds. The results can be seen in Table E.

Compound	LD_{50} – Rat (mg/kg)	Hall ADI (mg/day)	LeBlanc ADI (mg/day)	Risk-MaPP ADE (mg/day)
Isopropyl alcohol	4710	0.024	0.0047	50
Sodium lauryl sulfate	1288	0.006	0.0013	10
Sodium dodecylbenzene sulfonate	1260	0.006	0.0013	63
NaOH	4090	0.02	0.0041	20

Table E. Comparison of the Hall, LeBlanc, and full toxicological evaluation (ADE) approaches.

The results obtained by the Dr. Hall and LeBlanc approaches are not only different from the ADE calculated by a qualified toxicologist, they are almost 10,000 times lower. These results clearly demonstrate that approaches that only use a conversion factor with an LD_{50} result in excessively conservative limits and that the ADE approach of Risk-MaPP, which considers all available data, results in far less restrictive limits. These results also explain the obvious disconnect between the limits using the Hall and LeBlanc approaches and the well-known innocuous nature of these compounds. In many cases, the approaches used in the industry today for calculating limits for cleaning agents are a case of severe overkill.

Where Does the Industry Go From Here?

As discussed previously, the Layton article pointed out that ADIs calculated using the factors they presented (5×10^{-6} to 1×10^{-5} day^{-1}) should be considered *provisional*; Kramer, et. al., acknowledge that their approach may be *highly inaccurate for individual compounds*, and Conine, et. al., emphasize that *all data should be considered* in setting an ADI and not just LD_{50}s. As was pointed out above that guidelines involving chemicals no longer require LD_{50}s to be determined and toxicologists no longer derive them.[33] So, in the very near future, LD_{50}s will no longer be available and these calculations cannot be applied. The authors hope that readers would agree that simply using safety/conversion factors with LD_{50}s is too inaccurate and too conservative for use in setting limits for cleaning agents and that a qualified toxicologist should be used for this task. Using the approach described in the ISPE Risk-MaPP Guide, a qualified toxicologist can evaluate all the available data and determine an Acceptable Daily Exposure (ADE) for use in calculating Maximum Safe Carryover (MSC) limits for cleaning agents. The setting of limits also should not be restricted just to patient safety, but also to product quality and this should be part of the hazard identification step in a risk assessment. Subsequently, after cleaning data has been collected, Statistical Process Control (SPC) limits can be calculated for cleaning agents as described in the previous articles.[1-2]

Another point to consider is that the FDA expects limits to be scientifically justified. The FDA's guide specifically states this. In Section V. Establishments of Limits, the last sentence reads:

> *"The objective of the inspection is to ensure that the basis for any limits is scientifically justifiable."*

Clearly, there is not a strong scientific case for using conversion/safety factors from the sources that have been cited as they lead to grossly inaccurate and excessively low values. Having a qualified toxicologist evaluate all the available data and determine an acceptable daily exposure provides a scientifically justifiable approach.

Also as mentioned above, one reaction of the industry to these unachievable limits has been to avoid using detergents and cleaning agents altogether. There are many companies that are now arguing that since their API is water-soluble, then water is all they need to clean their equipment. Eliminating detergents from the cleaning process is actually a dangerous practice. Cleaning with water only, or with very low amounts of cleaning agents, can allow residues to build up over time in crevices and hard to reach areas (consider bathing for a month without soap or shampoo). This practice also has been associated with the occurrence of unknown (extraneous) peaks in cleaning validation HPLC samples.[34] Hopefully, using the ADE approach will develop more accurate and more reasonable limits which should enable companies to use cleaning agents freely and without concern. The development of ADEs of cleaning agents also should provide more assur-

ance to regulators about the relative safety of cleaning agents and encourage the return to their use in cleaning.

Summary

This article's brief review the origins of the safety/conversion factors used in the toxicology arena have shown these approaches to err deeply on the side of conservatism. The implementation of these approaches for setting acceptance limits for cleaning agents have likewise been overly conservative and have been problematic for the industry. It should be clear that an evaluation of a cleaning agent by a qualified toxicologist or pharmacologist, *considering all the available data,* to select conversion/safety factors (where appropriate) will provide legitimate and much more workable limits for cleaning agents for use in cleaning procedures. Table F below compares the two approaches.

This article should not be viewed as just a simple condemnation of current practices in the industry concerning setting limits for cleaning agents. Attempts were made in the past to provide an industry struggling with setting limits for cleaning agents with something to work with. However, without such a critical review, the industry cannot break from past practices, change, and move forward.

These changes in view and approach will hopefully free the pharmaceutical industry to return to using many common cleaning agents without undue concern and encourage the industry to truly clean their pharmaceutical manufacturing equipment. The appropriate use of cleaning agents should not be hindered by unnecessarily conservative limits and should allow for effective and complete removal of process residues, and in so doing, provide a higher degree of safety to the patient. The appropriate use of cleaning agents also can allow shortened cleaning times, reduced water usage, increased operator safety and improved operational efficiencies for the pharmaceutical industry.

LD_{50} Approach	ADE (Risk-MaPP) Approach
Uses LD_{50} values alone as indicator of patient health hazards *(provisional approach became first-line approach for estimation of limits)*	Holistic approach! Uses all the toxicological / pharmacological data to identify, assess and characterize risks that are relevant to patient exposure
LD_{50} determinations have been discontinued	ADE or Permitted Daily Exposure (EMA Term) are the current approach
Limit calculations based on LD_{50} can be performed by unqualified personnel	ADEs determined by Qualified Pharmacologist / Toxicologist
Safety factors are based on route of administration and not on the actual risk posed by the residue	Uses data-derived safety factors (where needed) in the estimation of acceptable (safe) exposure
Uses literature-based conversion factors to derive ADIs	Uses data to derive ADEs
Cannot be used for deriving limits for cleaning agents with limited data (e.g. when no valid LD_{50} value is available).	ADEs can be established for cleaning agents with limited data (e.g. by using approach based on Threshold of Toxicological Concern concept).
May not be applicable to routes for which LD_{50} values are not available	Route-to-route extrapolation possible. Can be used to characterize all the potential exposures
Derived Limits are overly conservative and often impractical, unachievable and unverifiable	Derived Limits are realistic and practical, achievable and verifiable and ***safe***

Table F. Comparison of two cleaning approaches.

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