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An Overview of Risk-Assessment Strategies for Extractables and Leachables

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This article is part I in a two-part series on extractables and leachables.

Several scientific, quality control, and regulatory approaches are used to control and assess the risk of foreign substances that are inadvertently added to products that humans consume. The term extractables describes substances that might leach from a material's surface into a solution while the term leachables describes substances that migrate from the material surface into the solution under the actual conditions of use.

In general, the following three possible negative effects result from the introduction of leachables into a pharmaceutical product stream.

- The leachable is toxic and poses a health risk to the consumer
- The leachable interacts with the drug product formulation so as to alter its stability and potency
- The leachable interferes with an assay that is crucial to measuring an important property of the drug product.

THE THRESHOLD OF TOXICOLOGICAL CONCERN

The *threshold of toxicological concern* (TTC) defines a generic exposure threshold value for groups of chemicals below which no appreciable risk to human health exists. The TTC approach is based on the analysis of the toxicological or structural data of a broad range of chemicals and was developed as a substitute for substance-specific information. The concept proposes that such a value can be identified for many chemicals, including those of unknown toxicity, when considering their chemical structures. Several excellent reviews have been recently published that summarize both the history and the scientific approach that TTC brings to risk assessment of chemicals (1–3).

In 1978, Cramer proposed that many chemicals, excluding polymers, could be categorized into three classes of compounds with three different potentials for toxicological risk (4). The categorization was based on a series of yes or no questions pertaining to structural-activity relationships (SARs), metabolic mechanisms, chemical reactivity, and other relevant information. Cramer class I substances have simple chemical structures and predictable and efficient modes of metabolism that suggest a low order of toxicity. Cramer class III substances permit no strong initial presumptions of safety, and may suggest significant toxicity, because their chemical structure has similarities to those of known toxins. Cramer class II substances cannot be placed in class I or class III and are therefore intermediate in

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Table I: Threshold of toxicological concern (TTC) summary. PDE is permitted daily exposure.

Unknown compound type	TTC for PDE (μg/person-day)
Structural alerts for carcinogency (but not in cohort of concern group)	0.15
Noncarcinogenic, possibly genotoxic	1.5
Nongenotoxic or carcinogenic grouped by structure-activity relationships (SAR) using modifications of the Cramer decision tree analysis	
Organophosphate neurotoxin structure	18.0
Cramer class III (high complexity by SARs)	90.0
Cramer class II (moderate complexity by SARs)	540.0
Cramer class I (low complexity by SARs)	1800.0

expected toxicology. Cramer did not identify safe daily intakes for the Cramer classes but rather calculated a protection index that could be used to establish priorities and the extent of appropriate toxicity testing.

Table I presents a summary of the permitted daily exposures for the various classes of chemicals using the TTC approach.

The European Medicines Agency (EMA) has used the TTC approach to develop guidelines for genotoxic impurities (5). The Pharmaceutical Research and Manufacturers of America (PhRMA) has also detailed a rationale for dealing with potentially genotoxic impurities in pharmaceuticals employing the TTC approach (6).

Perhaps the most notable use of TTC was in the 1996 report issued by the Pharmaceutical Quality Research Institute (PQRI) working group on leachables and extractables in orally inhaled and nasal drug products (OINDPs) (7). The PQRI working group concluded that the TTC level for carcinogens of 0.15 μg/person-day would be the safety threshold concern (STC) level for leachables in OINDPs. The qualification threshold for noncarcinogenic or nongenotoxic impurities was recommended to be 5 μg/person-day, rather than the 18 μg derived in the above table for food, based on an analysis of data of respiratory toxicities from three toxicological databases. The recommended threshold reflects the commonly observed trend that respiratory toxicities are generally greater than systemic, such as oral, toxicities.

There have been several compelling driving forces for approaching toxicological risk assessments from the TTC perspective. The first were regulatory requirements for public safety, such as the Delaney Clause. The Delaney Clause is a 1958 amendment to the Food, Drug, and Cosmetic Act of 1938 that states the following:

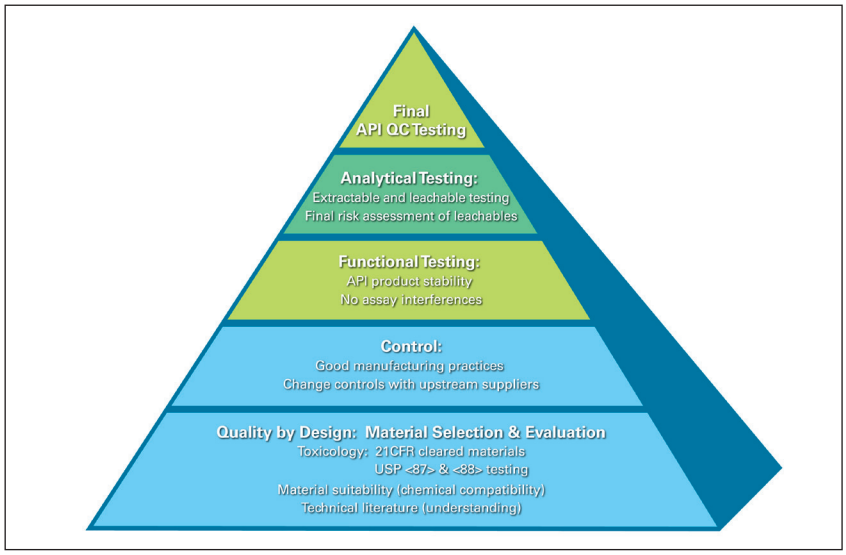
> *The Secretary of the Food and Drug Administration shall not approve for use in food any chemical additive found to induce cancer in man, or, after tests, found to induce cancer in animals.*

This requirement ultimately led to the Rawley proposal of the FDA Center for Food Safety and Applied Nutrition's (CFSAN) Threshold of Regulation (TOR) approach. This approach determined the upper limit of concentration of a substance so that levels below that limit raised no concern that it might cause cancer at a statistically minimal (i.e., one in 10^6) rate (8). Although proposed in 1986, a series of legal challenges prevented the codification of the TOR until 1995 (9).

The risk of inducing cancer in man or animals is not zero unless the impurity believed to induce cancer is also at zero concentration. The development of the TOR policy effectively resolves the issue that concentrations of impurities cannot be proven to be zero. Rather, impurity concentrations can only be shown to be less than the detection limit. According to data from the National Cancer Institute collected between 2002–2004, the lifetime risk of developing any form of cancer in the US is approximately one in three. Given this statistic, a risk of less than one in a million additional cancer cases for impurities below the TOR was as close to zero as the Delaney Clause could have intended. For example, an American's current probability of getting cancer is 1 in 3, or 0.333333. Adding a 1 in 10^6 additional risk would increase the probability of an individual getting cancer to 0.333334, clearly an immeasurable increase.

A second driving force for approaching toxicological risk assessments from the TTC perspective has been the increasing sensitivity of analytical methods used to detect and measure impurities, as well as ever more powerful techniques to obtain structural information on unknown compounds. While routine analytical methods in the 1950s measured most impurities in the fractions of percents, by the end of the century many analytical methods could often measure impurities in the parts-per-billion range, and much lower in certain cases.

Figure 1: Strategies for mimimizing the risks of leachables.



The commercial development of mass spectrometers (MS) of numerous types, but especially those attached as detectors to gas chromatography (GC–MS) and high-performance liquid chromatography (HPLC–MS) instruments, makes possible the identification, or partial or tentative identification, of many of these trace impurities. Once such trace-level impurities can be detected and identified, it becomes feasible to analyze the risk that they might pose. However, the effort and cost required to perform a risk assessment on one or two impurities are dramatically increased as the list of impurities for a risk assessment increases, even if the concentrations of the additionally detected impurities are extremely low.

The final driving force for approaching toxicological risk assessments from the TTC perspective has been recent concerns surrounding both the financial cost and ethics of animal testing (10). The European Union Registration, Evaluation, Authorization and restriction of CHemicals (REACH) program has been estimated to cost €1–2 billion (USD $1.56–3.13 billion) and would require more than a million animals if testing were done using current best practices (11). Despite a large effort to further develop *in vitro* tests to minimize the number of *in vivo* animal tests, to date, only animal testing data can be reasonably extrapolated into humans. But a TTC approach to risk assessment may make some animal testing unnecessary. Some have proposed a combination of the TTC approach with intelligent testing strategies (ITS), which is premised on the idea that significant benefits will result from considering the methods used for hazard assessment in a holistic manner, rather than examining each method separately (12).

The most reliable data on human toxicological response are unquestionably from human epidemiology studies of historical chemical exposures, particularly when the dose can be reliably estimated. However, such data are only rarely available. Currently, animal testing is the next-most-reliable indicator of human toxicological response, and using SARs to predict toxicity, as is used in the total TTC approach, is currently the least reliable approach of the three. As more and more structures and toxicological information are entered into toxicology databases and as the algorithms using SARs improve, TTC will offer greater value. Furthermore, while *in vitro* and cell-based testing can be the "canary in the coal mine," their ability to predict a safe human dose is currently extremely limited.

REGULATORY GUIDANCE IN PHARMACEUTICAL APPLICATIONS

General guidance from FDA on impurities in pharmaceuticals can primarily be found in ICH guidelines Q3A, Q3B, and Q3C (13–15). The guidance in these documents focuses primarily on impurities caused by the synthesis of the drug, degradation of the drug, or residual solvents in the drug from the manufacturing process. These guidance documents do not directly address impurities from in-process leachables, but merely refer to "extraneous contamination that should not be present" that should be controlled by current good manufacturing practices (cGMP). General guidance on equipment and materials used in manufacturing pharmaceutical can be found in 21 *CFR* 221.65 which states the following:

> *Equipment shall be constructed so that surfaces that contact components, in-process materials, or drug products shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements. (16)*

Perhaps the most specific FDA guidance in the area of leach-

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Table II: Safety guidance for drug containers from *FDA Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics (17).*

Route of administration or dosage form	Safety guidance
➢ Inhalation aerosols, solutions, and nasal sprays	**Case 1s:** Typically provided are *US Pharmacopeia* (*USP*) biological reactivity test data, extraction-toxicological evaluation, limits on extractables, and batch-to-batch monitoring of extractables.
➢ Injections and injectable suspensions ➢ Sterile powders and powders for injection ➢ Ophthalmic solutions and suspensions	**Case 2s:** Typically provided are *USP* biological reactivity test data and possibly extraction–toxicological evaluation.
➢ Topical delivery systems ➢ Topical solutions and suspensions, and topical and lingual aerosols ➢ Oral solutions and suspensions ➢ Oral powders	**Case 3s:** Typically, an appropriate reference to the indirect food additive regulations is sufficient for drug products with aqueous based solvents. Drug products with nonaqueous-based solvent systems or aqueous-based systems containing cosolvents generally require additional suitability information.
➢ Oral tablets and oral (i.e., hard and soft gelatin) capsules ➢ Topical powders	**Case 4s:** Typically, an appropriate reference to the indirect food additive regulations is sufficient.

ables pertains to the final container closure (17). Focus on container closure is natural because the exposure time can be extensive—months to years—and there are no further purification steps to lessen any concerns about leachables. Table II is drawn from the FDA guidance for final container-closure systems and clearly delineates the importance of the route of administration of the drug.

The guidance on upstream, in-process leachables is appropriately less detailed because the risk is lower. A biopharmaceutical process extractables team recommended that the relative risk of various product-contact materials be evaluated with a risk-evaluation worksheet so that the highest priority will be given to materials known to potentially pose the highest risk. Among the variables in the worksheet are proximity to the API; extraction capability of the solution relative to the material and its potential extractables, time, temperature, and area or volume of contact; and cytotoxicity of extractables from the materials in tests such as *USP* <87> (18).

One of the common difficulties in the use of polymeric materials in a regulated environment such as pharmaceutical manufacturing is that the commercial lifetime of any polymeric material, or one of its components, is likely to be shorter than the commercial lifetime of a successful pharmaceutical drug. Most polymers are commodities subject to intense cost pressures over time, including newer manufacturing processes and lower-cost manufacturing sites. In the European Union, the Polymerforum Group was formed to foster better communication and strategies between polymer and pharmaceutical manufacturers around the issue (19).

The literature contains an illustrative example of a comprehensive analytical leachables study conducted after a film used as container closure was changed, although the risk-assessment portion of the study that presumably justified the change of materials was not included (20). The importance of change controls and supply-chain management when using commodity products such as plastics was recently emphasized (21). A comprehensive review of safety considerations related to leachables when using polymeric materials in pharmaceutical applications was recently published (22).

QUALITY BY DESIGN

In a quality-by-design (QbD) approach to manufacturing, the goal is to design in the quality of the final product by understanding all critical parameters and implementing robust manufacturing processes to control those parameters, as opposed to attempting to test in the quality from an unstable, poorly understood manufacturing process. The importance of QbD in extractables and leachables risk assessments, particularly in the OINDP application, was recently discussed (23).

In the risk assessment of leachables, the critical QbD goal is to understand and control the safety of the tool in the application. The author's preferred process for achieving this safety is shown in Figure 1. The base of the pyramid is the responsibility of the tool manufacturer and is where most of the safety is built in, as indicated by its size. Knowledge of the technical literature could, for example, be used to understand and predict the impact of gamma sterilization on physical properties and the amount and type of gamma-induced leachables.

The green levels in the figure represent steps only the user of the tool can perform because they are highly application spe-

Table III: Toxicological risk assessment of leachables for three devices/applications. OINDP is orally inhaled and nasal drug product.

Risk variable	Device and risk levels		
	Disposable bag (50-L bag)	Disposable assembly (50-L bag, tubing set, filter)	OINDP in MDI
Proximity to API[1]	Low	Medium	High
Contact area/volume[2]	Low	Medium	Medium
Contact time[3]	Low	Low	High
Contact temperature[4]	Low	Low	Low
Difference of Hildebrand solubility parameter of extraction solution to material[5]	Low	Low	High
Material susceptibility to extraction[6]	Medium	Medium	High
Subtotal concentration assessment[7]	Low	Low–Medium	High
Exclusive use of 21 *CFR* cleared materials[8]	Low	Low	High
Cytotoxicity of leachables (*USP* <87>)[9]	Low	Low	High
Subtotal toxicology assessment	Low	Low	High
Overall toxicological risk assessment	Very low	Low	Very high

[1]High risk = final formulation; medium risk = downstream purification; low risk = upstream fermentation.
[2]High risk = > 1 cm^2/mL; medium risk = 0.1-1.0 cm^2/mL; low risk < 0.1 cm^2/mL.
[3]High risk > 30 days; medium risk = 24 hours to 30 days; low risk < 24 hours.
[4]High risk > 70 °C; medium risk = 37 ºC-70 °C; low risk = 2°C-36°C.
[5]High risk < 3 MPa$^{1/2}$; medium risk = 3 to X MPa$^{1/2}$; low risk < X MPa$^{1/2}$.
[6]High risk = elastomers or plasticized polymers; medium risk are thermoplastic polymers; low risk are metals or glass.
[7]TOC or NVR measurements from model streams can be used to estimate total concentration of leachables
[8]High risk = not 21 *CFR* cleared; medium risk =21 *CFR* cleared but significant; low risk = 21 *CFR* cleared under comparable conditions of use application differences.
[9]High risk = 100% cell death; medium risk = > 50% cell death; low risk = 0% cell death.

cific. The brown level represents steps that both the manufacturer and user of the tool can perform. The manufacturer of the tool tends to perform generic analytical testing, whereas the end user is more likely to perform analytical testing closely aligned with the application of the tool. The size of each level reflects the degree to which it helps lower the risk of leachables that affect safety. The key point in the graphic is to not be overly reliant on analytical chemistry and subsequent toxicological assessment of the analytical data, but to understand, robustly design in, and control the safety of leachables, rather than to test in the quality in the final application.

RISK ASSESSMENT

When Fawley published his milestone paper on the threshold approach to toxicology, the phrase "common sense" was prominent in the title (24). While it took many years to gain legal acceptance, the threshold strategy is now well entrenched and is being expanded on a global basis to a multilevel threshold strategy using the TTC approach. The FDA CFSAN still has only the single-level TOR, which individual scientists at FDA have described as too inflexible (25).

The pharmaceutical arena has seen some well-publicized examples of leachables that potentially might affect patient health; virtually all were from container closures. Examples in the past few decades have included polycyclic aromatic hydrocarbons from carbon black fillers in elastomers, *N*-nitrosoamines or mercaptothiazole in rubbers, and diethylhexylphthalates from plasticized polyvinyl chloride blood and intravenous bags and tubing (26, 27). Even permeation of leachables from labels and their adhesives through a low-density polyethylene film into a drug-containing vial has been observed (28).

In the biopharmaceutical industry, the published leachable examples are fewer due to the relatively short time that biologics have been manufactured. The issues in biopharmaceuticals seem more centered on API interactions with leachables and less about potential direct toxicological issues, undoubtedly due to the greater inherent instability of biologicals relative to traditional small-molecule pharmaceuticals (29). Nevertheless, a rubber leachable after a formulation change apparently caused an increased risk of red-cell aplasia in European patients receiving EPO therapy (30).

Case histories of leachable problems present several clear trends in risks due to leachables. Because of their complex formulations and manufacturing processes, cured elastomers often have a much greater chance of having leachables with direct health risks than thermoplastics, and drug-leachable instability interactions are much more prevalent problems than direct leachable toxicity concerns. The higher risk of cured elastomer issues should be addressed by minimizing contact area and time, or selecting noncured (i.e., TPE) elastomers or over-molded elastomers (31). Drug-stability studies should be performed early in the material evaluation process, and analytical-leachables studies done to characterize the performance of acceptable materials or establish root cause for materials that reduce drug stability.

THE KNOWLEDGE APPROACH IN RISK ASSESSMENT

The goal of any risk assessment should be to promote a rational resource allocation to address potential problems, with the highest risk areas receiving the highest scrutiny. To assess the toxicological risk of leachables from product-contact surfaces, one must understand material science, solubility parameters, the effects of sterilization procedures such as gamma irradiation, application-specific parameters (i.e., contact time, temperature, surface area and volume, solution properties, and proximity to the final formulation), and relevant toxicology to assess the value of extractables and leachables testing.

This scientific assessment must be combined with information from the material supplier. Supplier information should substantiate that the raw materials have appropriate 21 *CFR* clearance for the application, the proper controls are in place for cGMP manufacturing, and whether available generic extractables or leachables data can help in the risk assessment. Often the risk assessment using the combination of the manufacturer's generic leachables data with the end-use application-specific parameters and a TTC approach will conclude that further leachables studies are not necessary to establish the safety of the leachables in terms of direct toxicity.

Table III shows the analysis of the toxicology risk using a series of potentially important variables when using three devices in three applications, roughly based on the protocol suggested by the Biopharmaceutical Process Extractables Core Team (17). Other possible risks from leachables, such as product formulation instability or assay interferences, would be assessed separately.

The first section of the table contains estimations of six variables that could affect the concentration of observed leachables. The second section contains estimations of two variables related to the potential toxicological risk of the leachables. Rather than assign numerical values to each risk level, such as the 1–10 scale previously suggested, the overall risk is estimated with high, medium, or low categories. Rather than sum up the numerical risk levels to achieve an overall risk assessment, the relative risk of toxicology of the leachables and the relative risk of the amount of leachables are evaluated separately. The two risks are viewed as multiplicative, in line with the normal definition of risk as equal to the degree of the hazard times the level of the exposure. This separate evaluation allows for the possibility that if the toxicology is estimated to be low risk, then the concentrations of the leachable are not as important, much as in the TTC approach.

SUMMARY

As scientific progress continues to be made, methodologies are advanced, sources are better controlled, materials improve, and processes are upgraded and better measured and controlled, the best practice to assess the risk of leachables will further evolve. Science and understanding are not static. However, the fundamental understanding of all the technical issues regarding leachables and toxicological safety will continue to be applied to achieve a knowledge-based risk assessment.

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