Toxicological Risk Assessments: Addressing Concerns about Exposure to Potentially Hazardous Substances

By Jeffrey W. Card, PhD and Hana Fikree, MS
Manufacturers use a variety of control measures to ensure their products meet established levels of quality. This includes ensuring each batch or lot produced meets established release specifications and known or suspected hazardous substances are not present at levels of concern in their products.

But, how do we know whether certain compounds or substances might be potentially dangerous or toxic? How is the acceptability of the presence of specific levels of potentially dangerous compounds established? And what happens when a batch of an active ingredient or a finished product is found to contain such a substance?

Toxicological risk assessments address the risks associated with exposure to potentially hazardous substances and can be conducted in one of two ways. The first is a proactive approach in which the safety of a given substance is evaluated prior to exposure. This approach can be used as a tool to find substances of concern and set limits for them.

The second is a reactive approach that similarly evaluates the safety profile of a given substance, but then uses this information to determine the risks associated with an exposure that might already exist. Both of these approaches can be used to determine risks associated with exposure to residual solvents, process impurities, leachables and extractables, contaminants and other substances that may find their way into a given product or its components.

This article provides information on the conduct of risk assessments and pertinent examples that demonstrate their utility in various scenarios.

**Proactive Risk Assessments**

Following the identification of a substance of concern, the risk assessment begins with the collection and analysis of relevant nonclinical and clinical information on the effects and safety of the substance in question. Knowledge of potential class effects of substances with similar chemical composition is useful and should be taken into consideration.

Using all of the acquired information, a safe level of exposure for the substance can be derived based on the known or anticipated use pattern for the product in question (daily tablet, weekly injection, implanted device, etc.). A specification limit for the substance can be established based on this information to identify a level of the substance in the finished product or its components (e.g., active ingredient) that is considered suitable given the product’s intended use.

The following examples highlight the proactive risk assessment procedure.

**Leachables From a Medical Device**

An implantable cardiovascular drug delivery system is being developed and forced extraction tests are performed to determine whether there may be leachable substances of concern. The tests reveal a variety of extraction patterns that vary according to the degree of hydrophilicity of the substances.

Highly hydrophilic substances are extracted rapidly and in relatively large amounts, while hydrophobic substances are extracted in much lesser amounts and over a prolonged period of time. Thus, the hydrophilic substances are considered likely to leach quickly from the implanted device and to have a short residence time within the body (less than seven days).

Conversely, hydrophobic substances are considered likely to leach much more gradually from the device and in lower daily amounts, resulting in a longer exposure period (more than 90 days). The toxicity profiles of the extracted compounds and related substances are evaluated and do not indicate significant toxicity concerns, but the data are limited.

The problem becomes whether the presence of these leachable compounds at the analyzed levels may be of concern, and regulatory guidelines and worst-case scenarios are considered. Based on this evaluation, the predicted patterns and levels of exposure for the various substances identified in the forced extraction tests are determined to be of minimal concern, so product development may continue at the manufacturer’s discretion.

**Genotoxic Impurity in an Oral Capsule**

A specification limit is required for a substance that may be present as a process impurity in a daily-use oral capsule. As the substance is potentially a genotoxic carcinogen and the administration route is oral, the margin of exposure approach is considered suitable.

This approach involves the derivation of a benchmark dose for the most sensitive tumorigenic effect observed in an animal carcinogenesis study and a comparison of this limit to the estimated normal human background (e.g., dietary) exposure. A margin of exposure of less than or equal to 10,000 is considered to be of low concern from a public health point of view and might reasonably be considered as a low priority for risk management actions.

A determination is made of the additional exposure to the substance that could arise due to its presence in the capsule such that the overall margin of exposure remains acceptable. These data provide the basis for deriving a science-based specification limit for the substance that is used during the manufacturing process for the capsules.

**Reactive Risk Assessments**

Reactive risk assessments are conducted after a potentially hazardous substance, not previously addressed, has been detected in a product or its components. In such cases, the approach is much...
the same as for proactive assessments in the sense that relevant information on the effects and safety of the substance is compiled to generate a picture of the safety profile of the substance.

Consideration is then given to the amount of the substance that has been detected in the product and to the use pattern of the product so that an estimate can be made of the level of exposure to the substance that may occur or already has occurred. This exposure level is then put into perspective with regard to the identified safety information to provide an evaluation of the risks associated with the exposure.

The following examples highlight the reactive risk assessment procedure.

**Degradation Product in an Ophthalmic Solution**

An unknown impurity is detected in an ophthalmic drug formulation that has a dose administration schedule of twice daily for 10 days. It is determined the impurity is a degradation product with a chemical structure similar to that of the active ingredient. Specifically, it resembles the active ingredient, but with a chemical linker that, if cleaved, would release the active ingredient and a weak acid.

Both the impurity and the substance potentially produced via cleavage of the chemical link are very weak acids that would only be administered to the eyes in nanogram quantities. Moreover, their physicochemical characteristics suggest that they would be readily excreted. Given that the active ingredient is not of concern, the focus of the assessment turns to the weak acid.

This substance is noted to be similar to another weak acid (a metabolic product present at high concentrations in human blood), and to have itself been detected in the plasma and cerebrospinal fluid of healthy humans. After comparing both potential local and systemic toxicity, it is determined that patient safety is unlikely to have been compromised.

**Contaminant in an Oral Tablet**

Gram quantities of a silicone gasket are found to be missing from a production line and presumed to be present in two batches of an active ingredient destined for incorporation into daily-use oral tablets. The missing portion of the gasket is presumed to have been shredded during the production process, as it was reported to have passed through a 1.5 mm sieve.

In this case, there is only one chemical substance to be addressed, so information on the oral toxicity of silicone polymers is reviewed. A calculation is made of the likely maximum exposure given the amount of gasket that is missing, the possible sizes of the shredded pieces and the quantity of active ingredient with which the shredded pieces may have been mixed.

Based on this evaluation, it is determined that relative to the amount of silicone that is considered safe for oral consumption due to its presence in food, the minor amount that would potentially be consumed in this particular tablet is not of toxicological concern. As a result, it is determined that patient safety is unlikely to be compromised should the manufacturer decide to continue production of the oral tablets with the batches of active ingredient in question.

**Residual Solvent in a Subcutaneous Drug Product**

During routine analysis of a subcutaneous drug product, a residual solvent is found to be present at an unexpectedly high level. The product in question is intended for monthly administration, whereas regulatory guidelines have provided recommended exposure levels for residual solvents that are based on an assumption of daily exposure.6

As such, the manufacturer wishes to determine if a higher exposure level due to the intended use of this product may be considered acceptable. The nonclinical and, if appropriate, clinical effects and toxicology of the solvent are reviewed, focusing on studies conducted using relevant routes of administration. Based on the rapid systemic metabolism and elimination of the solvent and its toxicity profile, it is determined that once-monthly exposure is unlikely to have posed a safety risk.

**Conclusion**

Toxicological risk assessments provide an indication of the risks associated with exposure to a given substance based on an evaluation of the hazards that are associated with that substance. Information on the physicochemical characteristics and effects of a given substance is important and must be considered in conjunction with the known or anticipated conditions of exposure to the substance.

In the absence of sufficient safety data for a substance, read-across information from structurally similar substances can be used and worst-case exposure assumptions can be made. All of these factors combine to generate a scientifically defensible approach, whether proactive or reactive, that addresses the risks of exposure to potentially hazardous substances and that can help establish specification limits, resolve contamination issues, and improve product quality.

**References**


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Acknowledgements

The authors would like to acknowledge the helpful comments of Lois Haighton, DABT, ERT, and Valentia Lee-Brotherton, PhD, of Cantox.

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