

Sapphire News

A Chemical Engineer's Guide to Toxicology by Lisa M. Sweeney, Ph.D.

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Knowledge of the science of toxicology is a critical component to understanding current issues important in the professional, civic and personal lives of chemical engineers. Topics such as children's health, endocrine disrupters, development of new drugs, and the high-production-volume (HPV) chemical testing initiative are examples of such issues. This article discusses what toxicology is, the basic principles of toxicology, and its roles in public health and the pharmaceutical and chemical process industries.

What is toxicology?

Toxicology, as defined in the subtitle of one of the field's classic texts, is the "science of poisons" (1). Toxicology may also be defined as the study of the adverse effects that physical agents (e.g., radiation) or chemicals can cause to biological systems. The adverse effects may cover the spectrum from those that are unwanted but not harmful (e.g., dry mouth) to those that are lethal. Effects may be immediate or delayed (e.g., asthma vs. cancer), reversible or irreversible, localized or systemic. Toxicologists study what these effects are, study how they occur, and make or influence decisions on how to use (or not use) chemicals because of these effects.

The study of toxicology may be organized in different ways - by agent of interest (radiation, metals, pharmaceuticals, pesticides, endocrine-active compounds, naturally occurring toxins), organ systems affected by the agent (liver, kidney, reproductive system), types of effects (cancer), techniques used (inhalation, dermal exposure, computational toxicology, epidemiology, risk assessment), and species or settings of interest (ecological toxicology, veterinary toxicology, occupational toxicology, food safety). Very few undergraduate toxicology programs exist. Therefore, practicing "toxicologists" typically draw on their training in other fields, such as biological sciences, chemistry, mathematics and statistics, and, yes, chemical engineering, in addition to formal or informal training in toxicology, typically at the graduate or postgraduate level.

While a wide range of data may be of value in evaluating the hazards of a given compound, stakeholders from around the world - members of the Organization for Economic Cooperation and Development (OECD) - have specified a Screening Information Data Set (SIDS) that should be available for HPV chemicals (defined as compounds produced at or in excess of 1 million lb/yr). The SIDS for individual chemicals sponsored by member countries are typically summarized by industry representatives (who hold the unpublished data), reviewed by the sponsor country, then the reports are reviewed and approved by the OECD, and finally the reports are published.

Toxicological endpoints required or recommended for the SIDS are summarized in the table. In general, toxicity testing is driven by specified regulatory requirements, product stewardship concerns, or a desire to move from a default chemical risk assessment by providing chemical-specific data to replace conservative assumptions. The SIDS also includes physical and chemical data (e.g., melting and boiling points) and environmental fate data (e.g., biodegradability) that help scientists assess where the compound is likely to be found (e.g., air, water, sediment) and how persistent it is likely to be in the environment.

Basic principles of toxicology

Three "laws" capture the essence of toxicology and organize the study of the science (2):

- "the dose makes the poison"
- chemical structure and biology determine the specific response observed
- humans are animals, so the study of animals is of value in understanding the effects in humans.

These three principles describe the concepts of dosimetry, mode of action, and risk/hazard assessment.

Dosimetry

The first law of toxicology, that the dose makes the poison (i.e., the dose-response relationship), is commonly attributed to Paracelsus (1493-1541), who wrote "All substances are poisons: there is none which is not a poison. The right dose differentiates a poison and a remedy." The first law embodies the common-sense understanding that a tiny amount of a substance generally considered safe is highly unlikely to result in an adverse effect, but large amounts of these same compounds may overwhelm the processes the body uses to keep things in balance. For example, humans need to have copper and vitamin A in their diet for essential metabolic functions, but too much of either can be toxic.

Another aspect of the dose-response relationship is that increasing doses may lead to increasing severity of effect (e.g., "variations," a mild effect, or "malformations," a severe effect in developing animals). "Dose" refers not only to the amount of the compound, but also how it is administered. Humans usually experience exposure by inhalation, ingestion or absorption through skin. In the laboratory or clinical setting, animals and humans may be dosed by injection. Injections may be delivered as a bolus (over a short period of time) or by continuous infusion over a longer time.

Dosimetry is the stronghold of the more mathematically inclined toxicologist, and the realm in which a chemical engineer is likely to feel most at home. Target tissue dosimetry (concentrations in affected organs) may be estimated through techniques such as physiologically based pharmacokinetic (PBPK) modeling. This technique uses mass balance equations to describe the uptake into the animal, distribution throughout the body, chemical reactions that transform the compound into other compounds, and direct elimination of compounds through excretion (Figure). The basic motivation for PBPK modeling is the belief that the amount of active chemical at a relevant site at a given time is a consistent determinant of outcome, no matter how it got there (route, produced by metabolism, or administered directly).

Each compartment of the PBPK model is represented by a mass balance equation. For the generic model shown in the figure, the mass balance of the lung consists of input flows due to the inhalation of a gas and venous blood flow returning the compound from tissues (e.g., liver), and losses from the lung due to the exhalation of unabsorbed gas and arterial blood flowing away from the lung. The concentrations of chemicals in exhaled air and arterial blood can typically be considered to be at thermodynamic equilibrium. Standard techniques exist for measuring the relative solubilities (known as partition coefficients, P) of volatile compounds in air and liquids (or a suspension of ground-up tissue in saline) *in vitro* (3).

PBPK models are frequently used for extrapolation between species, or from one route of exposure to another. For example, compound X may be believed to be a direct-acting reproductive toxicant (i.e., X itself is toxic, not a metabolite). The tissue dose, not the exposure dose, makes the poison. To evaluate risk to humans, one may wish to use a rodent PBPK model to determine reproductive tissue concentrations of X for an exposure known to be without hazard for animals (from experimentation). A PBPK model for X in a human can then be used to determine what human exposure concentration (the human equivalent concentration or HEC) would result in the same tissue concentration. If human exposures to X are in the range of the HEC, a concern exists, but if human exposures are orders of magnitude lower, concern is mitigated.

Extrapolation of effects

The second law of toxicology pertains to the specificity of the effects of toxic agents in target organisms, while the third law pertains to the extrapolation of results between species (e.g., from laboratory animals to humans). The second law refers to mode of action or mechanism, i.e., how does chemical X do what it does to target Y? The third law observes that understanding the mode of action in a test species is relevant to understanding effects in humans - that is, whether a demonstrated hazard in animals can be inferred or disputed for humans, based on the mode of action.

In the absence of evidence to the contrary, effects observed in animals are generally assumed to have a reasonable likelihood of occurring in exposed humans (third law) by the same mechanism as in animals (second law). For example, the monomer vinyl chloride was found to produce tumors in the liver that originated from blood vessels (hemangiosarcomas) in animal testing. The elevated occurrence of this otherwise rare tumor in a group of occupationally exposed workers was strong evidence that vinyl chloride caused these tumors, rather than another compound or random chance.

However, an understanding of the mode of action may suggest that humans may not be susceptible to certain effects. A certain type of kidney tumor can develop in male rats because of binding to a protein known as alpha_{2u} globulin, which male rats have but female rats do not have. Furthermore, humans do not produce this protein. Thus, compounds that induce kidney tumors in male rats via alpha_{2u} globulin are not anticipated to pose a cancer hazard to humans.

Applications of toxicology

Applied toxicology can be qualitative or quantitative. Examples of qualitative assessment of agents include the establishment of lists such as hazardous air pollutants, and classifications such as known/likely human carcinogen, known/likely animal carcinogen and known reproductive toxicant.

Quantitative assessments may result in occupational exposure limits for the workplace or for environmental exposures. These assessments may result in advisory guidelines or regulations that carry the weight of law. They are conducted by various entities, including the federal government (e.g., the Occupational Safety and Health Administration [OSHA], Environmental Protection Agency [EPA], Agency for Toxic Substances and Disease Registry [ATSDR]), state governments, professional organizations such as the American Conference of Governmental Industrial Hygienists, and manufacturers.

Toxicology testing by the chemical and pharmaceutical industries is driven by regulatory requirements and product stewardship concerns, as well as for use in standard setting. Relatively few industrial chemical engineers will work directly with toxicologists, although toxicological information can impact their work.

Toxicity is a potential concern for all involved in production, handling and use of a compound. Workplace exposure standards and materials handling procedures may have been established based on toxicity information, but the chemical engineer is likely to interact with an industrial hygienist, rather than directly with a toxicologist, about these matters. New markets or applications for an existing compound or product may open up after a manufacturer completes specified toxicity testing and receives the necessary approvals.

Toxicity may be an indirect concern when it comes to the economics of a given process. For example, use of a toxic solvent in a process is likely to subject the company to additional reporting requirements and increase disposal or waste treatment costs, due to the government's interest in tracking and minimizing exposure of the public to these compounds.

Drug development and safety assessment. Toxicity testing in the drug industry is frequently referred to as safety assessment. The therapeutic ratio of a drug is calculated as the lethal dose to 1% of the population divided by the effective dose for 99% of the population. While high therapeutic ratios are preferred, drugs with lower therapeutic ratios may still be clinically acceptable when there are few alternatives and the consequences of not being treated are dire. The impact on a chemical engineer is that if clinical trials indicate that a therapeutic compound has unacceptable side effects or is ineffective, the production scale-up or purification process the engineer is developing for that compound may be canceled.

Standard setting for the chemical process industries. The process of setting a standard or reference exposure level with minimal acceptable risk to human health is a multi-step process, and is always subject to revision based on new knowledge about a chemical or refined interpretation of previous studies.

In establishing an exposure standard, the exposure scenario is first defined. What is the route of exposure? Breathing, ingestion and skin contact are the most commonly assessed routes of exposure. Who is being exposed and who needs to be protected? Is the population of concern a group of generally healthy adult workers, or is it a mixture of children and adults of varying health status (e.g., immune-compromised), or is it an endangered species exposed to a plant effluent? How long will the population be exposed? People may be exposed for their lifetime, or the exposure may be brief, such as a worker exposed during a remediation project.

Studies of the compound of concern are then examined, and critical effects (those occurring at the lowest levels of exposure) identified. To make a risk estimate for the population and exposure scenario of concern, the risk assessor may make various extrapolations or apply safety/uncertainty factors to account for insufficient quantitative information on differences between tested species and the population of concern.

Approval of specific product applications. Medical devices and food contact substances are examples of products requiring materials toxicity testing prior to use. For medical devices, the extent of testing will vary with the expected duration of use (short- or long-term) and whether the device is external or implanted. Testing required for food contact substances includes, in addition to certain toxicity tests, simulating the possible extraction of leachable compounds from the product during use.

Toxic tort. Toxicologists may be called upon to advise lawyers or serve as expert witnesses when individuals or groups (such as employees or nearby residents) request compensation for harm they attribute to a chemical exposure. The toxicologist will typically consider the strength of the evidence that an exposure occurred, when and what the level of the exposure may have been, the nature of the alleged harm, and the likelihood that the exposure produced the harm. For example, the effect claimed may only occur at exposure levels above the odor threshold, so if the claimant never smelled the chemical, the resulting harm may not be attributed to the exposure. If exposure can be demonstrated and the effect is relatively rare in the general population but has been observed in controlled animal experiments, and the timing of the effect relative to the occurrence of the exposure is reasonable, the case is stronger.

Current topics

This section is not intended to be a comprehensive discussion, but rather a sample of two important issues currently faced by the toxicology community - sensitive populations and children's health, and assessment of large numbers of chemicals.

Sensitive populations and children's health. The subjects of sensitive populations in general, and children's health in particular, have been hot topics in the fields of toxicology and risk assessment. Traditionally, safety factors and uncertainty factors have been used in standard setting to protect against potential differences between not only the tested species and the species of concern

(frequently humans), but also between the "average" human and sensitive humans, referred to as interindividual variability. These differences may derive from both the delivery of the active compound to the target tissue (pharmacokinetics) and the type of response that results from the presence of the active compound at the target site (pharmacodynamics).

Researchers in this area are striving to characterize whether the traditional safety/uncertainty factors are adequate for protecting certain subpopulations, in particular, children. In addition to scientific questions, difficult policy questions, such as what percentage of the population should be protected - 90%? 95%? 99%?, 99.9999%? are also being debated.

Assessment of large numbers of chemicals. The EPA's HPV Chemical Testing Initiative, announced in 1998, called for chemical manufacturers to voluntarily provide basic toxicological information (similar to the SIDS endpoints in the table) on 2,800 chemicals for review by stakeholders. In many cases, the companies already had this information but had not publicly released it. For those endpoints for which data are not available, companies are asked to fill the data gaps.

This may be done by testing, but for both cost savings and animal welfare concern, it may be possible to use information on related chemicals to provide a reasonable estimate of toxicity. For example, one may consider the toxicities of a group of structurally related chemicals. For certain endpoints, there may be data indicating consistent, structure-related changes in toxicity (e.g., decreasing toxicity with increasing number or size of alkyl groups). For another endpoint, data may be available for some but not all members of the category. It may be possible to interpolate among category members to create strong arguments that the result of the missing test will fit within trends established in the category and that testing is not needed. In such cases, interpolation in the middle of the category is strongly preferred to extrapolation at the ends of the category. Such strategies can give quicker answers, reduce testing costs, and minimize animal usage for toxicity testing.

For More Information

Reporting of toxicology and risk assessment in the popular media is frequently shallow or one-sided. For example, reporting on new wonder drugs may discuss only benefits, while reporting on industrial chemicals is apt to focus on the negative. For specific topics, a good Internet search engine should cast a broad net, but as with all information on the Internet, be wary of the reliability or bias of the source. Chemical engineers who did not minor in pre-med may find a biomedical glossary or dictionary helpful. [ext goes here...](#)