

**Note on:  
What is a poison?**

*Although some chemicals such as arsenic compounds are popularly known as poisons it is not widely recognised that all substances have the potential to be poisonous depending on the degree of exposure. The dose is the key to the potential for adverse effects or poisoning to occur. While there is no such thing as a safe chemical, it must be realised that there is no chemical that cannot be used safely by limiting the dose or exposure. Poisons can be safely used and be of benefit to society when used appropriately. For example, Warfarin is used in high doses as a rat poison but low doses are used clinically to prevent blood clots after a stroke or heart attack.*

**Introduction**

All materials have the potential to be poisonous, in contrast to a common misconception that only certain chemicals and substances are poisonous. The dose is the key to the potential for adverse effects to occur, and this concept is known as the dose-response relationship.

The Swiss physician and alchemist Paracelsus first identified the relationship between the dose and the response, or effect it causes, during the Renaissance. It was Paracelsus's belief that it was not the substance which was toxic but the amount. The dose-response relationship is fundamental in determining safe concentrations. For example, paracetamol is a popular remedy for headaches, muscular pain and other ailments, and can be safely used without ill effect. However, paracetamol can cause fatal effects if sufficient quantities are ingested, namely an overdose. Hence the warning added to medicine labels not to exceed the stated dose.

While there is no such thing as a safe chemical (either naturally occurring or man-made) in respect of the potential to cause adverse effects under all conditions of exposure, it must be realised there is no chemical that cannot be used safely by limiting the dose or exposure.

It is also important to recognise that a chemical may have a number of inherent hazards. These include potential physicochemical, health-related or environmental hazards such as explosiveness, carcinogenicity or persistence in the environment. The likelihood of the hazardous properties of a chemical causing harm to people (or the environment) i.e. posing a risk depends upon exposure. The Royal Society of Chemistry's position is to promote the principle of risk based substitution (where both hazard and dose are taken into account) over hazard based control regimes (based on hazard alone) for chemicals. This approach recognises that chemicals may have a variety of hazards so simply substituting a chemical that is less toxic may not be appropriate as the new chemical may introduce other new hazards such as flammability or ecotoxicity.

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## **What is a Poison?**

A poison can be described as '*any substance which when introduced into or absorbed by a living organism, destroys life or injures health*'. Toxicology, or the science of poisons, is the study of the adverse effects of chemicals or physical agents on living organisms. The adverse effects may take many forms from immediate death to subtle changes not realised until months or years later.

Familiar poisons include arsenic compounds, carbon monoxide, hydrogen cyanide (prussic acid) and strychnine. A newsworthy example is ricin, a castor bean derivative, which is so toxic that poisoning can lead to death from 1 or 2 milligrams when taken orally (less than 1 milligram of ricin is lethal to humans if the poison is inhaled), and there is no known antidote in contrast to many other poisons. Comparing these poisons with more innocuous medicines in every day use it is interesting to note that poisoning from such medicines is among the most common cause of deaths among adults. The top five causes of poisoning in a recent study were, in order, antidepressant medications, analgesics such as aspirin, street drugs, cardiovascular drugs and alcohol.

## **A Brief History**

Toxicology has its origins with cave dwellers who used poisonous extracts from plants and animals in hunting and warfare. Well known historical victims of poisoning include Cleopatra and Claudius. Moving to the time of the Renaissance and the 'Age of Enlightenment', concepts fundamental to toxicology were identified by Paracelsus and later Orfila.

Paracelsus (1493-1541) is referred to as the 'Father of Toxicology'. He determined that specific chemicals were responsible for the toxicity of a plant or animal poison. Most notably he documented that the body's response to those chemicals depended on the dose received. Paracelsus's studies showed that low doses of a substance could be harmless or beneficial, whereas higher doses could be toxic. This is known as the dose-response relationship, a fundamental concept of toxicology.

The importance of Paracelsus's discovery should be considered alongside the achievements of his contemporaries at the time, Da Vinci, Columbus and Botticelli. Co-incident with Paracelsus's birth year, Columbus had returned from his first trans-Atlantic voyage and had already set sail for a second venture. At the same time Leonardo Da Vinci and Sandro Botticelli flourished as artists.

Paracelsus is often quoted for his statement "All substances are poisonous; there is none which is not a poison. The right dose differentiates a poison and a remedy". His work laid the foundation for transforming medical science from the medieval to modern forms. In fact he believed that certain substances, such as arsenic, mercury and lead could be beneficial in the treatment of disease if administered in very small controlled doses.

Orfila (1787-1853), a Spanish physician, was the founder of modern forensic toxicology. He identified a systematic correlation between the chemical and biological properties of poisons of the time. He demonstrated the effects of poisons on specific sites by analysing autopsy materials for poisons and assessing the associated tissue damage. He is best known in French Legal Medicine for demonstrating arsenic in tissues using the Marsh test.

## **How do Poisons Work?**

Toxic substances are not necessarily toxins. Toxins are substances produced by a living organism that are poisonous to other organisms, for example bacterial toxins, fungal toxins and amphibian skin secretions. The term toxicant is used herein to include toxic substances and toxins. The routes by which toxicants exert their effects can be through skin absorption, inhalation, and ingestion or by injection. Toxic substances may have different modes of action, that is they may be systemic or organ toxicants. A systemic toxicant is one that affects the entire body, or a number of organs rather than one specific site. For example, cyanides affect

virtually every cell and organ in the body by interfering with the cell's ability to use oxygen. Toxicants may also affect specific target organs or tissues. For example, lead is a specific organ toxicant that affects three target sites; the kidney, the central nervous system, and the haematopoietic (blood forming) system. The effect of toxicants on the target organ may vary depending on dosage and the route of exposure. For example, a poison may affect the nervous system after acute exposure but may affect the liver after chronic exposure.

The effect of poisons may be acute, that is they are able to cause sudden and severe adverse effects within a short time of exposure. Chronic toxicity is characterised by adverse effects that occur following continued exposure over an extended period of time.

Dosage is the most important factor influencing toxicity. The dose is the total amount of a substance administered to, taken or absorbed by an organism. An example of dose-related toxicity is ingestion of common salt, sodium chloride, which is essential for human health in small doses but large doses may be harmful.

Substances may also accumulate with repeated exposure over time to a total dose that may instigate toxicity. Cumulative effects are overall adverse changes that occur when repeated doses of a harmful substance have biological consequences that are mutually enhancing. For example, polychlorinated biphenyls (PCBs) are organic compounds that tend to accumulate in animal fatty tissue and have potential health impacts because the body is not able to break them down. Such effects, depending on the type of PCB, could range from neurotoxicity to disruption cell function by altering the transcription of genes.

The toxicity of a substance may depend upon its chemical and physical form. For example, chromium, Cr (VI) in the form of a chromate is readily absorbed into cells and is metabolised by reduction to a lower valency form which can cause renal toxicity. Chromates (and dichromates) can also have an irritant and corrosive effect on the skin, eyes and lungs. More importantly, chromates are able to cause lung (bronchial) and nasal cancer. Chromium (III), for example in the form of chromium nicotinate or picolinate is believed to be an essential dietary nutrient involved in glucose metabolism of the body. Higher concentrations of substances than those required for nutritional benefit may sometimes, of course, be toxic. With chromium (III), excess chromium in the diet tends not to be absorbed but will be excreted. However, repeated skin exposure to high concentrations may cause dermal problems.

The toxicity of a substance is also affected by a number of other factors including the innate chemical activity, the dosage and dose-time relationship, exposure route, species, sex and age. Also the ability of a substance to be absorbed, distributed, metabolised and finally excreted from the body affects the toxicity. The toxicity may be affected positively or negatively by the presence of other substances e.g. alcohol.

The exposure is important in determining toxicity; some chemicals may be highly toxic by one route but not by others. Although many snake venoms are highly toxic when injected by snake bite they may be harmless when swallowed. Two major reasons for this are differences in absorption and distribution in the body. For example, ingested chemicals when absorbed from the intestine distribute first to the liver and may be detoxified by metabolism. The metabolite(s) themselves may be more toxic, less toxic or of equivalent toxicity to the ingested parent chemical. Inhaled toxicants immediately enter the blood circulation and can distribute throughout the body causing toxicity before they reach the liver.

Toxic responses may be different in humans from those in various animal species; most differences are associated with differences in metabolism, or physiological or anatomical differences. For example, morphine is used as an analgesic in humans but makes cats psychotic.

There is also a concept of selective toxicity (Adrian Albert 1907-1989) that is based on the species differences in sensitivity to toxicity to an individual compound. This is the basis for the effectiveness of certain pesticides and drugs. For example, antibiotics are selectively highly toxic to bacteria while much less toxic to humans.

## What is Safe and What is Toxic?

The difference between what is a safe and what is a toxic substance can be determined by assessing responses to the different doses and understanding the purpose of the chemical. The risk of limited or minor toxicity may be acceptable if exposure can be controlled and the benefits of its use outweigh the possibility or severity of side effects. The dose-response relationship is fundamental in determining safe concentrations. There is a graded dose-response relationship for a particular toxic substance in a given species by a particular exposure route, giving rise to a threshold dose for detectable occurrence of a particular toxic effect (the No Observed Effect Level). Alternatively, a median toxic or lethal dose, statistically derived to represent a 50% probability of toxic effect or death under particular dosage circumstances, may be derived. The latter of these is most relevant in judging what is safe and what is toxic. Thus whether something can be considered a poison depends on what is found to be a safe or toxic dose of the material, balanced against the likely exposure. The distinction depends on the risk of poisoning occurring rather than the qualitative hazard. Remember Paracelsus – ‘the dose makes the poison’.

While there is no such thing as a safe chemical in respect of the potential to cause adverse effects under all conditions of exposure, it must be realised there is no chemical that cannot be used safely by limiting the dose or exposure. Thus when we discuss how toxic or safe something is we are really assessing whether the dose is toxic or non-toxic.

## References

Tutorial on Toxicology (Pt.1) - Toxicology and Environmental Health Information Programme of the National Library of Medicine, US Department of Health and Human Services.

## Additional Reading

Introduction to Toxicology, 3<sup>rd</sup> ed. John Timbrell, Informa Healthcare. 2001

RSC Environment, Health and Safety Committee Note on COSHH in Laboratories. 2003

RSC Environment, Health and Safety Committee Note on Harmful Effects of Chemicals on Children. 2004

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