

EVALUATING THE TOXICITY AND HAZARDS OF CHEMICALS

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The increased domestic use of chemical materials and formulations along with the accelerated and widespread effort of industry to supply and formulate makes it imperative to understand certain basic concepts of toxicity and hazard. Under conditions of misuse, many chemicals are sufficiently toxic to present a health hazard.

TOXICITY is a physiological property of a chemical substance which produces harm in a living organism by means other than mechanical. Chemical and physical properties are established by well known laboratory methods and toxicological properties, likewise, may be determined in the laboratory by experiments on animals. It is of particular importance to appreciate that toxicity is quantitative: all chemicals are toxic, and the degree of toxicity is dependent upon the amount of substance required to produce harm.

To cite examples, consider oxygen and arsenic. Oxygen, being essential to life, is generally assumed to be non-toxic, but when misused, it is toxic. *Too much* oxygen when administered to the premature infant is capable of rendering him blind, a specific physiological property which can be demonstrated in laboratory animals, particularly kittens. Arsenic, on the other hand, is a highly toxic poison. When used in therapeutic doses, however, it may be beneficial and arsenic has been employed medicinally in treating several diseases. While in some cases poisons are defined as legal entities; in general, they may be considered as materials possessing a certain high degree of toxicity. Webster defines toxicology as the science which treats of poisonous or toxic substances. Vitamin D is a necessary component of the diet of man, as are the other vitamins. Too much or too little will cause illness. Toxicity is a property and possesses both qualitative and quantitative aspects.

Toxic materials are handled daily on both an industrial and domestic basis. They are subjected to extensive experiments and are produced, packaged and transported, and are frequently recommended to the consuming public for specific uses. Why is it then that we do not get into trouble more often? It is because we do not encounter *too much*. Toxicologists have to determine how much is *too much* and establish limitations sufficient to insure safety under various conditions of handling and use.

A material can be considered toxic if it renders living cells, tissues or organs incapable of functioning normally. All manner of chemical exposure and the subsequent effects on the living organism must be considered. In general, chemical injury results from direct contact with tissue. The eyes may be injured and the vision impaired. The skin may be irritated or burned to the extent that healing results in scar formation. The inhalation of toxic dust, vapours, mist, or fumes may result in injury to the respiratory tract and lungs. Swallowing may result in irritation or injury to the gastrointestinal tract. The degree of injury from direct chemical contact may be slight or severe and the time required to produce a response may be short or long. To produce systemic or internal injury, a chemical must first enter the blood stream. The common routes of entry are through lung tissue, through the gastrointestinal tract or from absorption through intact or abraded skin. Systemic injury may be of a general nature, but frequently a toxicant will elicit a specific effect on specific tissues, organs or enzyme systems.

Hazard

Hazard may be defined as the probability or likelihood that a chemical will cause harm. Several factors other than inherent toxicological properties may influence the extent of injury produced by a chemical substance. Examples are: chemical and physical properties, physical state and concentration, duration of exposure, warning properties such as odour and pain, the manner of recommended use and type and number of customers. It is important to understand the basic concepts of hazard and to recognize that toxicity is but one factor in its evaluation.

Degree of hazard may be illustrated by considering two chemical materials whose vapours are equally toxic when inhaled. One material may irritate the eye or nose or be detected by odour in concentrations below those which are harmful. The other material may be odourless and non-irritating. The material with warning properties presents the lesser hazard because it can be detected in time to avert injury from over-exposure. The type of customer and extent of use can be very important. A material presents a greater hazard when used as a cosmetic than when used as an industrial chemical. In the latter case, the chemical is being handled by trained personnel, while the cosmetic, on the other hand, is used extensively in intimate contact with skin by customers who are in no position to assess possible dangers.

Method of Evaluation

Several devices are available to the toxicologist for evaluating the toxicity of a chemical substance. For older materials such as caustic and kerosene, human experience and medical records are available. The blinding effect of caustic in the eye or its corrosiveness when swallowed have been reported in the medical records and by the press. Kerosene has received similar attention. Less notorious chemicals are frequently described in technical literature which is readily available to the enterprising toxicologist. It is not uncommon, however, for an entirely new substance to be encountered. Such materials have to be taken into the laboratory and subjected to experiments with animals to learn of their physiological properties.

A variety of methods has been developed and used through the years. The industrial toxicologist, in particular, who is confronted with the problem of evaluating the hazards of many chemical materials proposed for many and various uses must learn to apply his efforts judiciously. Some materials may require only limited range-finding studies involving perhaps only a few gross observations. Other

materials, to insure safe handling and use, may require long-term chronic exposure studies. Where then does the toxicologist begin and what is his course?

It is essential to begin with a study of the problem to learn what the material is and how it is to be handled. It is further important to assess all factors relating to the recommended use of a product and to anticipate possible misuse. In such a survey, all factors must be brought into focus and the problem placed in the proper perspective. Laboratory methods can then be devised to simulate use-conditions. The matter of problem evaluation must be emphasized. The toxicologist solicits information from everyone concerned—the bench chemist, product development personnel, the salesman. He wishes to know as many of the chemical and physical properties as are available, the stage of development, the form and concentration required for proposed uses, and the manner of handling both in industrial and consumer operations.

When this information has been gathered, laboratory studies can then be initiated. The animal of choice for a particular test is influenced by the type of information desired. For example, the rabbit is the animal of choice for the evaluation of eye irritating properties since its eye is large enough to provide facility in the direct application of materials and for subsequent washing. Experience has shown that a material that does not injure the rabbit eye will not, in all probability, injure the human eye. It is a routine practice to apply a measured amount of material to both eyes of the rabbit. Within 30 seconds, one eye is thoroughly washed with copious amounts of flowing water while the other eye is left unwashed. Both eyes are examined immediately after washing for evidence of conjunctival irritation, corneal injury, and internal effects, and again after one hour, 24 hours, 48 hours, and one week. The data reveal the type of injury, the extent of injury, the rapidity of tissue reaction, the possibility of delayed effects, warning properties such as pain or lachrymation, as well as the effectiveness of immediate washing to alleviate or diminish any irritation or injury. The last three factors are of particular importance in the evaluation of hazard. Materials which produce serious corneal or internal eye injury slowly, without pain, are highly hazardous. They do not warn of their damaging potentials. Materials which react rapidly are likewise hazardous as there is usually not sufficient time to wash the contaminated eye in order to avert injury. For handling such materials, where eye contact is likely, the toxicologist must prescribe tight fitting chemical worker's goggles or the equivalent. It is not uncommon for

a chemical to be encountered that is essentially harmless if leisurely washed from the eye, but which, if allowed to remain, would produce loss of vision. For manufacturing such chemicals, the strategic installation of eye-wash fountains in the industrial plant would be prescribed.

The albino rabbit is also useful in conducting skin contact irritation studies. By removing the hair, one can prepare a large area on the back or belly adequate for studies of irritation or absorption. The skin may be abraded to simulate lesions or rashes common to many industrial workers. Materials can be confined by bandaging to simulate conditions created by wearing contaminated gloves, socks, or clothing in general. The rabbit ear can be used to represent exposed skin exemplified by the face or ungloved hand.

Several specific types of reaction may result from direct chemical contact with the skin. A common reaction is a chemical burn characterized by necrosis or denaturation followed by scab formation and scarring. Some materials are vesicants to humans; in rabbits they usually produce extensive swelling or oedema. Another type of skin reaction is folliculitis and epithelial thickening. Such a reaction in the rabbit strongly suggest that the material is capable of causing acneform dermatitis in humans, a condition resembling acne of puberty.

Many chemicals, of course, are capable of producing slight or minor irritation manifested in the

rabbit by inflammation and epidermal sloughing. Organic solvents frequently cause such responses, sometimes referred to as eczema.

Some chemicals penetrate the skin. They are absorbed into the blood stream, and in many cases, small amounts are capable of producing serious systemic injury, even death. These materials are usually studied by applying measured amounts to intact or abraded rabbit skin under an impervious cuff or by applying them by inunction in either single or repeated doses.

Some chemicals are skin sensitizers. They produce an allergic, oedematous, contact dermatitis in humans. Skin sensitization may result from either single massive exposures or from frequently repeated contact with small amounts of material. The skin rash usually results from a challenge dose following an incubation period and in some individuals may be severe and extensive. Systemic injury and death have been reported from such allergic reactions. Examples of sensitizing materials are dinitrochlorobenzene, para phenylenediamine, and poison ivy. The guinea pig has been used to assess such properties but with a limited degree of success. These tests are more reliable when conducted on human subjects.

Perhaps one of the easiest ways to become exposed to a chemical is by contact with air-borne materials such as vapours, mists, fumes, and dust. The toxicity of such materials is established in the laboratory by



Figure 1. Examining the Rabbit eye with an ophthalmoscope to observe possible internal injury.

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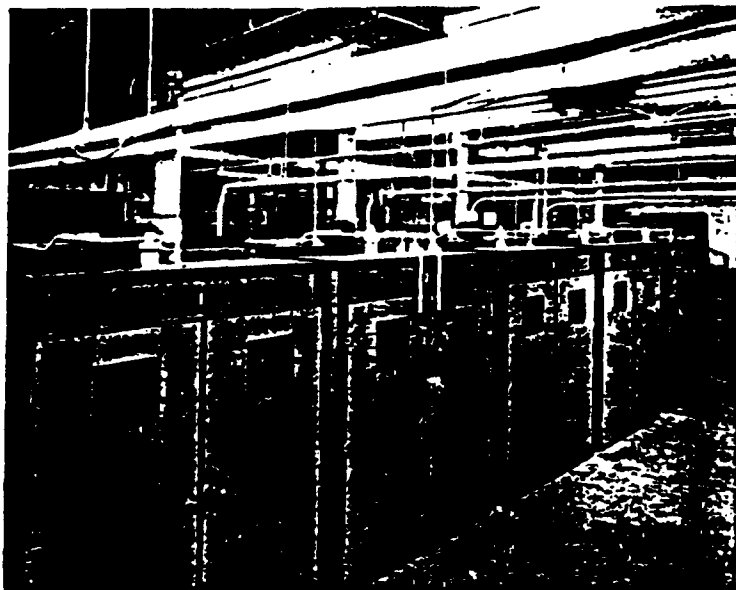


Figure 2. View of vapour exposure chambers. The Biochemical Research Laboratory
The Dow Chemical Company, Midland, Michigan.

actually exposing animals in fume chambers. Range-finding studies are usually conducted on rats by exposing them to saturated atmospheres for controlled periods of time. More definitive studies may involve several species of animals and involve quantification of exposure both in terms of concentration and duration. In more critical studies even larger groups of animals and several species are exposed to controlled concentrations for up to seven hours a day, five days a week for periods up to a year. In such cases, extreme care must be taken in selecting animals and in the subsequent care of the animals throughout the experimental period. Elaborate automatic equipment is employed to maintain and record accurately the intensity of the exposure. Animals must be observed daily to ascertain any physiological responses. On terminating such repeated exposure experiments, all animals are sacrificed and the internal organs are weighed and prepared for histopathological examination. In this manner, information is gained regarding no-effect levels as well as those levels which produce systemic injury of various types and degrees.

The animal pathologist plays a vital role in the ultimate evaluation of toxicity. He must be a trained specialist in order to detect any minute departure from normal in organs, tissues, or cells which may have resulted from the experimental routine.

During the course of such chronic experiments, various clinical studies are frequently conducted. They may include complete haematological examinations, liver and kidney function tests, enzyme studies such as cholinesterase and transaminase determinations, and any others which may be indicated. Needless to say, these studies are time consuming and costly.

It is sometimes desirable to conduct metabolic studies on animals. By knowing the mechanism of detoxification and the ultimate systemic fate of a material, it can frequently be established that the material is rendered innocuous and efficiently eliminated by various excretory mechanisms.

The effect of chemicals when taken by mouth are observed in the laboratory by feeding graded amounts to animals. The problems of ingestion generally fall into one of two categories—acute and chronic. The results obtained from single dose oral studies are usually sufficient for evaluating industrial handling hazards. Data from such a study should be adequate to allow the calculation of the dose expected to kill 50 per cent of a group of treated animals; such a figure is known as the acute oral LD_{50} dose for the given species.

The proposed use of some chemicals makes it necessary to determine the effects of ingesting small amounts of material over extended periods of time.

For such chronic feeding studies, the chemicals are usually incorporated into the animal diet at varying concentrations and fed *ad libitum* for periods ranging from thirty days to two years. Data from such tests, carefully interpreted, establishes the dose level which produces no effect as well as levels which produce injury to tissues and organs.

It should be recognized that animal data are of little use unless projected to the human counterpart. In general, it can be assumed that a chemical which will elicit a specific response in animals will do likewise in man and the seriousness of this effect will influence the prescription of precautions for safe handling. Obviously the experience of the toxicologist is invaluable.

Practical Application

It might be of interest to cite an example of how the toxicologist would evaluate the appropriateness of a chemical material for use as a 'bucket solvent'. The term 'bucket solvent' refers to an organic chemical used in small amounts for manual cleaning operations. Containers are usually small tanks or buckets holding a few quarts to several gallons. Such cleaning operations are common in the home as in industry.

'Bucket solvent' cleaning provides a good example, first, because of its universal use and second, because normal use assumes gross exposure to the liquid and vapour. A colourless, odourless, non-inflammable, non-irritating, non-toxic liquid would be ideal but, of course, no such solvent exists. Many organic substances can be used for miscellaneous cleaning purposes. The choice is surprisingly limited however, because of cost, inflammability, cleaning performance, and volatility. Possible solvents are certain aromatic hydrocarbons, benzene, toluene and xylene, certain petroleum fractions such as Stoddard solvent and the chlorinated aliphatic hydrocarbons, carbon tetrachloride, tetrachloroethylene, trichloroethylene, methylene chloride, and 1,1,1-trichloroethane, all of which are readily available.

In considering the problem of ingestion, all of these solvents have low acute oral toxicities, their LD_{50} values, for example, being within the range of several grams per kilogram of body weight. They should present no problem from ingestion incidental to handling or general use. Wilful or accidental swallowing, however, can cause harmful effects. Children have accidentally swallowed solvents and workmen have been known to drink them for intoxicating effects. It is readily possible to swallow a sufficient amount of any organic solvent to produce serious internal injury, even death. All solvents

should be stored in clearly labelled, appropriate containers, and 'coke bottle' storage should be avoided. Solvents, of course, are no substitute for alcohol.

In considering the eye irritating properties of 'bucket solvents' there is probably no real need to differentiate in this regard. Upon direct contact with the eye, all will produce transient local irritation to the conjunctiva. Prolonged corneal injury would not be likely. Due to the importance of the eye, however, protection from all foreign substances is recommended. Minimal eye protection or safety glasses should be adequate for most operations.

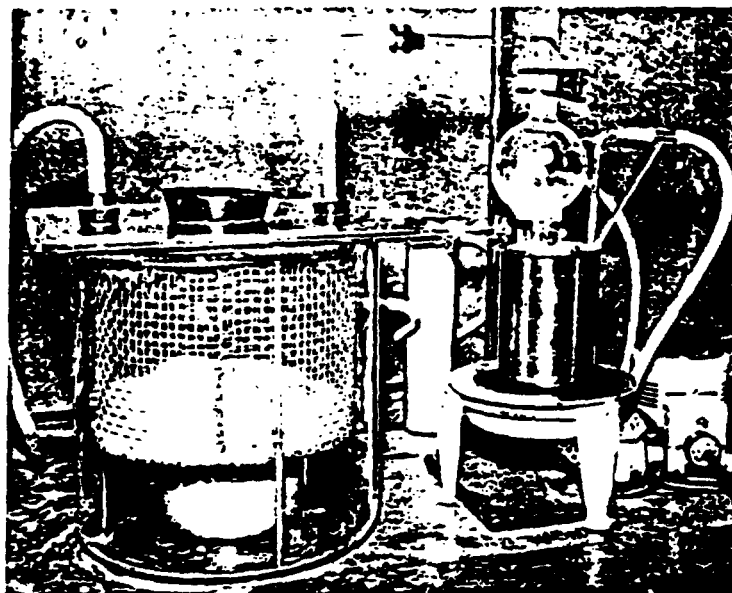
From the standpoint of skin irritation, almost any material will produce some adverse effects. All effective organic solvents remove natural oils from the skin leaving it dry in appearance and feeling. Excessive exposure may produce scaling and fissuring or may even burn, particularly if confined or if in contact with abraded skin. Solvents like xylene and ortho dichlorobenzene may be irritating upon relatively short contact. Crude petroleum fractions may produce acneform dermatitis.

It is important that a 'bucket solvent' be low in toxicity by absorption through the skin. It should be sufficiently low that occasional contacts are not harmful even though they may be extensive and prolonged. Some of these common solvents meet this qualification, but in general, prolonged and repeated skin contact with solvents should be avoided. Impervious gloves and garments are available for protection where excessive contact cannot be avoided.

The greatest hazard incidental to the use of 'bucket solvents' is that of vapour exposure. Cleaning operations are frequently conducted in small, poorly ventilated quarters. For purposes of comparison, consider two readily available solvents, carbon tetrachloride and 1,1,1-trichloroethane which have essentially the same vapour pressures. Carbon tetrachloride can be tolerated without adverse effects at levels up to 25 p.p.m. in the work atmosphere. Minimal effects can be expected from single exposures to 50-300 p.p.m. and serious effects from exposures of one-half hour to eight hours at concentrations from 300-1000 p.p.m. This latter condition can be anticipated in 'bucket solvent' applications and in the case of carbon tetrachloride may well prove fatal. Carbon bisulphide and benzene generally fall into the same category.

On the other hand, 1,1,1-trichloroethane can be tolerated without effect on a prolonged, repeated exposure basis at concentrations up to 500 p.p.m.

Figure 3. Apparatus designed for studying the effects of saturated or near saturated atmospheres on small laboratory animals.



Minimal effects can be expected from single exposures to 700–1000 p.p.m. Serious effects may result from one-half hour to eight hours exposure to concentrations of the order of 3000–5000 p.p.m. In 'bucket solvent' applications, it would be unlikely to exceed 500 p.p.m. vapour concentration in the work atmosphere where reasonable natural or artificial ventilation is present.

In the evaluation of hazard, the toxicologist must further consider the consequence of over-exposure. In the above example, 1,1,1-trichloroethane produces an anaesthesia but is not likely to produce serious organic injury. Carbon tetrachloride not only produces anaesthesia but also nausea accompanied by liver and kidney injury. If overcome by carbon tetrachloride vapour, one would probably recover from the anaesthesia but not from the organic injury. In the like case of 1,1,1-trichloroethane a few minutes in fresh air would probably result in complete and uneventful recovery.

The other solvents could be compared in a similar manner; but in short, except for benzene, they fall somewhere between 1,1,1-trichloroethane and carbon tetrachloride in suitability for use as a 'bucket solvent'. Benzene is highly toxic.

In connection with the subject of air-borne contaminants, it is pertinent to discuss the published MAC's — Maximum Allowable Concentrations. These values are also referred to as Industrial Hygiene Standards and more recently as Threshold

Limits. These terms are frequently misunderstood and misapplied. The presence of airborne contaminants is a major industrial problem because inhalation is one of the easiest ways to become over-exposed in a work atmosphere.

For this reason most environmental measurements are concerned with the amount of material that is being breathed. Acceptable exposure concentrations of vapours are usually expressed as parts per million by volume of air, and particulate matter such as mists and dusts as milligrams per cubic meter. This value may be determined by actual measurements taken in a work atmosphere known to be safe or just barely safe. It may represent results of careful toxicological evaluation with animals. In another case, the Threshold Limit may be set on the basis of similarity in chemical structure with an already established material. MAC's sometimes reveal the amount necessary to avoid systemic injury but other times are aimed at the levels which prevent unpleasant or painful exposure. In some cases, safety factors are built in while in others they are not. Three points have been established regarding these values.

- (1) There is no standardized procedure or method for arriving at a Maximum Allowable Concentration.
- (2) The endpoint is not consistent.
- (3) The value is not necessarily a measure of toxicity.

For example, one material is twice as toxic as another because it requires control to 100 p.p.m. rather than 200 p.p.m. When comparing the toxicity of materials, consequences of over-exposure must not be overlooked. A control value of 100 p.p.m. for one chemical may be necessary to prevent headache or dizziness whereas a control of 200 p.p.m. for another chemical might be designed to avoid serious liver injury. The dangers of such comparison becomes obvious. MAC values should be considered as guides for use in controlling environmental health hazards. If levels are always controlled below these quoted values, persons inhaling the atmosphere in question are not likely to experience injury.

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