Industrial Toxicology

Toxicology is the science that deals with the toxic properties of substances.

Everyone is exposed on or off job to a variety of chemical substances; most do not present a hazard under ordinary circumstances, but they all have the potential for **being injurious at some sufficiently high concentrations and level of exposure**.

Toxicology is the quantitative study of body's responses to toxic substances.

Toxic effects are undesirable disturbances of physiological function caused by poison.

A toxic effect can be defined as any noxious effect on the body – reversible or irreversible, any chemically induced tumor, any teratogenic or mutagenic effect or death – as a result of contact with a substance via respiratory tract, skin, eye, mouth, or any other route.

- There are approximately 10 million chemical compounds that have been synthesized in laboratories since the beginning of the last century.
- Approximately 1% of these (100 000 organic and inorganic chemicals are produces commercially.
- There is virtually no sector of human activity which does not use chemical products, and indeed these products have brought beneficial effects to society.

All chemicals are toxic to some degree, with **health risk being primarily a function of the toxicity and the extend of exposure.**

However, most chemicals have not been adequately tested to determine their toxicity. There is sufficient information to complete health hazard assessment of less than 2% of the chemicals produced commercially, while for only 14% of chemicals is there sufficient information to support even a partial hazard assessment.

Toxicity is a physiological property of matter that defines the capacity of a chemical to injure a living organism by other than mechanical means. The toxicity of a chemical depends upon the degree of exposure.

The responsibility of the industrial toxicologist is to define how much is too much, and to prescribe precautionary measures and limitations so that normal, recommended use does not result in the intake of too much of that particular material.

Toxicity v. hazard

A distinction must be made between toxicity and hazard.

Toxicity is the ability of a substance to produce an unwanted effect when the chemical has reached a sufficient concentration at a certain site in the body.

Hazard is the probability that this concentration in the body will occur.

Many **factors** contribute to determining the degree of hazard – **route of entry, dosage, physiological state, environmental variables** etc.

To some extent, **assessing a hazard involves estimating the probability that a substance will cause injury**.

To identify and categorize hazards of chemicals some knowledge is needed of:

- their physical and chemical properties
- their routes of entry
- their distribution an metabolism
- their effects on body systems

Chemical classification

There are numerous classification systems available.

The most popular consists of two major classes:

- ***inorganic chemicals*** (containing few carbon atoms)
- ***organic chemicals*** (their structure is based on carbon atoms)

1) Inorganic substances

- halogens - fluorine, bromine, iodine- respiratory tract irritants

- alkaline materials - ammonia, calcium hydroxide, calcium oxide, potassium hydroxide, sodium carbonate etc. – corrosive local action such as irritating to all mucous membranes; nitrous oxide is a weak narcotic

- trace metals – cadmium, chromium, copper, lead, manganese, mercury, nickel, arsenic – toxic and environmentally perssistant.

2) **Organic compounds**

- Aliphatic hydrocarbons – methane, ethane, propane, butane, octane

- Olefins (unsaturated hydrocarbons) – ethylene, propylene, isoprene

- Acyclic hydrocarbons – unsaturated are usually more toxic than the saturated ones

- Aromatic hydrocarbons contain one or more benzene rings. They are further classified:

- benzene and its derivates;**- polyphenyls; polynuclear.** Examples are benzene, toluene, styrene, naphthalene.

2) **Organic compounds**

- Halogenated hydrocarbons -

methylchloride, chloroform, carbon tetrachloride. Many of them are used in dry cleaning or solvents.

- Alcohols – methanol, ethanol, propanol etc. – most notable toxic to the central nervous system.

- Glycols and derivates – ethylene glycol are used as antifreezeing agents.

- Persistent organic pollutants (POPs) - often highly chlorinated and resistant to biological, chemical and breakdown. They include: - the first generation of organochlorine pesticides (DDT);

- polynuclear aromatic compounds – pyrens and anthracenes, generated in combustion of coal and petroleum products; - dioxins and furans – by-products of combustion/ insineration, polychlorinated biphenyls.

- Organic solvents - highly used in industry with potentially high exposure. Many of them are toxic, persistent in the environment and are known as suspected carcinogens (e.g. benzene, trichloroethylene). Some of these compounds (benzene and toluene) are also presented in combustion products of organic material, such as when tires are burned.

In evaluating a hazard, toxicity is but one factor. Others are **chemical and physical properties such as odor**.

By comparison, the material with the warning properties presents a lesser degree of hazard, because its presence can be detected in time to avert injury.

Two liquid materials can possess the same degree of toxicity but present different degree of hazard.

One material may be odorless and not irritating to the eyes and nose while the other material may have a disagreeable odor in minute concentration, or be an eye or respiratory irritant.

By comparison, the material with the warning properties presents a lesser degree of hazard, because its presence can be detected in time to avert injury.

Role of the physical and chemical properties of the substances

Although the toxic effects of many chemical agents used in industry are well known, there are many other commonly used chemicals that are not well defined. The **toxicity of a material is not a physical constant** – such as boiling point, melting point, or temperature – and usually only a **general statement can be made concerning the harmful nature of a chemical agent.**

The chemical properties of a compound often can be one of the main factors in its hazard potential.

The **vapour pressure** determines whether or not a given substance has the potential to pose **a hazard from inhalation**.

Many solvents are troublesome because they are quite **volatile** and vaporize readily into the air and produce high concentrations of vapour in a given set of circumstances.

Hence, a low-boiling solvent, other things being equal, would be a greater hazard than a high-boiling one simply because it is more volatile and it evaporates quicker.

While certain important analogies are apparent between structure and toxicity, important differences exist that require individual study of each compound.

Evaluation of chemical hazard involves also establishing the **amount and duration of exposure**, the **conditions** under which substance occurs, and determination of the effects of **other substances in a combined exposure**.

Routs of entry into body (Routs of exposure)

Chemical injury can be **local or systemic**. Local injury is the result of direct contact of the substance with tissue.

A systemic effect is generalized and changes the normal functioning of related organs operating as a system.

A material cannot produce systemic injury unless it gains entry into the bloodstream.

Common routes of entry are **ingestion, skin (eyes) absorption and inhalation.** Depending on the substance and its specific properties, entry and absorption may occur by **more than one route**. For instance, inhaling a solvent that can penetrate skin. Where **absorption into the bloodstream occurs**, a toxicant may elicit general effects or, more than likely, **the critical injury will be localized in specific tissue or organs**.

In workplaces, because of the mature of exposure, duration of the working day and the character of the compounds, **inhalation is the most significant route of entry,** followed by dermal exposure and ingestion.

Inhalation of toxic substances in the form of dust, fume, gas, vapour or mist accounts for the majority of deaths and illness.

The total amount of a toxic agent inhaled depends upon its **concentration** in the air, the **duration of exposure**, and pulmonary ventilation volumes, which increase with higher **work loads**.

The **results** may be

- acute (immediate) in the case of gassing accidents, e.g. chlorine, carbon monoxide (at high concentration), hydrogen sulphide and nitric oxide, **or**

- chronic (prolonged and cumulative) as with exposure to chlorinated hydrocarbons, lead compounds, dust inducing pneumoconiosis, paint spray and oil mists, and fume, notably that from welding operations.

Skin absorption is an important route of entry is absorption through either intact or damaged skin.

Intact skin is proof against most but not all inputs.

The resistance of skin to external irritants varies with age, sex, race, color, and, to certain extend – diet.

Contact of a substance with skin results in four possible actions:

1) the skin can act as an **effective barrier;**

2) the substance can react with the skin and cause **local irritation;**

3) the substance can produce **skin sensitization,** and

4) the substance can penetrate to the blood vessels under the skin and **enter the bloodstream.**

The cutaneous skin absorption rate of some organic compounds rises when temperature or perspiration increases. **Therefore, skin absorption is higher in warm climates or seasons.**

Absorption as a route of entry is normally associated with occupational dermatitis, the causes of which may be broadly divided into **two groups**:

- Primary irritants - will cause dermatitis at the site of contact if permitted to act for sufficient duration of time in sufficient concentration, e.g. strong acids, strong alkalis and solvents.

- Secondary sensitisizers – effect a specific skin sensitization. If a further contact occurs after approximately 7 or more days dermatitis will develop at the site of second contact. Such substances are some rubber additives, nickel, some wood dusts and proteolytic enzymes.

Ingestion – this problem is not widespread in industry.

Ingestion of toxic material may occur as a result of eating in contaminated work area, and contaminated fingers and hands can lead to accidental oral intake when a worker smokes on the job.

Like the lung, intestine behaves as a selective filter keeping out many, but not all harmful agents presented to it.

Distribution and metabolism

Once a chemical has entered the body it may be metabolized, excreted or accumulated.

Usually absorption is most rapid from the lungs, less rapid from the gastrointestinal tract and least rapid from the skin.

Once absorbed, chemicals from the lungs, skin and stomach may enter the general blood circulation directly and be rapidly spread through the body in an unmodified form. Chemicals absorbed from stomach and bowel enter the blood (hepatic portal system and are taken to the liver where they may be modified by a series of reactions.

This modification process in the liver is referred to as biotransformation.

These reactions have also been referred as **detoxification**, but this may be misleading as biotransformation may also **increase** the toxicity of a number of chemicals.

Types of toxicity

Toxicity was previously defined as any harmful effect of a chemical on a target organ.

Major types of health effects caused by toxic substances may be:

- **systemic toxicity** – serious, sometimes fatal poisoning that may occur after contact with certain organophosphate pesticides, ingestion of high dose of tranquillizer drugs or inhalation of organic solvents.

- **Organ toxicity** – certain chemicals have a target organ specificity (harm a certain organ rather than others) often because of biotransformation or bioconcentration. The route of exposure might also be responsible for specific organ injury.

- Liver toxicity –most chemicals are metabolized in the liver. Therefore the liver becomes a target organ for many substances. Organic solvents (ethanol), certain trace metals (copper, cadmium) often cause extensive liver damage – fatty changes, necrosure, fibrosis alteration of the structure.

Kidney toxicity – many xenibiotics are removed by glomerular filtration and tubular excretion, while essential elements are reabsorbed in the tubuli. Agents with kidney toxicity include metals (e.g. mercury, cadmium, lead) and drugs (sulphonamides).

Neurotoxicity – functional or organic alterations of neurotransmitters can cause symptoms of paralysis (organophosphates, chlorinated organic compounds, metals etc.)

Skin toxicity – **allergic** reactions can occur in sensitive individuals while skin **irritation** can occur in anyone exposed to a wide variety of irritating chemicals.

Immunotoxicity – the immune system ensures 1) non-specific defence mechanism against agents, for which no previous sensitization occurred, and 2) specific, adaptive mechanism directed against specific agent, for which the organism has previously been sensitized or infected.

Reproductive and developmental effects

Various agents have effects on the reproductive systems, both male and female. They may affect fertility, sexual function and libido, but of particular concern are the potential effects on foetus.

Genotoxicity – chemical agents can interact with structure and function of DNA, leading to alteration of genetic codes and information. This process involves gene mutation, chromosomal alteration (structural and numerical) and/or gene rearrangements.

Carcinogenity – cancer occurs as a consequence of multiple genetic and non-genetic events, leading to uncontrolled proliferation of cells.

The categorization of IARC, based on the evidences for carcinogenity is probably the most widely used by regulation agencies. **The categories are:**

1. There is sufficient evidence for carcinogenity in humans.

2A. An agent is probably carcinogenic to humans.

2B. An agent is possibly carcinogenic to humans.

3. There is inadequate evidence for carcinogenity to humans.

Groups of carcinogens

- **Inorganic –** arsenic, nickel and chromium are thought to cause cancer
- **Organic –** polycyclic aromatic hydrocarbons (β-naphtylamine, benzidine), benzene, nitrosamines
- **Asbestos and man-made mineral fibres –** glass fiber, aluminium inside etc. Asbestos fibers act as promoters and accentuate carcinogenic process initiated by cigarette smoke and other common environmental carcinogens.

Action of toxic substances

- The toxic action of a substance can be divided into **acute and chronic effects**. In addition, we can distinguish **acute and chronic exposures**.
- **Acute effects and acute exposures** involve short-term high concentrations and immediate results of some kind: **illness, irritation, or death.** They are usually related to an accident.

Chronic effect is characterized by symptoms or disease of long duration or frequent recurrence. **Chronic poisoning** assumes that **some level of material will be continuously present in the tissues**. It can also be produced by exposure to a material that produces irreversible damage, so **the injury accumulates rather than the poison**. **Acute exposure** generally refers to exposure to very high concentrations during very short time periods. **Chronic exposure** involves repetitive or continuous exposure during long time periods.

BASIS FOR WORKPLACE STANDARDS

Before chemical agents are introduced into the workplace, it is advisable to know their toxic effects. When dealing with a new chemical, animal or human toxicity data are usually unavailable.

In such case, it is important to apply the following methods to provide the needed information, which is the basis to determine the standards.

Chemical analogy

The nature of response to a chemical may be assumed to be analogous to that produced by contact with known substance with a similar chemical structure.

As a first approximation, some estimate of toxic potential can be obtained.

Animal experimentation

Groups of animals can be exposed to controlled, known concentrations for 8 hours a day, 5 days a week, for weeks, months, or periods up to year.

In such cases, extreme **care** must be taken not only **in the selection** but also in the **subsequent care** of the animals throughout the experimental period.

Toxicological screening should include **both acute toxicity and studies of repeated administration at short intervals.**

Long-term studies performed during the life span of the animal, and in some instances – if indicated – **over several generations**, should be part of the complete test program.

When the concentration reaches a certain level, some of the animals will be killed. Results of such studies are used to calculate the **lethal dose (LD)** of toxic substance. Several designations can be used such as LD50, LD0, LD100 and so on. The **LD50** is the calculated dose of a substance that kills 50 % of a defined experimental animal population by any route of exposure.

The **LD0**, which is not very often used, is the concentration that would produce no death in an experimental group and would be the highest concentration that would be tolerated in animals and result in zero deaths; **LD100** would be the lowest concentration that produce death in 100 % of the exposed animals. A similar designation, **lethal concentration (LC) is used for airborne materials, when the dose by inhalation is needed.**

After the toxic material has been administered, there are various criteria for evaluation of the ***response.***

Histopathological examination and weighing of organs removed from the animals reveals the **site of action, the mode of action** of the toxic agent and the cause of death. The liver and the kidney are particularly sensitive to the action of toxic agents.

The effect of the toxic agents on **the growth rate** of animals is another criterion.

Physiological function tests also provide useful criteria of response, both in experimental studies and in assessing the response of exposed workers.

They can be especially useful in studies of populations with chronic conditions.

A sufficiently small amount of chemicals (generally non carcinogenic) is not harmful. This means that there is a **threshold of effect or a "no effect" level**.

The chemical may damage one cell or several cells, but no effect, such as kidney dysfunction, will be measured.
As the dose is increased, there is a point when the first measurable effect is noted.

The toxic potency of a chemical is defined by the relationship between the dose (the amount) of the chemical and the response that is produced in a biological system.

From animal studies is determined a **"no-observed-adverse-effect level" (NOEL)** – also called "safe" level.

Calculations can also be made using the lowest dose that produced an effect – the "**minimum-observed-adverse-effect level" (MOEL) or "unsafe" level.**

Human epidemiological data

Records of human experience for exposures to many substances are available. The epidemiological analysis can also reveal the relationship between time of occurrence of an adverse effect and age at the first time of exposure, which help to establish or clarify the influence of variables other than the agent under study.

For example, cigarette smoking in study of lung cancer among asbestos workers, is such a variable.

Threshold limit values refer to airborne concentrations of substances and represent conditions under which it is believed that nearly all workers may be repeatedly exposed day after day without adverse effect.

They are based on the best available information from experimental animal studies, human studies and industrial experience, and, when possible, from combination of the three.

The basis on which the values are established differs from substance to substance; protection against impairment of health may be the guiding factor for some, whereas reasonable freedom from irritation narcosis or other forms of stress may form the basis for others.

There are three categories of **Threshold limit values**:

Threshold limit values – Time Weighted Average (*TLV-TWA*) – **the time-weighted concentration for a normal 8-hour workday and a 40-hour workweek**, to which nearly all workers may be repeatedly exposed, **day after day, without adverse effect**.

Threshold limit values – Short Term Exposure Limit (*TLV-STEL*) – is defined as a 15-minute time-weighted average exposure which should not be exceeded at any time during a work day even if the eight-hour time-weighted average is within the TLV. **Exposure to the STEL should be not longer than 15 min. and should be repeated more than four times per day.**

There should be at least 60 min. between successive exposures to STEL. **It is not a separate independent exposure limit, rather it supplements the TWA limit where are recognized acute effects from a substance whose toxic effects are primarily of a chronic nature.**

STEL's are recommended only where toxic effects have been reported from high short-term exposures in either in animals and humans.

Biological standards

One of the most useful means of assessing occupational exposure to a harmful material is the analysis of biological samples obtained from exposed people.

This analysis may provide indications of the **body burden** of the substance, the amount **circulating in the blood**, or the amount being **excreted**.

Every tissue and fluid in the body can be analyzed, but for practical reasons, **most bioassays are confined to specimens of urine or blood**. For substances such as carbon monoxide and many solvents, the analysis of exhaled breath provides information. Occasionally the analysis of samples of hair, nails, feces, or other tissues may be useful.

Examples of analyses, which can be performed on biological samples, are:

- Analysis for the **unchanged substance** (lead, arsenic, mercury) in body fluids and tissues.
- Analysis for a **metabolite of the substance** in body fluids or tissues, for example, phenol in urine resulting from exposure to benzene.

•Analysis to determine the **variations in the level of a naturally occurring enzyme or other biochemical substance** normally present in body fluids or tissues, for example, **depression of cholinesterase activity as a result of exposure to organic phosphate compounds.**

The concentrations of harmful substances are unlikely to have an even distribution in the body. In many cases the organ with the highest concentration of material is the liver or kidney, and in a number of other substances, both the liver and bones.

The organ that suffers the most severe damage and appears to store most of the toxic material is called the target or critical organ.

Solvents are stored in body fat, the lipid containing sheaths of nervous tissues, including the brain.

In many cases the body converts the material to something else that usually **reduces the ability to cause injury**. Occasionally, the conversion enhances the toxicity, but in any event, the process helps the body to dispose of the material. The conversion products may appear in the urine or blood as metabolites. For example, when body metabolizes benzene, increased levels of phenols are found in urine, which is determined as useful test and an index of exposure to benzene.