Toxicity characteristic classification

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Abstract. In this paper chemical amount rate to the exposed organism was examined. Dose characterizes the total amount of material to which an organism is exposed. The aim of this paper dynamic cumulative toxic effect was investigated. Single dosing and n-times dosing changes are expressed. This paper different routes of exposure and frequency of exposure were involved. Toxic effects also depend on the sensitivity of a biological system.

Keywords: Toxicology, type of toxic effects, dose, exposure, cummulative effects.

1. Introduction

Toxic effects may be divided according to time scale, (acute and delayed), general locus of action (local, systemic, organ specific), or basic mechanisms of toxicity (reversible versus irreversible).

Acute toxic effects are those that occur after brief exposure to a chemical. Acute toxic effects usually develop rapidly after single or multiple administrations of a chemical. However, acute exposure may also produce delayed toxicity. For example, inhalation of lethal dose of HCN causes death less than a minute, whereas lethal doses 2,3,7,8-tetrachlorodibenzodioxan will results in the death of experimental animals after more than two weeks[1]-[3].

Chronic effects are those that appear after repetitive exposure to a substance, many compounds require several months of continuous exposure to produce adverse effects. Often, the chronic effects of chemicals are different from those seen after acute exposure. Carcinogenic effects of chemicals usually have a long latency period. Tumors may be observed years (in rodents) or even decades (in humans) after exposure[4]-[6].

2. Toxic effects classification

Toxic effects of chemicals may be classified based on the type interactions between the chemical and the organism. Toxic effects may be caused by reversible and irreversible interactions.

When reversible interactions are responsible for toxic effects, the concentration of the chemical present at the site of action is the only determinant of toxic effect.

Irreversible toxic effects are often caused by a covalent binding of toxic chemicals to biological macromolecules. Under extreme conditions, the modified macromolecules is not repaired, after excretion of the toxic agent, the effect persists. Further exposure to the toxic agent will produce additive effects, many chemical carcinogens are believed to act through irreversible changes of macromolecules.

In principle, a poison is a chemical that has an adverse effect on a living organism. This is, however, not a useful definition because toxic effects are related to dose. The definition of a poison thus also involves quantitative biological aspects. At sufficiently high doses, every chemical may be toxic. The importance of dose is seen clearly with molecular oxygen or dietary metals. Oxygen at a concentration of 21% in the atmosphere is essential for life, in opposite 100% oxygen at atmospheric pressure causes massive lung injury in rodents, often resulting in death. Some metals such as iron, copper, and zinc are essential nutrients. When present in insufficient amounts in the human diet, specific disease patterns develop. At high doses these metals may cause fatal intoxications. Toxic compounds are not restricted to man made chemicals but also include many naturally occurring substances. Indeed, the agent with the highest toxicity is a natural poison found in the bacterium Clostridium botulinum (LD50 0.01 µg/kg).

Therefore, all toxic effects are products of the amount of chemical to which the organism is exposed and the inherent toxicity of the chemical, they also depend on the sensitivity of biological system.

The word dose is most frequently used to characterize the total amount of material to which an organism is exposed. Dose defines the amount of chemical given in relation to body weight. Dose is more meaningful and comparative indicator of exposure than the term exposure itself. Dose usually implies the exposure dose, the total amount of chemical administered to an organism or incorporated into a test system. However, dose may not be directly proportional to the toxic effects because toxicity
depends on the amount of chemical absorbed. Usually, dose correctly describes only the actual amount of chemical absorbed when the chemical is administered orally or by injection. Under these circumstances, the administered dose is identical to the absorbed dose, other routes of application such as dermal application or inhalation do not define the amount of agent absorbed.

Among different chemicals, a wide range of doses is needed to induce toxic effects or death. To characterize the acute toxicity of different chemicals LD$_{50}$ values are frequently used as a basis for comparison. The LD$_{50}$ values for number of chemicals administrated to rats are given in Table 1.

<table>
<thead>
<tr>
<th>Compound</th>
<th>LD$_{50}$ value, mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethanol</td>
<td>12500</td>
</tr>
<tr>
<td>Sodium bicarbonate</td>
<td>4200</td>
</tr>
<tr>
<td>Phenobarbital sodium</td>
<td>350</td>
</tr>
<tr>
<td>Paraquat</td>
<td>120</td>
</tr>
<tr>
<td>Aldrin</td>
<td>46</td>
</tr>
<tr>
<td>Sodium cyanide</td>
<td>6.4</td>
</tr>
<tr>
<td>Strychnine</td>
<td>5</td>
</tr>
<tr>
<td>1,2 Dibromoethane</td>
<td>0.4</td>
</tr>
<tr>
<td>Sodium fluoroacetate</td>
<td>0.2</td>
</tr>
<tr>
<td>2,3,7,8tetrachlorodibenzodioxan</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Table 1. Chemicals and their LD$_{50}$ values

Certain chemicals are very toxic and produce death after administration of microgram doses, whereas others are tolerated without serious toxicity in gram amounts. The data provided above clearly demonstrate that the toxicity of a specific chemical is related to dose. The dose dependence of the toxic effects of a specific chemical is termed on dose response relationship. Before dose response relationships can be appropriately used, several basic assumptions must be made. The first is that the response is due to the chemical given. The responses observed are usually assumed to be a result of the various doses of chemical administered. Under experimental conditions, the toxic response is usually correlated with the chemical given since both exposure and effect are well defined and can be quantified. However, a response is not always known to be the result of specific chemical exposure. For example, an epidemiologic study might result in the discovery of an association between a response (disease) and one or more variables, including estimated dose of a chemical. The true dose to which individuals have been exposed is often an estimate, and the specificity of the response for that chemical is doubtful. Further major assumptions necessary in establishing dose-response relationships are: 1) A molecular site, receptor, exists with which the chemical interacts to produce the response. Receptors are macromolecular components of tissues with which a chemical interacts and produces its characteristic effect. 2) The production of a response and the degree of the response are related to the concentration of the chemical at the receptor. 3) The concentration of the chemical at the receptor is related to the dose administered. Since, in most cases, the concentration of an administered chemical at the receptor cannot be determined, the administered dose or the blood levels or the chemical are as indicators for its concentration at the molecular site.

A further prerequisite for using the dose response relationship is that the toxic response can be measured exactly. A great variety of criteria or end points of toxicity may be used. The ideal end point should be closely associated with the molecular events resulting from exposure to the toxin and should be readily determined. However, although many end points are quantitative and precise, they are often only indirect measures of toxicity. For example, changes in enzyme levels in blood can be indicative of tissue damage. Patterns of alterations may provide insight as to the organ or system that is the site of toxic effects. These measures usually are not directly related to the mechanism of toxic action.

3. Dose- response relationship

The dose response relationship combines the characteristic of exposure and the inherent toxicity of the chemical. Since toxic responses to a chemical are usually functions of both time and dose in typical dose response relationships the maximum effect observed during the time of observation is plotted against the dose to yield time-independent curves. The time independent dose response relationship may be used to study dose-response for both reversible and irreversible toxic effects. However, in risk assessments that consider the induction of irreversible effects such as cancer, the time factor plays a major role and has important influences on the magnitude or likelihood of toxic response. Thus, for this type of mechanism of toxic action, dose-time-response relationships are better descriptors of toxic effects.

The dose response relationship is the most fundamental concept in toxicology. Indeed an understanding of this relationship is essential for the study of toxic chemicals.

From a practical point of view, two different types of dose-response relationship exist. Dose-response relationships may be quantal, all or none response-death, or graded. The graded or variable response involves a continual change in effect with increasing dose, enzyme inhibition or changes in physiological function such as heart rate. Graded response may be determined in an individual or simple biochemical systems. For example, increasing concentrations of
2,3,7,8- tetra chlorodibenzo-p-dioxin (TCDD) added to cultured mammalian cells result in an increase in the concentration of a specific cytochrome P450 enzyme in the cells. An example of of a graded toxic effect in an individual may be inflammation caused by skin contact with an irritant. Low doses cause slight irritation, as the amount increases, irritation turns to inflammation and the severity of inflammation increases.

In dose response studies in a population, a specific end point is also identified, and the dose required to produce this end point is determined for each individual in the population. Both dose-dependent graded effects and quantal responses (death induction of tumor) may be investigated. With increasing amounts of a chemicals given to a group of animals, the magnitude of the effect or the number of animals affected increases. For example, if an irritant chemical is applied to the skin, as the amount of the material increases the number of animals affected and the severity of inflammation increase.

Quantum response such as death induced by a potentially lethal chemical will also be dose dependent. The dose dependence of a quantal effect in a population is based on individual differences in response to the toxic chemical. a specific amount of the potentially lethal xenobiotic given to a group of animals may not kill all of them, but as the amount given increases, the proportion of animals killed increases.

Although the distinctions between graded and quantal dose –response relationships are useful, the two types of response are conceptually identical. The ordinate in both cases is simply labeled response, which may be the degree of response in an individual or the fraction of a population responding, the abscissa is the range of doses administrated. Typical dose-response curves for a toxic effect pplots are linera-linear, and log-linear.

4. Cumulative effects of toxic chemicals
After chronic exposure to a chemical, a toxic response may be caused by dose that do not show any effect after single dosing. Chronic toxic response are often based on accumulation of either the toxic effect or the chemical administered. Accumulation of the administered chemical is observed when the rate of elimination of the chemical is lower than the rate of administration. Since the rate of elimination depends on plasma concentrations, after long term application an equilibrium concentration of the chemical is reached in the blood. chemicals may also be stored in fat (DDT) or bone (lead). Stored chemicals usually do not cause toxic effects because of their low concentrations at the site of toxic action, receptor. After continous application, however, the capacities of the storage tissues may become saturated, xenobiotics may then be present in higher concentration in plasma and thus at the site of action, so toxic responses will results. Besides accumulation of the toxic agent, the toxic effect may also cumulate as shown in Fig. 1.

![Diagram showing accumulation of toxic chemicals](image)

**A-** The rate of excretion is equal to the rate of absorption, no accumulation occurs

**B-** Chemical accumulates due to a higher rate of uptake and inefficient excretion, the plasma concentrations are, however, not sufficient to exert toxic effects.

**C-** The plasma concentrations reached after accumulation are sufficient to exert toxicity

Fig.1 Accumulation of toxic chemicals based on their rate of excretion

Single dosing and n-times dosing changes are shown in Fig. 2 and equation (1).

\[ F_A c_X - F_E c_X = W \frac{dc_X}{dt} \quad \text{single dosing} \quad (1) \]

\[ (F_A c_X)^n - (F_E c_X)^n = W \frac{d}{dt} \left( \frac{dc_X}{dt} \right) = W \frac{d^n c_X}{dt^n} \quad (2) \]

where \( F \) means amount of chemical, \( c \) is concentration, \( W \) is body weight, and \( t \) is time. \( A \) is denoted absorbed, \( E \) is escertion, and \( X \) chemical.
For chemicals that bind irreversibly to macromolecules, the magnitude of toxic responses may be correlated with the total dose administered. In contrast to chemicals that act reversibly, the effects is not dependent on the frequency of dosing. Effect accumulation is often observed with carcinogens and ionizing radiation. In Fig.3 accumulation of effects is exemplified by the time and dose dependent induction of tumors by 4-dimethylaminoazobenzene, a potent chemical carcinogen. The LD_{50} (50% of treated animals carry tumors) are used to characterize the potency. Identical tumor incidences were observed after high doses and short exposure time or after low doses and long exposure, the tumor incidence was dependent only on the total dose administered.+

The reversibility of toxic responses also depends on the capacity of an organ or tissue to repair injury. For example, after survival of the acute phase of intoxication, kidney damage by xenobiotics is often, without further consequence because of the high capacity of the kidney for cell proliferation and for repair of organ damage[7]. In contrast, injury to the central nervous system can not divide and dead cells cannot be replaced.

5. Dose-response phases
In animals and humans, the nature, severity, and incidence of toxic responses depend on a large number of exogenous and endogenous factors. Important factors are the characteristics of exposure, the species and strain of animals used for the study, and interindividual variability in humans. Toxic responses are caused by a series of complex interactions of a potentially toxic chemicals with an organism. The type and magnitude of the toxic response are influenced by the concentration of the chemical at the receptor and by the type of interaction with the receptor. the concentration of chemical at the site of action is influenced by the kinetic of uptake and elimination,since these are time –dependent phenomena, toxic responses are also time dependent.
6. Exposure

The primary tissue of system through which a xenobiotic comes in contact with the body, and from which it may be absorbed in order to exert systematic toxicity, is called the route of exposure. Frequent routes of environmental exposure are ingestion (peroral), inhalation, and skin contact. For investigational and therapeutic purposes, intramuscular, intravenous, and subcutaneous injections may also be routes of exposure.

The major routes by which a potentially toxic chemical can enter the body are in descending order of effectiveness for systematic delivery: injection, inhalation, absorption from the intestinal tract, and cutaneous absorption. The relationship among route, exposure, biotransformation, and practical for toxicity may be complex and is also influenced by the magnitude and duration of dosing.

The route of exposure has a major influence on toxicity because it affects the bioavailability of the toxic agent. The maximum tissue levels achieved, the time to reach maximum tissue levels, and thus the duration of the effect are determined by the rate of absorption and the extent of distribution within the system.

Direct injection into veins is usually restricted to therapeutic applications it is, however, important for the toxicology of intravenously used drugs in addicts. Chemical applied by intravenous injection are distributed rapidly to wellperfused organs by blood and thus may result in the rapid induction of toxic effects. The rapid dilution of a chemical after intravenous injection by venous blood permits even the injection of locally acting or corrosive chemicals that are well tolerated. The likelihood of toxic effects from inhaled chemicals depends on a number of factors, especially the physics state and properties of the agent, concentration, and time and frequency of exposure. Major influences on the absorption and disposition of xenobiotics are exerted by species peculiarities since the anatomy of the respiratory tract and the physiology of respiration show major differences between rodents and humans. The water solubility of a gaseous xenobiotic strongly influences its penetration into the respiratory tract. As water solubility decreases and lipid solubility increases, penetration toward deeper regions of the lung, bronchioli, and the alveoli is more effective. Water soluble molecules, such as formaldehyde, are effectively scavenged by the upper respiratory tract and may have toxic effects on the eye and throat. In contrast, gases with low water solubility such as phosgene may penetrate through the bronchii and bronchioli to the alveoli. Damage to the alveolar surface may initiate a series of events finally resulting in lung edema. The degree to which inhaled gases, vapors, or particulates is absorbed and, hence, their potential to produces systematic toxicity depend on their diffusion rate through the alveolar membrane, their solubility in blood and tissue fluids, the rate of respiration, and blood flow through the capillaries.

Skin contact is an important route of exposures in the occupational and domestic environment. Local effects may include acute inflammation and corrosion, chronic inflammatory responses, immune mediated reactions, and neoplasia. Percutaneous absorption may also be a significant route for the absorption of systematically toxic materials. Factors influencing the percutaneous absorption of substancers include skin site, integrity of skin, temperature, formulation, and physicochemical characteristics, including charge, molecular mass, hydrophilicity, and lipophilicity.

The toxic effects observed after single exposure are often different from those seen after repeated exposure. For example, inhalation of high concentration of halothane causes anesthesia in animals and humans. In contrast, long term application of halothane in lower doses causes liver damage in sensitive species. The frequency of exposure in chronic studies is important for the temporal characterization of exposure. Chemicals with a slow rate of excretion may accumulate if applied in short dosing intervals, and toxic effects may result. Also, a chemical that produces a severe effect when given in a single high dose may have no detectable effects when given in several
smaller doses. Interspecies and strain differences in susceptibility to chemical induced toxicity may be due to heterogeneity of populations, species specific physiology (respiratory system), basal metabolic rate, size, and species specific toxicokinetics and routes of metabolism or excretion. In some cases, animal tests may give an underestimate, and in other cases an over estimate, of the potential toxicity to humans.

7. Conclusions
In this paper dose response relationship and cumulative effects were examined. Acute and chronic exposure to a chemical were investigated. Equations for accumulated chemical changes with time were derived.

Cumulative effect of toxic chemical was examined. Routes of exposure and frequency of exposure were considered.

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Notation
c - component concentration, mol/cm³
F - flow, mg/h
W - weight
time, day

Subscript
A - absorbed
E - excretion
X - chemical

References