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A REVIEW ARTICLE ON DOSE RESPONSE RELATIONSHIP IN TOXICOLOGY

[1]*Navika Gupta, [2]Anu T. Singh and [3]Manu Jaggi

[1]*M.sc (Dabur Research Foundation), India.

[2,3]PhD. (Dabur Research Foundation), India.

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***Corresponding Author**
Navika Gupta
M.sc (Dabur Research Foundation), India.

ABSTRACT

Keeping in mind the recent advances in the field of pharmacy, the studies of Toxicology has assumed significantly higher importance. One such field in toxicology involves the Dose - response relationship. It details the effect of the change in the concentration of drug on the human body. Moreover, it tells us about the safe level and lethal level of a particular chemical. It takes into account all the factors ranging from the physical conditions of the tested human to the interaction between the drug and the receptor. Also, the impact relies upon the dose of the drug being administered.

INTRODUCTION

The Principle of dose response depends on the amount of drug has been administrated to the patient and the kind of response it has shown.

Drug + Receptors ⟹ Drug Receptors complex = Response

In general, the relationship of dose response can be illustrated by a graphical representation which is known as dose response curve. Intensity of response is depend on how increase in dose. As intensity of response increase dose of response will also get increase which shows rectangular hyperbola curve.

1. Deciding factors for adverse effects

- Intrinsic toxicity- these include chemical properties like molecular structure & functional groups, solubility – insolubility, volatility, stability (light, water, acids, enzymes, etc.),

reactivity and physical properties like density, vapor pressure, size and shape of the crystal, etc.

- Exposure condition- this includes routes of exposure (maybe oral, dermal, parenteral or through inhalation), duration and frequency of exposure, environmental conditions, mixed exposures
- Response of host- Some xenobiotics may affect certain target organs whereas some may damage any cell they come across. Toxic effects may include cellular, macromolecular or biochemical modifications. Toxic effects depend upon certain other factors including dose-time relationship, size, age, sex, species, route of exposure, etc.
- Dose- it is the amount of drug given at one time. Types of doses include:

Exposure dose-it is the amount of drug administered in the environment**.**

Absorbed dose- it is the actual amount of dose that enters into the body.

Administered dose- the amount of xenobiotic administered.

Total dose- it comprises of the sum of all the doses.

The toxicity of the xenobiotic can be significantly reduced by fractionating it because here, the dose, harmful if taken all at one time, doesn't produce toxic effects if taken in specified periods of time.

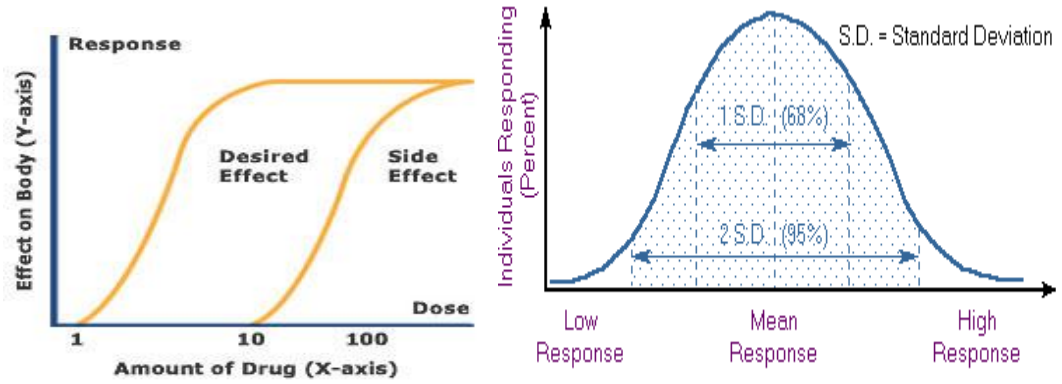
2. Dose- Response Relationship

It is also known as- "Exposure-response relationship" and it gives an idea about the variation in the effect on an organism with the corresponding change in the amount of the stressor (dose, chemical, etc.). This may be done on the individual level or on the population level. By studying the dose-response model, we determine the "safe" level and the "hazardous" level of a chemical.

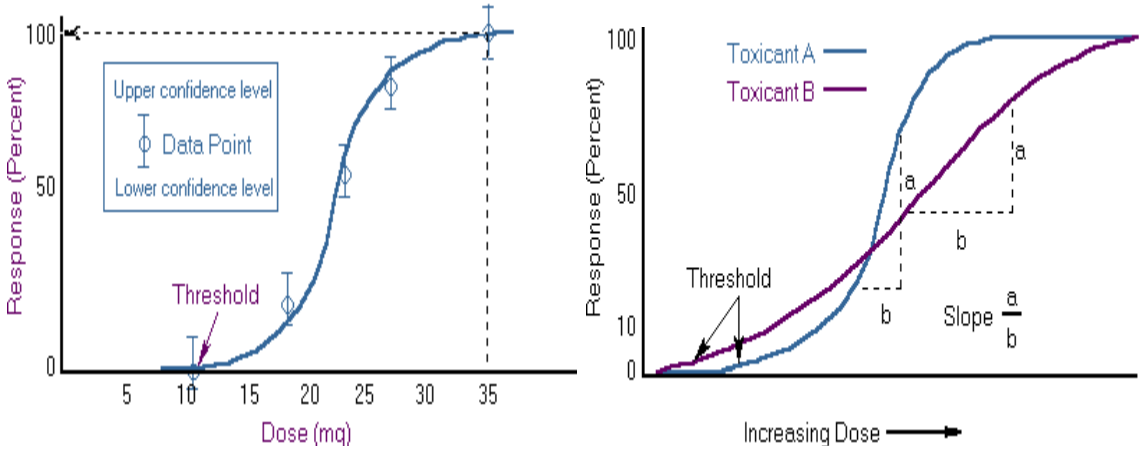
A dose- response curve is an invaluable tool which tells us the relationship between the effect and the dosage of the drug (chemical). This is important to decipher whether the drug is acting in accordance with the interaction between different molecules in the body.

A dose–response bend is a straightforward X–Y chart relating the extent of a stressor (e.g. concentration of a pollutant, amount of a drug, temperature, intensity of radiation) to the reaction of the receptor (e.g. creature under review). The reaction might be a physiological or biochemical reaction, or even passing (mortality), and in this manner can be checks (or extent, e.g., death rate), seriousness of an injury, or continuous estimations (e.g., blood

pressure). Various impacts (or endpoints) can be examined, frequently at various authoritative levels (e.g., population, entire creature, tissue, and cell).



Dose-effect relationship



Dose-resp curve **dose-resp curve**

The deliberate measurement dose (more often than not in milligrams, micrograms, or grams per kilogram of body-weight for oral exposures or milligrams per cubic meter of encompassing air for inward breath exposures) is by and large plotted on the X axis and the reaction is plotted on the Y axis. Other measurements units incorporate moles per body-weight, moles per creature, and for dermal introduction, moles per square centimeter. Now and again, it is the logarithm of the dose is plotted on the X axis, and in such cases the bend is regularly sigmoid, with the steepest part in the center. Naturally based models utilizing dosage are favored over the utilization of log (dose) on the grounds that the last can outwardly suggest a threshold dose when in certainty there is none. The primary point along the chart where a reaction over zero (or over the control reaction) is come to is generally regarded to as a limit dosage (threshold dose). For most helpful medications, the coveted impacts are found at measurements marginally more noteworthy than the threshold dosage. At higher measurements, undesired symptoms show up and become more grounded as the

dosage increments. The more powerful a specific substance is, the steeper the bend will be. In quantitative circumstances, the Y-axis frequently is assigned by rates, which allude to the rate of exposed people showing a standard reaction (which might be demise, as in LD50). Such a bend is alluded to as a quantal dosage response curve recognizing it from graded dose-response curve, where reaction is constant (either measured, or by judgment).

Factors Affecting Drug Response

There are many factors that affect Drug Reponse**s -**

- Weight
- Age
- Gender
- Fever
- Shock
- Environment conditions
- Body surface
- Pathological state of mind
- Placebo effect
- Tolerance.

3. DISCUSSION

A usually utilized dosage reaction curve is the EC50 curve, the half maximal effective concentration, where the EC50 point is characterized as the inflection point of the curve. Dose–response curves are by and large sigmoidal and monophasic and can be fit to an established Hill equation. Dose-response, which includes the standards of pharmacokinetics and pharmacodynamics, decides the required dosage and recurrence and in addition the therapeutic index for a medication in a population. Therapeutic index (ratio of the minimum toxic concentration to the median effective concentration) decides the adequacy and well-being of a medication. Expanding the dosage of a medication with a little therapeutic index builds the likelihood of danger or ineffectiveness of the medication. Nonetheless, these components contrast by population and are influenced by patient-related variables, for example, pregnancy, age, and organ work (e.g., assessed GFR).

The dosage of a toxic substance will decide the level of impact it produces. The accompanying case shows this rule. Assume ten goldfish are in a ten-gallon tank and we

include one ounce of 100-proof bourbon to the water at regular intervals until all the fish get smashed and swim topsy turvy(upside down). Likely none would swim topsy turvy after the initial a few shots. After four or five, an exceptionally weak fish may. After six or eight shots another or two may. With a measurement of ten shots, five of the ten fish may be swimming topsy turvy. After fifteen shots, there may be just a single fish swimming legitimately and it too would turn over after seventeen or eighteen shots. The impact measured in this illustration is swimming upside down. Individual sensitivity to alcohol changes, as does individual affectability to different toxic substances. There is a measurement level at which there is no visible impact. There is likewise a measurement level at which the greater part of the fish swim topsy turvy. The dosage level at which 50 percent of the fish have turned over is known as the **ED50**, which implies effective dose for 50 percent of the fishes that have been tested. The ED50 of any toxic substance shifts relying upon the impact measured. As a rule, the less extreme the impact measured, the lower the ED50 for that specific impact.

ED0	Effective for 0% population
ED10	Effective for 10% population
ED50	Effective for 50% population
ED90	Effective for 90% population

One of the all the more generally utilized measures of poisonous quality is the **LD50**. The **LD50** (the deadly measurement for 50 percent of the animals tested) of a toxic substance is generally calculated in milligrams of chemical per kilogram of body weight (mg/kg). A compound with a little LD50 (like 5 mg/kg) is exceptionally dangerous. A compound with an extensive LD50 (1,000 to 5,000 mg/kg) is essentially non-dangerous. The LD50 says nothing in regards to non-deadly lethal impacts however. A chemical may have a substantial LD50, however may deliver disease at little concentration levels. It is mistaken to state that chemicals with little LD50s are more unsafe than chemicals with expansive LD50s, they are essentially more dangerous. The threat, or danger of antagonistic impact of chemicals, is generally controlled by how they are utilized, not by the innate poisonous quality of the chemical itself.

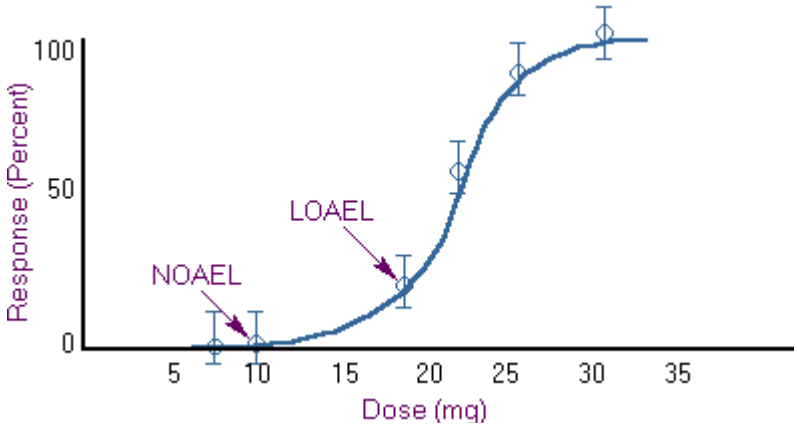
The **TD50** is the toxic dose for 50 percent of the animals tested. The bigger the TD the more poison it takes to create indications of poisonous quality. The toxic dose does not give any data about the deadly dosage in light of the fact that poisonous impacts (for example, nausea and vomiting) may not be specifically identified with the way that the chemical causes death. The lethality of a compound is an intrinsic property of the substance itself. It is additionally

genuine that chemicals can cause distinctive sorts of poisonous impacts, at various measurements levels, depending on the animal species tested.

The **NOEL** (No Observable Effect Level) is the largest dose of the chemical that produces no visible impact. The maximum allowable level of the toxin that is allowed to be added in food or drinking water is 100 to 1000 times less than the NOEL to enhance the safety for the humans.

The **NOAEL** (No Observed Adverse Effect Level) is the largest dose at which no toxic effects are observed.

The **LOAEL** (Lowest observed adverse effect level) is the lowest dose at which toxic effects are observed.



The **TLV** (Threshold Limit Value) is the amount of chemical present in the air that produces no harmful effects on the workers that are exposed to it for a minimum of 8hrs/day for approximately 5 days a week.

Table: Toxicity rating scale and labeling requirements for pesticides

Category	Signal word required on label	LD50 oral mg/kg(ppm)	LD50 dermal mg/kg(ppm)	Probable oral lethal dode
I(Highly toxic)	DANGER-POISON	<50	<200	A few drops to a spoon
II(Moderately toxic)	WARNING	51-500	200-2000	Over 1tsp to 1 ounce
III(Slightly toxic)	CAUTION	>500	>2000	Over 1 ounce
IV(Practically non-toxic)	None required			

4. Pharmacokinetics

This studies the effect that the human body causes on the drug from its movement through various body parts to the excretion of the same. Pharmacokinetics is affected by the patient-

related variables which may include sex, age, GRF, genetic constitution, etc.). The condition of the body (obesity, renal failure, dehydration, etc.) also has an effect of the pharmacokinetics of a drug. The major processes involved are referred to as "ADME" where A stands for Absorption, D for Distribution, M for Metabolism, E for Excretion.

Absorption: Entering of drug into the body. To enter the blood, the drug must cross the membranes of the tissue except if it is administered orally.

Distribution: Movement of drugs around the body. To enter the tissues, the drug must cross the walls of the capillaries.

Metabolism: The drugs are made water-soluble for excretion by modifying them chemically. This process majorly occurs in liver, gut wall, kidney and skin.

Excretion: Process of expulsion of the drug from the body. Water- soluble drugs pass unaided whereas the lipid-soluble drugs need to be modified to their water-soluble counterparts before their excretion.

5. Pharmacodynamics

It studies the effect of the drug on the body of an organism. The 7 major actions of drugs include:

- Stimulatory Action by direct receptor agonism and downstream effects
- Depressing Action through direct receptor agonism and downstream effects as that in inverse agonist
- Antagonizing action (as with silent antagonists), the drug binds the receptor without activating it.
- Stabilizing action, the drug seems to act neither as a stimulant or as a depressant exchanging/replacing substances or accumulating them to form a direct beneficial chemical reaction as in free radical scavenging
- Direct harmful chemical reaction which might result in damage or destruction of the cells, through induced toxic or lethal damage.

Pharmacokinetics and pharmacodynamics are considered as TOXIKINETICS OR TOXIDYNAMICS in the field of ecotoxicology.

6. Effect Anti-Cancer Effect of Sulphoraphane

Sulphoraphane is a phytochemical which is extracted from Broccoli roots. It is known to have anti-carcinogenic properties. It provides a strong logic to study the root extract and the evaluation of sulphoraphane for the chemoprevention of breast cancer. Mouse models have proved that sulphoraphane eliminated breast cancer tumors. Broccoli and its sprouts are known to have glucosinolates (Zhang Y, et al.). It is advised to consume cruciferous vegetables in high concentration to stimulate the activity of isothiocyanate which are hydrolysed with the help of enzymes from glucosinolates (Clarke JD, et al.). A main glucosinolate from broccoli/broccoli sprouts, glucoraphanin is known to be converted into sulphoraphane(Fahey JW, et al.). Both blocking and suppressing effects are known to contribute to the anti-cancer properties of broccoli's root extract (Zhang Y, et al.).

The blocking effect is evident through the halting the enzymes of phase 1 metabolism which converts pro-carcinogen to carcinogen and the enzymes of metabolism 2 that enhances the process of excretion of these carcinogens(Clarke JD, et al.). Consequent reviews uncovered the suppressing impacts of sulforaphane in balancing diverse cell exercises to hinder the development of cells that have undergone transformation (Clarke JD, et al.) (Zhang Y, et al.). The capacity of sulforaphane to prompt apoptosis and cell cycle capture is related with control of numerous molecules including Bcl-2 family proteins, caspases, p21, cyclins, and cyclin-subordinate kinases (Zhang Y, et al.). Sulforaphane was additionally appeared to suppress angiogenesis and metastasis by down regulating vascular endothelial development factor, HIF-1α, framework metalloproteinase-2 and network metalloproteinase-9 (Zhang Y, et al.).

7. CONCLUSION

Knowledge of drug-response relation is useful in clinical and public health setting. Dose-response is one criterion which is used to evaluate cause-and-effect relation in observational studies. Dose-response helps us understand the biology behind physical activity-disease relation. Most of the evidence currently available seems to be related to the effects (benefits or risks) of regular physical activity rather than to the relationship between dose and response. These studies require full use of the knowledge of pharmacokinetics and pharmacodynamics. Also, the effect of an anti-cancer compound "Sulphoraphane" from the broccoli's root extract has been studied.

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