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In-vitro, In-vivo, Computational toxicology screening models in drug discovery

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ABSTRACT

Toxicology, a field of science, used to study the adverse effects of chemical, biological substances on living organisms. It is the practice of diagnosing and treating exposure to toxins and toxicants. Toxicity studies are important throughout the drug development process and performed during preclinical and clinical stages. Toxicity studies include in vitro cell culture, Organotypic culture, ex-vivo models, organ-on-a-chip, etc., and *in-vivo* animal models comprise of rodents (albino mice and wistar rats), rabbits, dogs, guinea pigs. CPCSEA guideline compilation is required during experimentation on animals for maintaining safety. Zebra fish is used as a model organism for toxicology and biomedical research to study embryo toxicity, neurotoxicity, ocular toxicity, ototoxicity. Availability of computational methods aims to complement in vitro and in vivo toxicity studies and minimize the need of animals. Evaluation of medical devices safety using toxicology studies is recommended by the ISO committee. In Current review we explained on in-vitro and iv-vivo, in-silico toxicological studies of small molecules and medical devices. Clinical toxicology studies using in-vivo, in-vitro, or in-silico methods can provide important information about the safety of a drug and can support the entry of Investigational New Drug (IND) into the market by reducing toxic effects.

INTRODUCTION

Toxicology studies are vital in the drug development process and include the characteristics, consequences, detection, and diagnosis of toxic effects of new chemical entities. Fundamental aim of toxicology is to understand how a dose affects the organism to which it is administered. Toxicity studies look into the potential compound's safety record and offer crucial details concerning the compound's *absorption, distribution, metabolism, and excretion (ADME)*. Prior to being used on humans, new medications must undergo extensive toxicity testing.

Toxicity is a measure of any undesirable or adverse effect of chemicals. Specific types of these adverse effects are called toxicity endpoints, such as carcinogenicity or genotoxicity, and can be quantitative (e.g., LD50: lethal dose to 50% of tested individuals) or qualitative, such as binary (e.g., toxic or non-toxic) or ordinary (e.g., low, moderate, or high toxicity). Toxicity tests aim to identify harmful effects caused by substances on humans, animals, plants, or the environment through acute-exposure (single dose) or multiple-exposure (multiple doses).

1.1 PRECLINICAL TOXICITY STUDIES

Preclinical toxicity study is an important part of drug development as it is used to evaluate potential safety and toxicity of a drug candidate before testing in humans. Preclinical Studies thus can be defined as "Testing the newly discovered compound in animals with the objective of gaining information regarding safety and efficacy of the compound with respect to the biological systems so that the same can be extrapolated for the use of that compound in humans".(1)

Types of Preclinical toxicity testing:-

1. Acute Toxicity: Acute toxicity study is conducted to determine the adverse effects of a single exposure of a substance over a short period, usually within 24 to 72 hours. It is used to determine LD_{50} during short term exposure.

2. Sub-acute Toxicity: In sub-acute toxicity testing, the test substance is administered daily for several weeks to assess

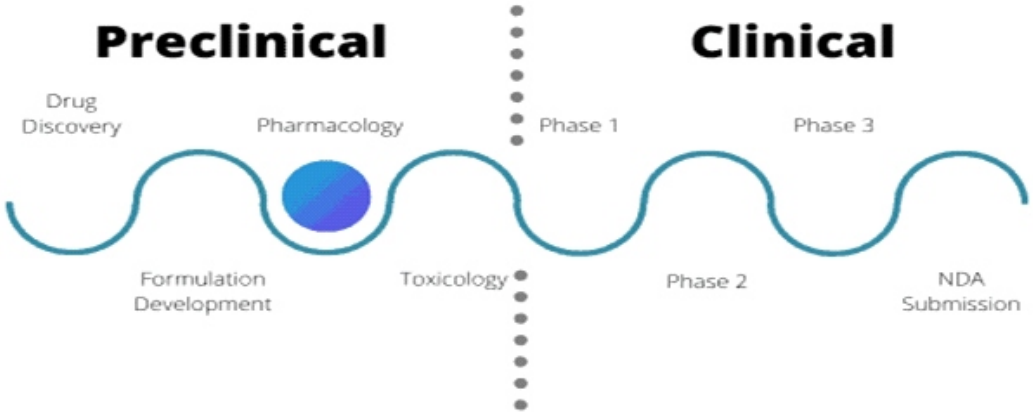


Fig 1: Preclinical and clinical phases of Drug Discovery and development.

potential toxic effects that may arise from repeated exposure for 14 days, 28 days, or 2-4 weeks.

3. Chronic Toxicity: Small doses are given for a long time period and then their effects are determined, typically six months to one year.

4. Carcinogenicity: Carcinogenicity studies aim to assess whether a substance has the potential to induce cancer or promote its development over an extended period. The duration of this test is about 18 24 months.

5. Genotoxicity: Genotoxicity tests carried to evaluate a substance's potential to damage genetic material, including DNA, and increase the risk of mutations or cancer. Common tests include the *Ames test* and *chromosome aberration assays.*

6. Reproductive and Developmental Toxicity: Reproductive toxicity studies investigate the effects of a substance on fertility, pregnancy, and the development of offspring. Developmental toxicity pertains to adverse effects to the developing embryo or factors. It is a requirement for any new drug compound before administration to any female of child bearing age.

Types:

Segment I fertility

Segment II Pre/post natal toxicity

and III Embryo toxicity, Teratogenicity (2)

These studies are an integral part of the drug development and help to determine the potential adverse effects and risks associated with the experimental product.

1.2 Clinical toxicity studies: The different phases of clinical toxicity studies include

1. Phase 0 Studies (Exploratory IND Studies or Micro dosing Studies)
2. Phase I Studies (Toxicity Studies)
3. Phase II Studies
4. Phase III Studies

Table 1 : SOCIO-DEMOGRAPHIC CATEGORIZATION

Phases	Objective	Number of Participants	Duration
Phase 1	Studies the safety of medication and dosage, Identifies Side effects.	20-100	< 1 year
Phase 2	Studies the efficacy, Further evaluate safety	100-300	Up to 2 years
Phase 3	-Confirms effectiveness -Monitor side effects	300-3000	1-4 years
Phase 4	Monitor long term safety and efficacy of a therapy after its approval	Thousands of population	1+ year

Phase IV Studies (Post-Marketing Surveillance or Pharmacovigilance) **(3)**

1.3 In-vitro and In-vivo animal models:

1.3.1 In-vitro models:

In vitro models, also known as *cell-based or tissue-based models,* are widely used in toxicological studies. The major aims of in vitro systems are to develop, stimulate, and predict biological reactions to materials when placed into or on tissue in the body. These models include

1.3.1.1 Cell Cultures: *Cell culture models* are relatively simple, cost-effective, reproducible, easy to interpret and offer high-throughput screening capabilities. Cell culture can be used to screen for toxicity both by estimation of the basal functions of the cell or by tests on specialized cell functions. General toxicity tests, aimed mainly at detection of the biological activity of test substances, can be carried out on many cell types (e.g., fibroblasts, HeLa and hepatoma cells). A number of parameters including vital staining, cytosolic enzyme release, cell growth and cloning efficiency are used as end-points to measure toxicity. Organ -specific toxic effects are tested using specialized cells by specific cell functions (e.g., glycogen metabolism in primary hepatocyte cultures, beating rate in mixed myocardial cells or myocytes, and phagocytosis in macrophages).

Cell lines are classified into:

Primary cell lines:

They are derived directly from tissues or organs and are used in various research fields. Many primary cell types have not yet been isolated and cultured successfully, with cells isolated from a tissue biopsy often failing to adhere and proliferate in vitro. Eg: Human Kidney-2 (HK-2) cells derived from tissue and not modified are similar to in-vivo state and exhibit normal physiology.

Secondary cell lines:

They are also known as immortalized cells, are derived from primary cells but have undergone genetic modifications or other techniques to extend their lifespan, making them suitable for long-term in-vitro research.

Eg.: HepG2: HepG2 is a human liver cancer cell line that is commonly used in toxicology studies because it has many of the same metabolic functions as a normal liver. HepG2 cells have been used to evaluate the toxic effects of drugs, chemicals, and environmental pollutants on liver cells.(6)

A549: A549 Is a human lung cancer cell line that is often used in inhalation toxicology studies. Researchers use A549 cells to study the effects of airborne pollutants and toxic substances on lung cells.(7)

CHO: CHO (*Chinese hamster ovary*) cells are a commonly used cell line for toxicity testing of biologics such as vaccines and therapeutic proteins. These cells are able to produce large quantities of proteins, making them useful for studying the effects of these substances on cells.(8)

Some of the key parameters studied for toxicity studies include:

1. **Cell viability:** It is a crucial parameter and is often assessed using assays like the (3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide(MTT), methyl nitro sulfophenyl-tetrazolium carboxanilide(XTT) assay or *trypan blue exclusion* study. These assays measure the proportion of live cells in a culture after exposure to a toxic substance.

2. **Morphological changes:** Alterations in cell shape provide valuable information about toxicity. Researchers examine changes in cells under a microscope. Common morphological changes include *cell shrinkage, membrane blebbing and cell detachment*.

Apoptosis is the process of programmed cell death. It is used during early development to eliminate unwanted cells; *for example, those between the fingers of a developing hand.*

Necrosis is the *death of body tissue*. It occurs when too little blood flows to the tissue. This can be from injury, radiation, or chemicals. Necrosis cannot be reversed. When large areas of tissue die due to a lack of blood supply, the condition is called **gangrene**.

3. **Cell membrane integrity:** The integrity of cell membrane is assessed using assays like *Lactate Dehydrogenase (LDH) release assays*. An increase in LDH release indicates

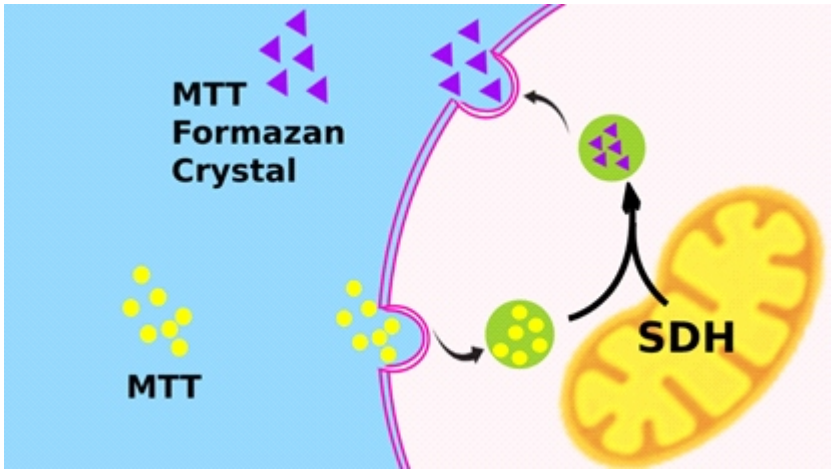


Figure 4 : *MTT assay* used to study Cell viability. The viable cells are detected by color change from *yellow to purple*. MTT salt is reduced to MTT formazan crystals in presence of *succinate dehydrogenase(SDH)* in mitochondria of cells which can be studied as *absorbance at 570 nm.*

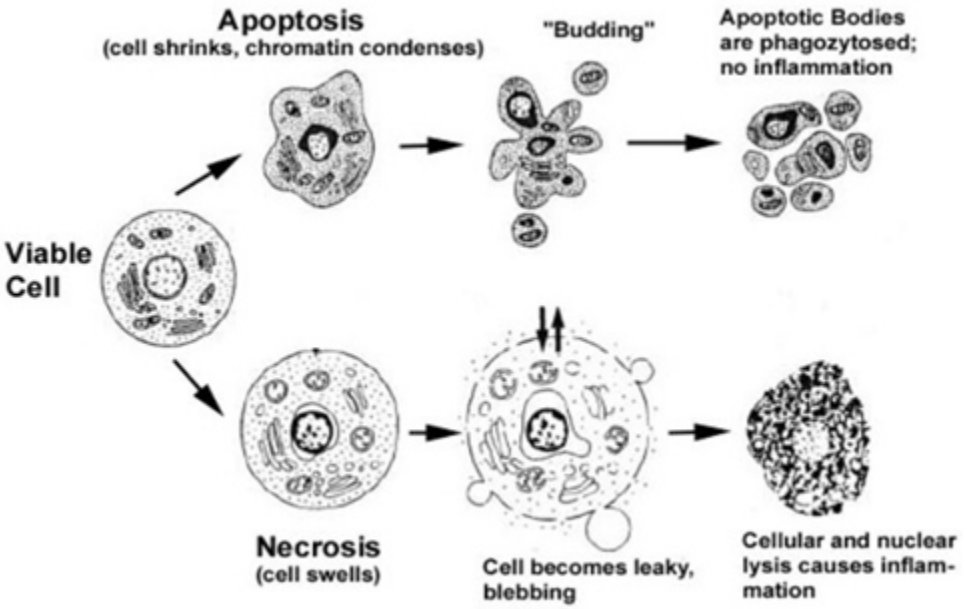


Figure 5 : Morphological changes during Necrosis and Apoptosis

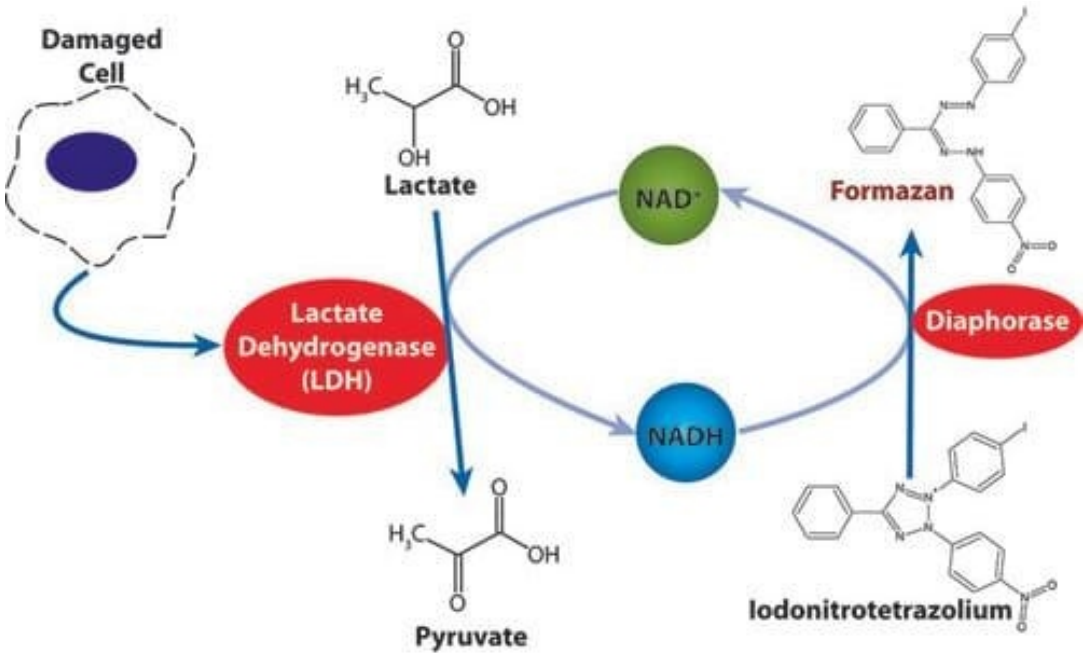


Figure 6 : Schematic representation of the principle of the LDH release assay.

damage to the cell membrane.

4. **Cell cycle analysis:** *flow cytometry* is used to analyze the cell cycle distribution. Toxicity can lead to cell cycle arrest or alterations in the distribution of cells in different phases (G1, S, G2, M) of the cell cycle.

5. **DNA damage:** the extent of DNA damage can be assessed using techniques such as the *comet assay or gammaH2AX staining*. DNA damage is a common response to genotoxic substances.

1.3.1.2 Organotypic Cultures: These models maintain the three-dimensional structure and function of specific tissues or organs. Eg.: researchers can create brain slice cultures to study neurotoxicity or liver slices (Fig.2) to assess hepatotoxicity.

Rat brain slice cultures used to study the *neurotoxic effects* of *amyloid beta protein*, a protein associated with Alzheimer's disease.

1.3.1.3 Co-culture Systems: Co-culture systems involve culturing different cell types together, reflecting the interactions

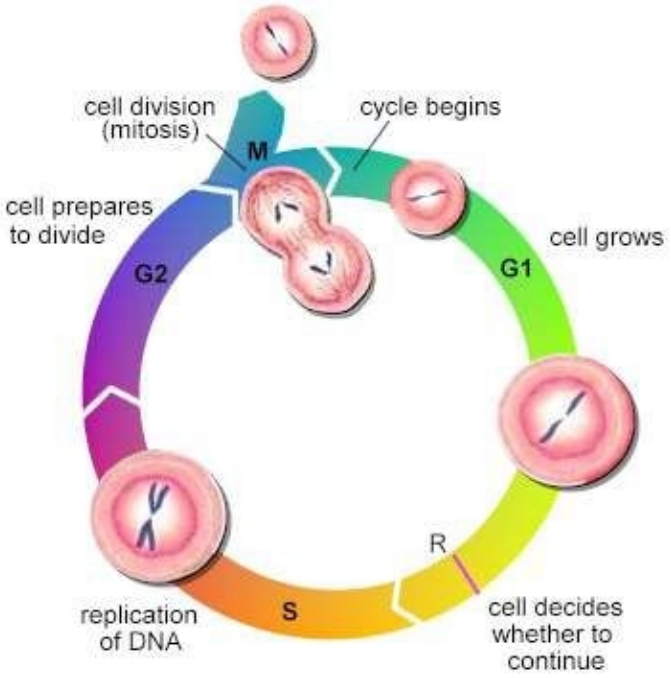


Figure 7 : Cell cycle analysis by Flow cytometry

that occur in the actual organism.

eg.: **Cancer-stromal Cell Co-cultures**

Immune Cell Co-cultures

Hepatocyte-Non parenchymal Cell Co-cultures

1.3.1.4 Micro fluidic Organ-on-a-Chip: This is an advanced in vitro model that attempts to mimic the structure and function of organs by incorporating multiple cell types and physiological flow patterns. Organ-on-a-chip models provide a more accurate representation of organ function and interactions than traditional cell culture systems. These contain engineered or natural miniature tissues grown inside microfluidic chips.

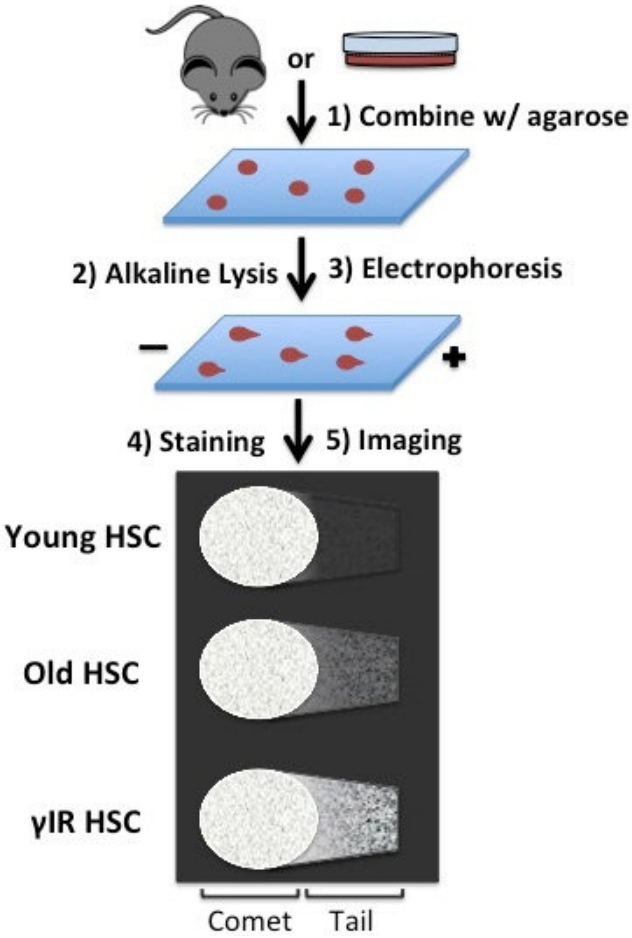
1.3.2 In-vivo animal models:

In vivo animal models are essential tools in toxicological studies for understanding the effects of substances on whole living organisms.These models provide a more comprehensive picture of how a substance behaves in a complex biological system and how it affects various organs and physiological processes.

Commonly used in-vivo models are:

Rodents (Mice and Rats): Mice and rats are the most commonly used animals in toxicological research due to their physiological and genetic similarities to humans, ease of handling, and cost-effectiveness. eg: Sprague-Dawley rats, Wistar rats, Lewis rats, albino rats, brown norway rats and Albino mice.

Rabbits: Rabbits are used in ocular toxicology studies due to the similarities between rabbit and human eyes. Studies like *acute oral toxicity, Dermal irritation, Ocular irritation, Reproductive toxicity can be studied in rabbits.*



Hematopoietic stem cells (HSC)
Fig 8: DNA damage by Comet assay

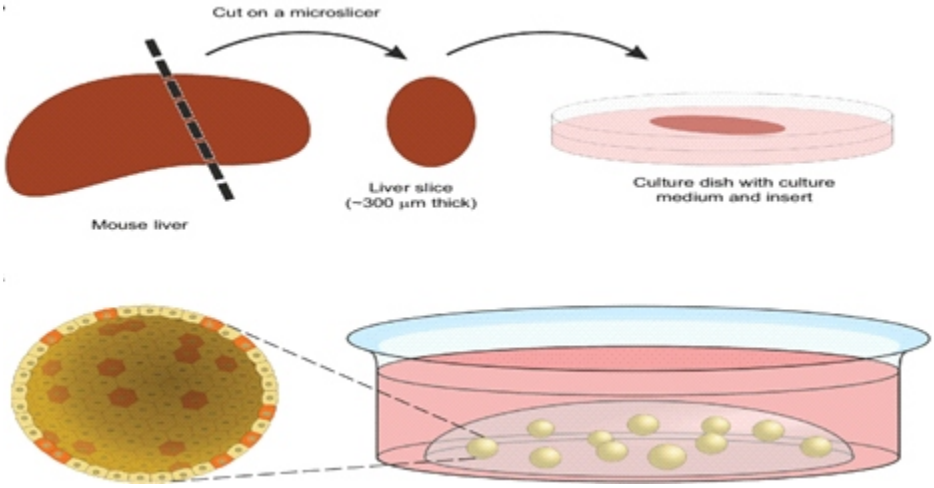


Figure 2 : Organotypic tissue slices and organoides

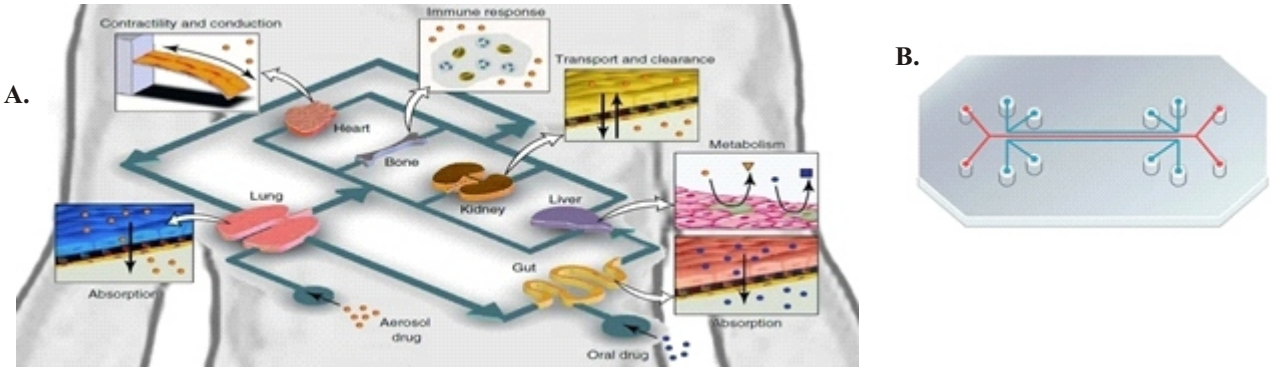


Figure 3 : A. Multi organ microfluidic chip to study ADME of drug.
B. Heart-on-a-chip contains human cardiomyocytes to study toxic effects of doxorubicin. (4,5)

Dogs: Dogs have similarities to humans in terms of physiology and metabolism. They are sometimes used in toxicological studies, particularly for pharmaceutical drug development or specific safety assessments. They have approximately the same no.of genes as humans and their genome is sequenced.

Non-human Primates: Non-human primates, such as *monkeys,* are used in some cases for toxicology studies when the results cannot be reliably extrapolated from other animal models to humans.

Eg.: Macaques(rhesus monkeys, cynomolgus monkeys)

African species(African green monkeys and baboons)

Guinea Pigs: Guinea pigs are used for *skin sensitization* studies and are valuable for assessing allergic reactions to substances. Also used for development of vaccines like diphtheria, Tuberculosis, *etc.*

Fish and Aquatic Organisms: Zebrafish, are popular due to their transparent embryos and rapid development. Is a tractable animal model for identifying the development of neurons and the architecture of the brain from neurogenesis at early stage to adult stage brain Eg :*Daphnia, sea urchins* (6)

2. COMMITTEE FOR THE PURPOSE OF CONTROL AND SUPERVISION OF EXPERIMENTS ON ANIMALS (CPCSEA)

Article 51A (g) of constitution of India states that it is the fundamental responsibility of every citizen of India to protect and improve the natural environment including forest, lakes and wildlife to have compassion for living creatures. In 1960, the prevention of cruelty to animals Act came into force by the Indian Parliament to ensure animals are not subjected to unnecessary pain or suffering during experiments in animals. For this purpose, under the delegated powers, the Committee formulated the 'Breeding of and Experiments on Animals (Control and Supervision) Rules, 1998 which were amended 2001 and then in 2006 to regulate the experimentation on animals. The act is designed to ensure that experiments performed in any institution must be registered as (Prevention to the cruelty to animals) PCA Act 1960. Experiments are performed with due care and humanity, if the experiments require any operation it should be done under the influence of anesthetic to prevent the animals from suffering.(10)

The experiments are avoided in the following cases

- The experiments on animals are avoided if books,

Table 3 : Animal Models Used in Selective Toxicity Tests

Order	Species	Toxicity Tests
Rodentia	Rat	Developmental toxicity
		Carcinogenicity
		Cutaneous toxicity
		Genotoxicity
		Immunotoxicity
		Neurotoxicity
		Developmental neurotoxicity
		Reproductive toxicity
	Mice	Carcinogenicity
		Skin sensitization
		Genotoxicity
		Immunotoxicity
		Neurotoxicity
		Reproductive toxicity
	Hamsters	Carcinogenicity
		Genotoxicity
	Guinea pigs	Cutaneous toxicity/skin sensitization
		Developmental neurotoxicity
Lagomorpha	Rabbit	Developmental toxicity
		Cutaneous toxicity
		Reproductive toxicity
Canine	Dog	Carcinogenicity
		Cutaneous toxicity
		Neurotoxicity
		Developmental neurotoxicity
Nonhuman primates	Monkey	Developmental toxicity
		Cutaneous toxicity

models, are equally sufficient.

- The experiments are avoided in large animals if results are the same with small animals like guinea-pigs, rabbits, frogs and rats.
- The animals' experiments are performed for acquiring manual skills.
- The records are to be maintained and animals should be properly taken care before and after the experiments
- The area should be maintained properly according to their habitat.(11)

3. TOXICITY STUDIES IN ZEBRA-FISH:

Zebrafish is a member of the minnow family of fish and used as a model organism to study development of vertebrates. Worldwide, use of Zebrafish models for toxicology and biomedical research is receiving increasing attention, as they are considered as a replacement method for animal experiments. Zebra fish provide analysis from acute to complex functional genetic and physiological analysis. Zebra fish provide 3Rs value in toxicology studies including *Replacement, Reduction and Refinement* (12).

Embryo toxicity:

Zebrafish embryos are widely used for toxicity screening for drugs and chemicals in vertebrate development toxicology. Zebrafish model is accepted for fish acute toxicity and good replacement for the in-vivo regulatory mammalian embryo fetal developmental toxicology studies as per ICH S5 guidelines for detection of toxicology in reproduction for human pharmaceuticals (13).

Neurotoxicity and Behavioral analyses:

The zebrafish is overall broadly applied to concentrate on mechanism and pathogenesis of neurological issues and illnesses. The CNS of zebrafish is similarly organized to that of other vertebrates and is well described at multiple life stages. The important difference between the zebrafish and mammals is no direct telencephalic tract [CST] to the spinal card but it is clearly seen in the mammals. Neurotransmitters like *Dopamine, serotonin, AAdrenaline , Noradrenaline (14).*

Ototoxicity:

Screening of ototoxicity in mammalian preclinical models is very difficult and is rarely done. The Zebrafish model may fill gaps in preclinical testing. Hearing loss is a defect that may occur because of many factors but most common is from drug induced toxicity. Many studies has shown lateral hair cells of mammalian inner ear are toxic to ototoxic drug such as *Cisplatin(15), Amikacin, etimicin* are the few drugs which causes ototoxicity

Pancreas Toxicity:

The zebrafish pancreas has both exocrine and endocrine in nature, endocrine produces *somatostatin, ghrelin, glucagon, insulin(16).*Most studies involve the endocrine portion includes islets of Langerhans which is responsible for Diabetes research (17).

Cardiovascular Toxicity:

Cardiovascular physiology is similar between zebrafish and human at cellular, anatomical and membrane biological level; it provides good compatibility for cardiotoxicity. The drugs acting on the QT interval show more than >95% conservation in zebrafish during new drug development (18). Moreover zebrafish can regenerate heart muscle.

4. IN-SILICO TOXICITY STUDIES: TOOLS AVAILABLE AND WEBSITES:

In-silico toxicology (computational toxicology) is one type of toxicity assessment that uses computational resources (i.e., methods, algorithms, software, data, etc.) to organize, analyze, model, simulate, visualize, or predict toxicity of chemicals. It is intertwined with *in-silico* pharmacology, which uses information from computational tools to analyze beneficial or adverse effects of drugs for therapeutic purposes. (19)

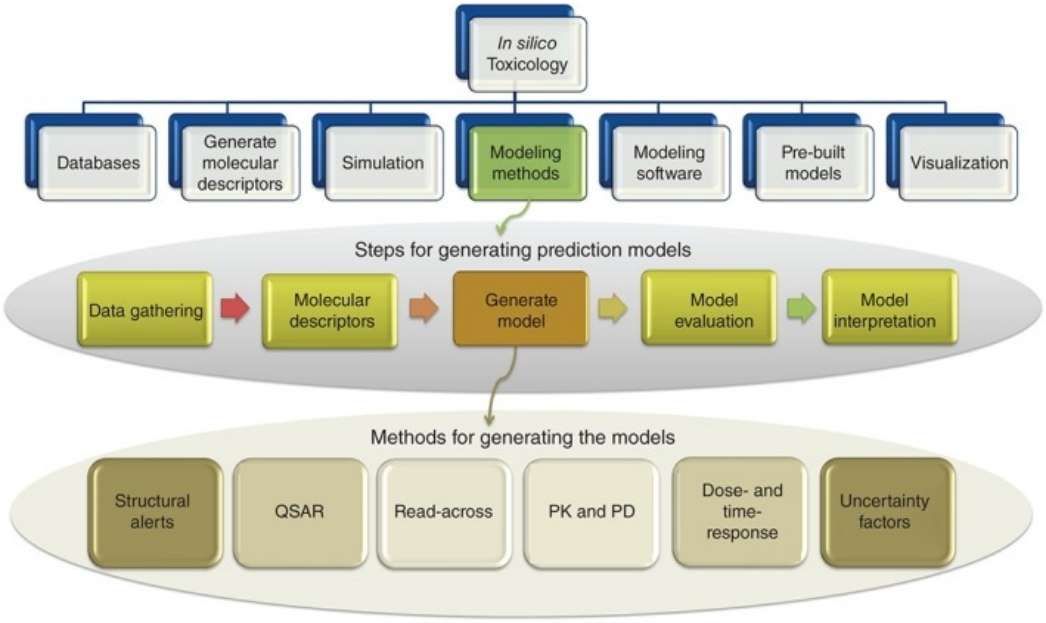


Figure 9 : In Silico toxicology tools, steps to generate prediction models, and categories of prediction models.

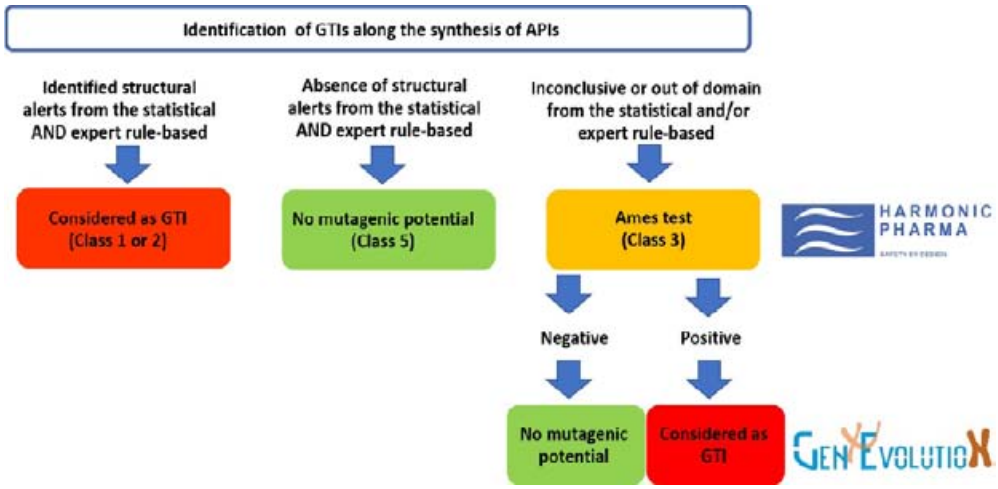


Figure 10 : Prediction of Toxicity of chemicals

Table 3 : Commonly used freely available databases and website details for further information

Database	Website details and further information
AMBIT	*http://cefic-lri.org/toolbox/ambit/* Developed by European Chemical Industry Council's Long-Range Initiative (Cefic-LRI), it contains information on >450,000 chemicals including the European Chemicals Agency's (ECHA's) REACH data.
Chemspider	*http://www.chemspider.com/* Developed by the Royal Society of Chemistry, it provides information on over 83 million chemicals, using 275 data sources; includes direct links to other relevant resources.
ChemIDplus	*https://chem.nlm.nih.gov/chemidplus/* Developed by the US National Library of Medicine; contains information relating to >300,000 chemical structures including physico-chemical property and toxicity data.
Computational Toxicology Dashboard	*https://comptox.epa.gov/dashboard* Hosted by the US Environmental Protection Agency (US EPA); a repository of data currently for 875,000 chemicals; links out to additional data sources; integrates data e.g. from ToxCast/Tox21 high-throughput screening initiatives.
eChemPortal	*http://www.echemportal.org* Developed in collaboration with the Organisation for Economic Cooperation and Development (OECD), provides links to information prepared for governmental chemical reviews at national and international levels, including submissions to the European Chemicals Agency (ECHA); provides exposure and use information.
EMBLEBI/ ChEMBL	*https://www.ebi.ac.uk/* *https://www.ebi.ac.uk/chembl/* European Molecular Biology Laboratory's European Bioinformatics Institute (EMBL-EBI); source of biological and biomolecular data incorporating the ChEMBL database of bioactive molecules with drug-like properties (>15 million values from >1.8 million chemicals).

Table 4 : Commonly used freely available software tools

Software	Website details and further information
ACD/PhysChem Suite	*http://www.acdlabs.com/products/percepta/* Prediction of properties: physico-chemical; ADME; toxicity.
ADMET Predictor	*http://www.simulations-plus.com/* Prediction of properties: physico-chemical; ADME; toxicity.
AMBIT	*http://cefic-lri.org/toolbox/ambit/* Freely available: incorporates extensive database, integrates models for toxicity prediction; provides a workflow to support category formation and read-across.
AutoDock	*http://autodock.scripps.edu/* Freely available suite of automated docking tools to predict interaction between small molecules (e.g., substrates or drug candidates) and receptors.
ChemMine Tools	*https://chemminetools.ucr.edu/* Freely available: tool for similarity analysis or clustering of chemicals based on physico-chemical or structural similarity.
Cloe PK	*www.cyprotex.com* Prediction of human pharmacokinetic properties; physiologically- based pharmacokinetic modelling.
Derek Nexus; Meteor Nexus; Sarah Nexus	*https://www.lhasalimited.org/products/* Derek: predicts toxicity from expert knowledge; Meteor: rule-based prediction of metabolites (customisable to enable predictions for individual enzymes); Sarah: statistically-based prediction of mutagenicity.
EPI SUITE	*http://www.epa.gov/opptintr/exposure/pubs/episuitedl.htm* Freely available suite of programs from the US EPA; prediction of properties: physico-chemical; dermal uptake; toxicity to aquatic organisms (Fish, *Daphnia*, algae).
KNIME	*https://www.knime.com/* Open platform enabling development of nodes for multiple applications, e.g., Indigo, CDK and RDKit chemoinformatic tools for QSAR descriptor generation, 2-D and 3-D model building, conversion of chemical identifiers, structure generation, substructure searching, fingerprinting, etc.
Molecular Operating Environment (MOE)	*https://www.chemcomp.com/Products.htm* Computer-aided design platform: calculation of >400 descriptors; 3-D pharmacophore mapping; docking, screening, etc.
Molinspiration	*http://www.molinspiration.com/* Freely available web tool: calculates Lipinski Rule of Fives violations.

Generally, modeling methods include five major steps while developing prediction models19 (Figure 1): (1) gathering biological data that contain associations between chemicals and toxicity endpoints, (2) calculating molecular descriptors of the chemicals, (3) generating a prediction model, (4) evaluating the accuracy of the model, and (5) interpreting the model.

5. TOXICITY STUDIES OF MEDICAL DEVICES

Medical devices are complex as they include a variety of products and technologies. Such as instruments, apparatus, materials, or other articles including software used alone or in combination for diagnosis ,monitoring, cure, mitigation ,treatment, compensation, and prevention of diseases or function

in humans and animals as determined by the Food and Drug Administration (FDA) Center for Devices and Radiation Health and the European Commission Medical Device Directive 93/42/EEC.

Biocompatibility testing

It involves biological testing of medical devices to identify a range of potential hazards and ensure that these products do not have adverse effects on patients. The purpose of the biocompatibility testing is to establish the potential for adverse effects when a medical device is used in a clinical application.

Eg: in vitro Diagnostics and x-ray equipment.

Table 5 :

Body Contact	Tissue Contact
Surface devices	Skin Mucosal membranes Breached(or) compromised surfaces
External communicating devices	Blood path, indirect Tissue ,bone ,or dentin communicating Circulating blood
Implant devices	Tissue or bone Blood

Categories of body contact and tissue exposure for medical devices:

Twelve categories of biocompatibility tests are listed in ISO 10993, Part 1, and FDA's Blue Book Memorandum G95-1 (Center for Devices and Radiological Health 1995)

1)Cytotoxicity

Part 5 of ISO 10993, Tests for cytotoxicity- in vitro methods, Contains methods for cytotoxicity testing of materials and extracts.

Four assay methods are provided:

1. Tests of extracts
2. Direct contact
3. Agar diffusion
4. Filter diffusion

2) Sensitization

The maximization and closed-patch assays for evaluating the Delayed contact sensitization potential of extracts of medical devices are contained in Part 10 of ISO 10993, Tests for irritation and sensitization.

1. Local Lymph Node Assay (LLNA)
2. Guinea pig skin sensitization test
3. Closed patch sensitization assay

3)Irritation

Methods for evaluating the irritation potential of medical devices are contained in Part 10 of ISO 10993, Tests for irritation and sensitization.

Test materials that have a pH of 2 or < /> 11.5 are declared to be irritants and no further testing is required.

1. Skin irritation assay
2. Intracutaneous irritation assay
3. Ocular irritation assay

4) Genotoxicity

ISO 10993-3, Tests for Genotoxicity, carcinogenicity, and reproductive toxicity requires a battery of three Genotoxicity tests. Most medical devices with prolonged or permanent contact require evaluation for Genotoxicity.

The in vitro assays most commonly conducted are the Ames test for bacterial reverse mutations using *Salmonella typhimurium* and a chromosome aberration assay in Mammalian cells.

In vivo Genotoxicity assays such as the Rodent micronucleus, rodent bone marrow, or dominant lethal assay may be appropriate for selected medical devices.

5)Implantation

Part 6 of the ISO standards, Tests for local effects after implantation, assesses the local effects of an implanted material on living tissue. Medical devices having prolonged or permanent contact with tissues, bone, or dentin and prolonged contact with blood require testing by implantation.

6)Carcinogenicity

Materials that are found to be genotoxic in mammalian cells would be required to be tested for carcinogenicity in animals before proceeding to clinical trials.

According to ISO 10993-3, Tests for Genotoxicity, carcinogenicity and reproductive toxicity, carcinogenicity assays may be required for resorbable materials and devices unless there is data on the identity and biological effects of the degradants.

7) Reproductive Toxicity

Guidance on the selection of tests for reproductive toxicity are found in ISO 10993-3.

Intrauterine devices (IUDs) and Other long-term contact devices that are likely to come into direct contact with reproductive tissues or the embryo/fetus should be evaluated for reproductive toxicity.

Energy-depositing devices(electromagnetic, ultrasonic, or ionic Radiation) and resorbable or leachable materials and devices may also require reproductive toxicity testing.(20)

REGULATORY GUIDELINES FOR MEDICAL DEVICES

Medical device can be any instrument, apparatus, implement, machine, implant, appliance, reagent for in-vitro use, software, intended by manufacturer to be used alone or in combination for a medical purpose.

There are two regulatory bodies:

- Central Drugs Standard Control Organization (CDSCO) and
- Indian Council of Medical Research (ICMR)

GOVERNING AND ALLOWING AUTHORITY

The Drugs and Cosmetics Act, 1940 ("DCA") governs the quality and safety of medical devices in India. Only "notified medical devices" that are periodically notified by the government as "drugs" are covered by the DCA.

Under the DCA, the Medical Devices Regulations, 2017 ("MDR") were drafted. (21).

IMPORT OF MEDICAL DEVICES

Presently, the Indian market for medical devices is largely unregulated. Medical devices are freely imported into India. The regulatory procedure will be clear only after the government notifies the regulations and the CDSCO provides the import guidelines.

MANUFACTURE OF MEDICAL DEVICES IN THE COUNTRY

- Application for the grant of license for manufacture shall be made in Form 27 to the State Licensing Authority.
- A period of 60 days would be provided for making the Application for manufacture from the date of publication of these guidelines.

SALE OF MEDICAL DEVICES IN THE COUNTRY

Importers, stockiest, and retail sellers of Medical Devices shall obtain appropriate sale licenses from the State Licensing Authorities for these medical devices within a period of 3 Months from the issue of these guidelines.

CLINICAL TRIALS

Clinical trials and clinical evaluation of medical devices in India are as per Global harmonization task force (GHTF) Guidance USA, Australia, Japan, Canada, and European Union.

LICENSING

Guidance document Requirements for grant of license in Form-28 for manufacturing of medical devices in India. Application for the grant of license for manufacture of Medical Devices in India shall be made in Form 27.(22)

CONCLUSION

Clinical toxicology studies using in-vivo, in-vitro, or in-silico methods can provide important information about the safety of a drug and can support the entry of Investigational New Drug (IND) into the market by reducing toxic effects. According to the FDA, the PT (Pharmacology and Toxicology) Information component of an IND application is expected to contain information about pharmacological and toxicological effects of the drug in animals. Non-clinical studies, including regulatory toxicology studies, are mandatory in the drug development process and aim to evaluate the toxicity level of a substance using in-vivo, in-vitro, or in-silico methods. The obtained outcomes are fundamental for characterizing the toxicity of the test article and the toxicity data described in the guidelines suggested by the FDA comprise an important basis for IND application. Therefore, clinical toxicology studies using in-vivo, in-vitro, or in-silico methods can provide valuable information to support the safety of a drug and encourage the entry of IND into the market.

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