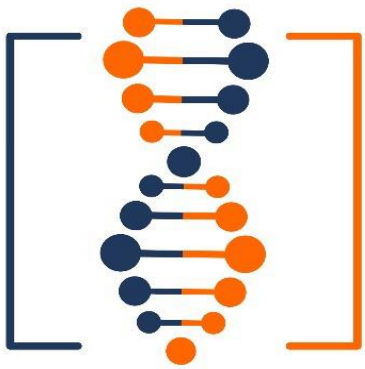

DESTINATION PHARMAGENS

Definition of poison.

Poisoning is commonly due to ingestion but can result from injection, inhalation, or exposure of body surfaces (eg, skin, eye, mucous membranes). Many commonly ingested nonfood substances are generally nontoxic. however, almost any substance can be toxic if ingested in excessive amounts In common usage: poisons are chemicals or chemical products that are distinctly harmful to human, More precisely: a poison is a foreign chemical (xenobiotic) that is capable of producing a harmful effect on a biologic system

General principles of treatment of Poisoning.

Diagnosis

- Consideration of poisoning in patients with altered consciousness or unexplained symptoms
- History from all available sources
- Selective, directed testing

The first step of diagnosis of poisoning is to assess the overall status of the patient. Severe poisoning may require rapid intervention to treat airway compromise or cardiopulmonary collapse.

Testing

- In most cases, laboratory testing provides limited help. Standard, readily available tests to identify common drugs of abuse (often called toxic screens) are qualitative, not quantitative.
- These tests may provide false-positive or false-negative results, and they check for only a limited number of substances. Also, the presence of a drug of abuse does not necessarily indicate that the drug caused the patient's symptoms or signs.
- Urine drug screening is used most often but has limited value and usually detects classes of drugs or metabolites rather than specific drugs.

Treatment

1 Initial stabilization

Airway, breathing, and circulation

It must be maintained in patients suspected of a systemic poisoning. Patients without a pulse or BP require emergency cardiopulmonary resuscitation. If patients have apnea or compromised airways (eg, foreign material in the oropharynx, decreased gag reflex), an endotracheal tube should be inserted. If patients have respiratory depression or hypoxia, supplemental O_2 or mechanical ventilation should be provided as needed.

- **IV naloxone** should be tried in patients with apnea or severe respiratory depression while maintaining airway support. In opioid addicts, naloxone may precipitate withdrawal, but withdrawal is preferable to severe respiratory depression.
- **IV dextrose** (50 mL of a 50% solution for adults; 2 to 4 mL/kg of a 25% solution for children) should be given to patients with altered consciousness or CNS depression, unless hypoglycemia has been ruled out by immediate bedside determination of blood glucose.
- **Thiamine** (100 mg IV) is given with or before glucose to adults with suspected thiamine deficiency (eg, alcoholics, undernourished patients).
- **IV fluids** are given for hypotension. If fluids are ineffective, invasive hemodynamic monitoring may be necessary to guide fluid and vasopressor therapy.
- The **first-choice vasopressor** for most poison-induced hypotension is norepinephrine 0.5 to 1 mg/min IV infusion, but treatment should not be delayed if another vasopressor is more immediately available.

2 Topical decontamination

- Any bodies surface (including the eyes) exposed to a toxin is flushed with large amounts of water or saline.
- Contaminated clothing, including shoes and socks, and jewelry should be removed.
- Topical patches and transdermal delivery systems are removed.

3 Activated charcoal

- Charcoal is usually given, particularly when multiple or unknown substances have been ingested. Use of charcoal adds little risk (unless patients are at risk of vomiting and aspiration) but has not been proved to reduce overall morbidity or mortality.
- When used, charcoal is given as soon as possible.
- Activated charcoal adsorbs most toxins because of its molecular configuration and large surface area.
- Charcoal may be given at 4- to 6-h intervals for serious poisoning with such substances unless bowel sounds are hypoactive.
- Charcoal is ineffective for caustics, alcohols, and simple ions (eg, cyanide, iron, other metals, lithium).

4 Gastric emptying

- Gastric emptying, which used to be well-accepted and seems intuitively beneficial, should not be routinely done. It does not clearly reduce overall morbidity or mortality and has risks.
- Gastric emptying is considered if it can be done within 1 h of a life-threatening ingestion. However, many poisonings manifest too late, and whether a poisoning is life threatening is not always clear.
- Thus, gastric emptying is seldom indicated and, if a caustic substance has been ingested, is contraindicated (see Caustic Ingestion).

- If gastric emptying is used, **gastric lavage** is the preferred method.
- Syrup of ipecac has unpredictable effects, often causes prolonged vomiting, and may not remove substantial amounts of poison from the stomach.
- Gastric lavage may cause complications such as epistaxis, aspiration, or, rarely, oropharyngeal or esophageal injury.

5 Whole-bowel irrigation

This procedure flushes the GI tract and theoretically decreases GI transit time for pills and tablets. Irrigation has not been proved to reduce morbidity or mortality. Irrigation is indicated for any of the following:

- Some serious poisonings due to sustained-release preparations or substances that are not adsorbed by charcoal (eg, heavy metals)
- Drug packets (eg, latex-coated packets of heroin or cocaine ingested by body packers)
- A suspected bezoar

A commercially prepared solution of polyethylene glycol (which is non absorbable) and electrolytes is given at a rate of 1 to 2 L/h for adults or at 25 to 40 mL/kg/h for children until the rectal effluent is clear; this process may require many hours or even days.

The solution is usually given via a gastric tube, although some motivated patients can drink these large volumes.

6 Alkaline diuresis

- Alkaline diuresis enhances elimination of weak acids (eg, salicylates, phenobarbital).
- A solution made by combining 1 L of 5% D/W with 3 50-mEq ampules of $NaHCO_3$ and 20 to 40 mEq of K can be given at a rate of 250 mL/h in adults and 2 to 3 mL/kg/h in children.
- Urine pH is kept at > 8, and K must be repleted.
- Hypernatremia, alkalemia, and fluid overload may occur but are usually not serious.
- However, alkaline diuresis is contraindicated in patients with renal insufficiency.

7 Dialysis

Common toxins that may require dialysis or hemoperfusion include

- Ethylene glycol
- Lithium
- Methanol

- Salicylates
- Theophylline

The need for dialysis is usually determined by both laboratory values and clinical status.

Methods of dialysis include hemodialysis, peritoneal dialysis, and lipid dialysis (which removes lipid-soluble substances from the blood), as well as hemoperfusion.

8 Specific antidotes

Acetaminophen	**N-acetyl cysteine**
Anti-cholinergics	**Physostigmine**
Benzodiazepenes	**Flumazenil**
Ca channel blockers	**Glucagon, Insulin + dextrose, Calcium**
Carbamate	**Atropine**
Cyanide	**Thiosulphate, nitrate**
Digoxin	**Digoxin antibodies**
INAH	**Pyridoxine**
Methanol	**Ethanol, Fomepizole**
Glycol	**Ethanol, Fomepizole**
Opioid	**Naloxone**
Oral hypoglycaemics	**Glucose**
Organophosphate	**Atropine,? P2AM**
Warfarin	**Vitamin K**

9 Ongoing supportive measures

- For refractory hypotension, dopamine, epinephrine, other vasopressors, an intra-aortic balloon pump, or even extracorporeal circulatory support may be considered.
- For refractory arrhythmias, cardiac pacing may be necessary.
- Seizures are first treated with benzodiazepines.
- Hyperthermia is treated with aggressive sedation and physical cooling measures rather than with antipyretics.

10 Hospital admission

General indications for hospital admission include altered consciousness, persistently abnormal vital signs, and predicted delayed toxicity.

Treatment of poisoning due to Heavy metals,insecticides,opiods and other addict forming drugs.

1. **Opiate poisoning**

Symptoms includes

Coma, Miosis, Respiratory depression, Peripheral vasodilation, Orthostatic hypotension, Flushing (histamine), Bronchospasm, Pulmonary edema, Seizures (meperidine, propoxyphene).

Competitive opioid antagonist: **Naloxone**

• Goal of return of spontaneous respirations sufficient to ventilate the patient appropriately

• May have to re-dose as opiates may act longer than antagonist

2. **INSECTISIDES POISONING**

Local muscarinic **manifestations** at the site of exposure (skin, eye, g.i.t.) occur immediately and are followed by complex systemic effects due to muscarinic, nicotinic and central actions. They are—

• Irritation of eye, lacrimation, salivation, sweating, copious tracheo-bronchial secretions, miosis, blurring of vision, bronchospasm, breathlessness, colic, involuntary defecation and urination.

• Fall in BP, bradycardia or tachycardia, cardiac arrhythmias, vascular collapse.

• Muscular fasciculations, weakness, respiratory paralysis (central as well as peripheral).

• Irritability, disorientation, unsteadiness, tremor, ataxia, convulsions, coma and death.

• Death is generally due to respiratory failure.

Treatment

1. Termination of further exposure to the poison— fresh air, wash the skin and mucous membranes with soap and water, gastric lavage according to need.

2. Maintain patent airway, positive pressure respiration if it is failing.

3. Supportive measures—maintain BP, hydration, control of convulsions with judicious use of diazepam.

4. Specific antidotes— ATROPIN AND PRALIDOXIME

3. HABBIT FORMING BZD AND BARBITURATES

Sedative-Hypnotic

• Sedative-hypnotics are a group of drugs that cause CNS depression. Benzodiazepines and barbiturates are the most commonly used agents in this class. • Different agents have different mechanisms • Many interfere in the GABA system

SYMPTOMS

• CNS depression, lethargy • Can induce respiratory depression • Can produce bradycardia or hypotension

TREATMENT

• Supportive care • Flumazinil**?** / Meprobamate / Methaqualone

Study of acute, sub acute and chronic toxicity as per OECD guidelines.

Toxicity is the degree to which a substance (a toxin or poison) can harm humans or animals. Toxicity can refer to the effect on a cell (cytotoxicity), an organ (e.g. renal or liver toxicity), or the whole organism thus explaining why scientists use different procedures to assess toxicity and to provide an estimate of how much of a substance causes a kind of harm. All substances are potentially toxic depending on the quantity.

There is no measure of toxicity, and its effects may occur in short term (acute effects), or after repeated exposure over a long period (sub-acute or chronic effects).

The following tests are performed in the Centre for Study and Therapy of Pain and Central Drug Testing Laboratory, "Gr.T.Popa" University of Medicine and Pharmacy Iasi, using rodent models, for detection:

• Acute toxicity tests (single dose)

• Sub-acute toxicity test (daily dose - 14 to 28 days)

• Sub-chronic toxicity test (daily dose – up to 90 days)

• Chronic toxicity test (daily dose – up to 12 months)

ACUTE TOXICITY TEST

Definition: The Globally Harmonized System (GHS) defines Acute Toxicity as "those adverse effects occurring following oral or dermal administration of a single dose of a substance, or multiple doses given within 24 hours, or an inhalation exposure of 4 hours".

Acute toxicity tests are generally the first tests conducted and they provide critical data on the relative toxicity likely to arise from a single or brief exposure. Standardized tests are available for oral, dermal and inhalation exposures and the preferred species for oral and inhalation testing is the rat, and for dermal testing the rat or the rabbit. Oral administration is the most common form of acute systemic toxicity testing.

The Organization for Economic Cooperation and Development (OECD) elaborate five Test Guidelines for describing acute systemic testing:

• Fixed Dose Procedure (OECD TG 420)

• Acute toxic Class method (OECD TG 423)

• Up-and-Down Procedure (OECD TG 425)

• Acute Dermal Toxicity (OECD TG 402)

• Acute Inhalation Toxicity (OECD TG 403)

Acute Toxic Class Method

The substance is administered orally to a group of experimental animals at one of the defined doses. The substance is then tested using a stepwise procedure, each step using three animals of single sex (normally females).

Absence or presence of compound-related mortality of the animals, dosed at one step, will determine the next step, i.e.: • no further testing is needed, • dosing of three additional animals, with the same dose • dosing of three additional animals at the next higher or the next lower dose level This method is the most used in our laboratory.

Fixed Dose Procedure

Groups of animals of a single sex are dosed in a stepwise procedure using the fixed doses of 5, 50, 300 and 2000 mg/kg. The initial dose level is selected on the basis of a sighting study as the dose expected to produce some signs of toxicity, without causing severe toxic effects or mortality.

Further groups of animals may be dosed at higher or lower fixed doses, depending on the presence or absence of signs of toxicity or mortality.

This procedure continues until the dose causing evident toxicity, or no more than one death is identified, or when no effects are seen at the highest dose, or when deaths occur at the lowest dose.

Up-and-Down-Procedure (UDP)

The Limit Test is a sequential test that uses a maximum of 5 animals. A maximum test dose of 2000 mg/kg may be used. The selection of a sequential test plan increases the statistical power and also has been made to intentionally bias the procedure towards rejection of the limit test for compounds with LD50s near the limit dose; i.e., to error on the side of safety.

As with any limit test protocol, the probability of correctly classifying a compound will decrease, as the actual LD50 better resembles the limit dose.

Acute Dermal Toxicity

The test substance is applied to the skin, in graduated doses, to several groups of experimental animals, one dose being used per group. Subsequently, observations of effects and deaths are made.

Animals that die during the test are forensically investigated, and at the conclusion of the test the surviving animals are also sacrificed and forensic analysis performed. Animals showing severe and enduring signs of distress and pain may need to be sacrificed.

Administration of test substances in a way known to cause marked pain and distress due to corrosive or irritating properties is not carried out. This test is particularly useful in testing novel analgesic combinations with dermal administration

SUB-ACUTE AND CHRONIC TOXICITY TEST

Introduction

Sub-acute and chronic toxicity test determine toxicity from exposure for a substantial portion of a subject's life and the Globally Harmonized System (GHS) defines it as "specific target organ/systemic toxicity arising from a repeated exposure".

In rats these studies range in duration from 28-days (sub-acute studies) to 90-day (sub-chronic studies), and even 12-months (chronic studies), and consist of repeated doses in oral, inhalation and dermal administration.

These studies are conducted in stages so that the results of one study can be used to design the subsequent study of longer duration. The first are usually 2 weeks in length followed by 1- month, 3-month, 6-month, and then 1-year studies.

The endpoints for repeat dose testing consist of an evaluation of clinical observations, blood analysis, whole body gross necropsy, and microscopic examination of all organs and tissues (histopathology). The data from these studies provide valuable information on the cumulative exposure of target organs, and on general health hazards likely to occur as a consequence of repeated low-dose exposure to a chemical.

There are six OECD (Organization for Economic Cooperation and Development) Test Guidelines describing short-term repeat-dose toxicity testing:

• Repeated Dose 28-day Oral Toxicity Study in Rodents (OECD TG407)

• Repeated Dose 90-Day Oral Toxicity Study in Rodents (OECD TG 408)

• Repeated Dose Dermal Toxicity: 21/28-day Study (OECD TG 410)

• Sub-chronic Dermal Toxicity: 90-day Study (OECD TG 411)

• Repeated Dose Inhalation Toxicity: 28-day or 14-day Study (OECD TG 412)

• Sub-chronic Inhalation Toxicity: 90-day Study (OECD TG 413)

• Repeated Dose 28-Day Oral Toxicity: "The test substance is orally administered daily in graduated doses to several groups of experimental animals, one dose level per group for a period of 28 days. During the period of administration the animals are observed closely, each day for signs of toxicity. Animals that die or are euthanized during the test are necropsied and at the conclusion of the test surviving animals are euthanized and necropsied. A 28-day study provides information on the effects of repeated oral exposure and can indicate the need for further longer-term studies. It can also provide information on the selection of concentrations for longer-term studies. The data derived from using the TG should allow for the characterization of the test substance toxicity, for an indication of the dose response relationship and the determination of the No Observed Adverse Effect Level (NOAEL)".

• Repeated Dose 90-day Oral Toxicity: "The test substance is orally administered daily in graduated doses to several groups of experimental animals, one dose level per group for a period of 90 days. During the period of administration the animals are observed closely for signs of toxicity. Animals which die or are killed during the test are necropsied and, at the conclusion of the test, surviving animals are also killed and necropsied".

• Sub-chronic Dermal Toxicity 90-day Study: "The test substance is applied daily to the skin in graduated doses to several groups of experimental animals, one dose per group, for a period of 90 days. During the period of application the animals are observed daily to detect signs of toxicity. Animals which die during the test are necropsied, and at the conclusion of the test the surviving animals are sacrificed and necropsied".

• Repeated Dose Dermal Toxicity 21/28-day Study: "The test substance is applied daily to the skin in graduated doses to several groups of experimental animals, one dose per group, for a period of 21/28 days. During the period of application the animals are observed daily to detect signs of toxicity. Animals which die during the test are necropsied, and at the conclusion of the test the surviving animals are sacrificed and necropsied".

Genotoxicity, Carcinogenicity, teratogenicity and mutagenicity studies

Carcinogenicity

- Carcinogenicity is ability of a carcinogen to cause cancer. A carcinogen is an agent whose administration to animals leads to a statistically significant increased incidence of neoplasms compared to untreated controls. Neoplasm is a heritably altered, relatively autonomous growth of tissue.
- Genotoxicity The ability of an agent to damage or alter the genetic information (DNA)
- Carcinogenicity can be a result of a genotoxic insult, but can also be induced by nongenotoxic mechanisms

carcinogenicity studies

- The objectives of carcinogenicity studies are to identify a tumorigenic potential in animals and to assess the relevant risk in humans, Any cause for concern derived from laboratory investigations, animal toxicology studies, and data in humans may lead to a need for carcinogenicity studies.
- The practice of requiring carcinogenicity studies in rodents was instituted for pharmaceuticals that were expected to be administered regularly over a substantial part of a patient's lifetime.
- The design and interpretation of the results from these studies preceded much of the available current technology to test for genotoxic potential and the more recent advances in technologies to assess systemic exposure. These studies also preceded our current understanding of tumorigenesis with non-genotoxic agents.

Factors to be considered in carcinogenicity studies

Duration and exposure, cause, genotoxicity, indication and patient population, route of exposure, Extent of systemic exposure , endogenous peptide and proteins analouges carcinogenocity.

genotoxic

All chemicals that produce DNA damage leading to mutation or cancer are described as genotoxic.

In genetics, genotoxicity describes the property of chemical agents that damages the genetic information within a cell causing mutations, which may lead to cancer. While genotoxicity is often confused with mutagenicity, it is important to note that all mutagens are genotoxic,

however, not all genotoxic substances are mutagenic. The alteration can have direct or indirect effects on the DNA: the induction of mutations, mistimed event activation, and direct DNA damage leading to mutations3. The permanent, hereditary changes can affect either somatic cells of the organism or germ cells to be passed on to future generations. Cells prevent expression of the genotoxic mutation by either DNA repair or apoptosis; however, the damage may not always be fixed leading to mutagenesis.

IN VIVO TESTING- genotoxicity

The purpose for *in vivo* testing is to determine the potential of DNA damage that can affect chromosomal structure or disturb the mitotic apparatus that changes chromosome number; the factors that could influence the genotoxicity are ADME and DNA repair. It can also detect genotoxic agents missed in *in vitro* tests.

The positive result of induced chromosomal damage is an increase in frequency of micronucleated PCEs. A micronucleus is a small structure separate from the nucleus containing nuclear DNA arisen from DNA fragments or whole chromosomes that were not incorporated in the daughter cell during mitosis.

Causes for this structure are mitotic loss of acentric chromosomal fragments (clastogenicity), mechanical problems from chromosomal breakage and exchange, mitotic loss of chromosomes (aneugenicity), and apoptosis.

The micronucleus test *in vivo* is similar to the *in vitro* one because it tests for structural and numerical chromosomal aberrations in mammalian cells, especially in rats' blood cells

***IN VITRO* TESTING- genotoxicity**

The purpose of *in vitro* testing is to determine whether a substrate, product, or environmental factor induces genetic damage. One technique is cytogenetic assays using different mammalian cells. The types of aberrations detected in cells affected by a genotoxic substance are chromatid and chromosome gaps, chromosome breaks, chromatid deletions, fragmentation, translocation, complex rearrangements, and many more. The clastogenic or aneugenic effects from the genotoxic damage will cause an increase in frequency of structural or numerical aberrations of the genetic material. This is similar to the micronucleus test and chromosome aberration assay, which detect structural and numerical chromosomal aberrations in mammalian cells.

Mutagenicity

Mutagenicity refers to the induction of permanent transmissible changes in the structure of the genetic material of cells or organisms. These changes (mutations) may involve a single gene or a block of genes. Genotoxicity is a broader term that refers to the ability to interact with DNA and/or the cellular apparatus that regulates the fidelity of the genome, such as the spindle apparatus and topoisomerase enzymes.

Genotoxicity and mutagenicity testing are an important part of the hazard assessment of chemicals for regulatory purposes. To assess genotoxicity and/or mutagenicity, different endpoints must be taken into considerations: beside point mutations induction, a compound can induce changes in chromosomal number (polyploidy or aneuploidy) or in chromosome structure (breaks, deletions, rearrangements). However, aneuploidy can arise as a result of both genotoxic and non-genotoxic events, since loss of chromosomes can be caused either by direct effects on the chromosome to produce an acentric fragment, or by interference with the site of attachment of the chromosome on the spindle.

Due to the diversity of the endpoints, it is then clear that the potential genotoxicity and/or mutagenicity of a compound cannot be assessed by a single assay system.

For this reason, the group of experts has attempted to suggest a strategy to better investigate the mutagenic and/or genotoxic potential of the cosmetic products taking into consideration the needs of the cosmetic industry.

Strategy is divided in 4 stages:

- **Stage 1** characterizes the substance based on existing data and knowledge

- **Stage 2** is a basic *in vitro* test battery for hazard identification

- **Stage 3** is a follow up stage in *in vitro* model systems. This stage is reached if one or

more tests are positive in Stage 2

- **Stage 4** is *in vivo.* This stage is reached if one or more tests in Stage 3 are positive

Teratogenicity

Teratogenicity is the presence of major congenital malformations..

- Major malformations are those that are either life threatening,, require major surgery,, or have serious cosmetic effects..

- The more inclusive term off all these major defects is congenital anomalies or “birth defects”