State Toxicology Center Present & Future:

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Aim of the session

- **To provide you with a solid background for work with toxicological risk assessment**

- **Necessary basic knowledge**
- **Examples**
- **Reference to further reading**

Toxicology

*The Greek word for bow is **"toxon"** and something bow-like or pertaining to the bow is "**toxikos."***

*It was discovered that it was far more effective against the enemy to smear a little poison on the end of the arrow, thus making **toxicon pharmakon** a poison for (smearing) arrows.*

- The study of adverse effects of chemical substances on living systems
- The prediction of effects in man based on data from animals or other test systems

What is Toxicology?

The traditional definition of Toxicology is *"the science of poisons."* As our understanding of the working of biological systems improved, a more comprehensive definition has been put forth by *Society of Toxicology*.

"Toxicology is the study of adverse physico-chemical effects of chemical , physical or biological agents on living organisms and the ecosystems including prevention and amelioration of such effects"

A Toxic agent is anything that can produce an adverse biological effect. It may be chemical, physical, or biological in form. For example, toxic agents may be

chemical *(such as cyanide)*, physical *(such as radiation)* and biological *(such as snake venom)*.

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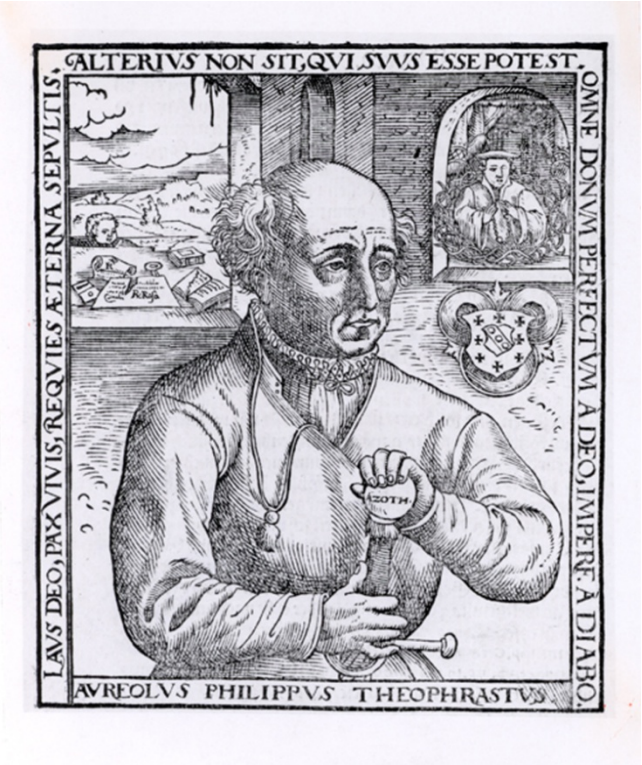
Types of Toxic Effects

- Acute effects occur after limited exposure and shortly (hours, days) after exposure and may be reversible or irreversible.
- Chronic effects occur after prolonged exposure (months, years, decades) and/or persist after exposure has ceased.

  Tobacco related cancers. e.g., Cancer of mouth due to tobacco chewing, cancer lung due to smoking are chronic toxic effects

Dose Response Relationship



"All substances are poisons; there is none which is not a poison.
The right dose differentiates a poison from a remedy."

Paracelsus (1493-1541)

Fundamental principle of Toxicology

Dose Response Relationship

% Alcohol in Blood	Observed Effect
0.05	Stimulant, Social Relaxation
> 0.1	Incoordination
0.3	Unconsciousness
0.4	Possible Death

Modern Day Toxicology

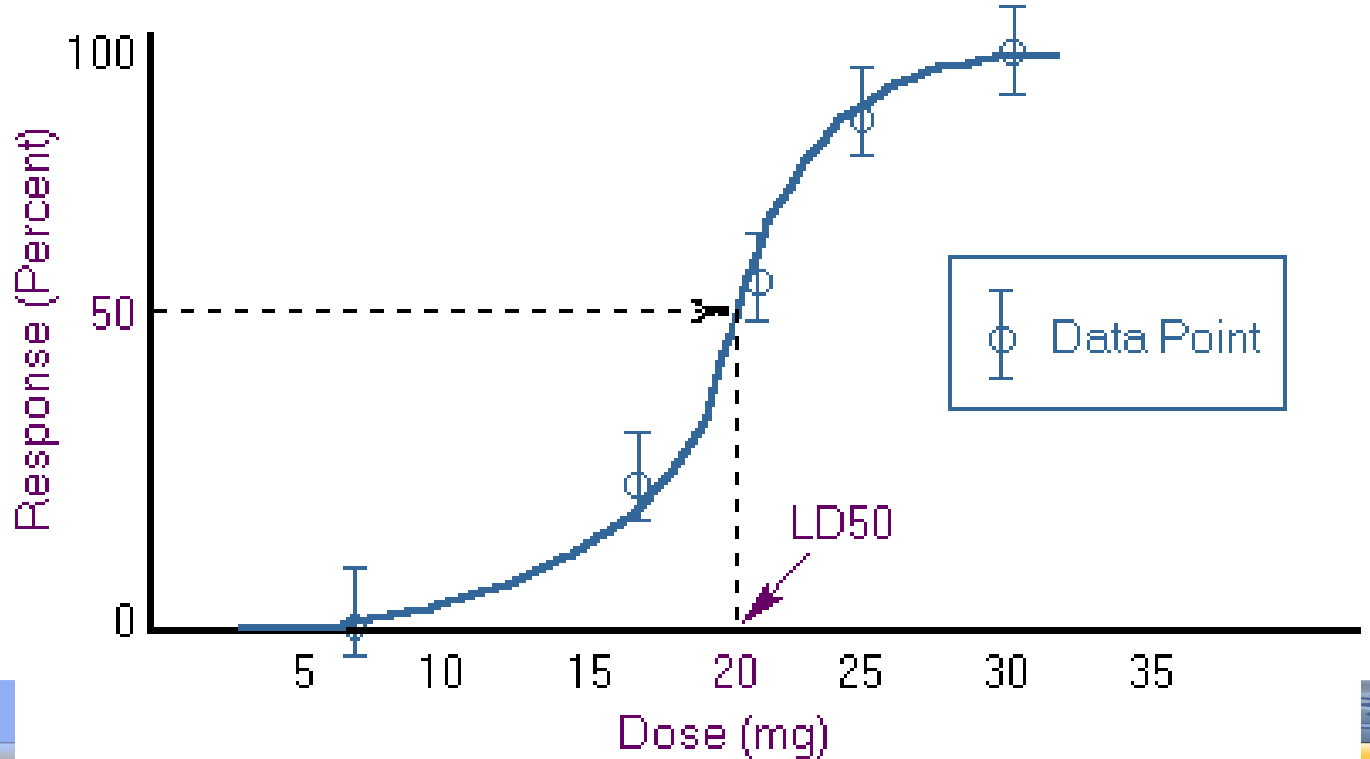
Toxicology developed as a modern science in the 20th Century especially after the Second World War. This was partly due to rapid development and production of many new drugs and industrial chemicals

Toxicology issues

- Arsenic poisoning from well water in Bangladesh 1980 onwards
- Leakage of methyl isocyanate at Bhopal 1984
- Sarin gas attack in Tokyo subway 1995
- Poisoning of Ukrainian President Yuschenko with Dioxin in 2004
- Poisoning of Alexander Litvinenko with Polonium 210 in 2006

What is LD_{50} ?

The **median lethal dose**, **LD_{50}** (abbreviation for "Lethal Dose, 50%"), **LC_{50}** (Lethal Concentration, 50%) or **LCt_{50}** (Lethal Concentration & Time) of a toxic substance or radiation is the dose required to kill half the members of a tested population after a specified test duration. LD_{50} figures are frequently used as a general indicator of a substance's acute toxicity.



Approximate Acute LD_{50} Values of some Representative chemicals

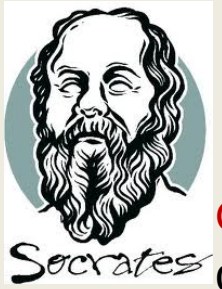
Agent	LD_{50} mg/kg
Ethyl Alcohol	10000
Ferrous Sulfate	1500
Morphine Sulfate	900
Phenobarbital Sodium	150
Strychnine sulfate	2
d- Tubocurarine	0.5
Dioxin(TCDD)	0.001
Botulinum toxin	0.00001

Some Important Toxicological Events

Poisoning and knowledge of poisons have a long and colourful history although science of toxicology has recently come into existence as a distinct discipline.

Famous early victims of poisoning were

Poison Hemlock



Greek Philosopher Socrates
c. 469 BC–399 BC

Asp (Poisonous Snake)

Egyptian queen Cleopatra
(69 BC- 30 BC)

Modern Day Toxicology

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Toxicology issues often make news headlines

- Arsenic poisoning from well water in Bangladesh 1980 onwards
- Leakage of methyl isocyanate at Bhopal 1984
- Sarin gas attack in Tokyo subway 1995
- Poisoning of Ukrainian President Yuschenko with Dioxin in 2004
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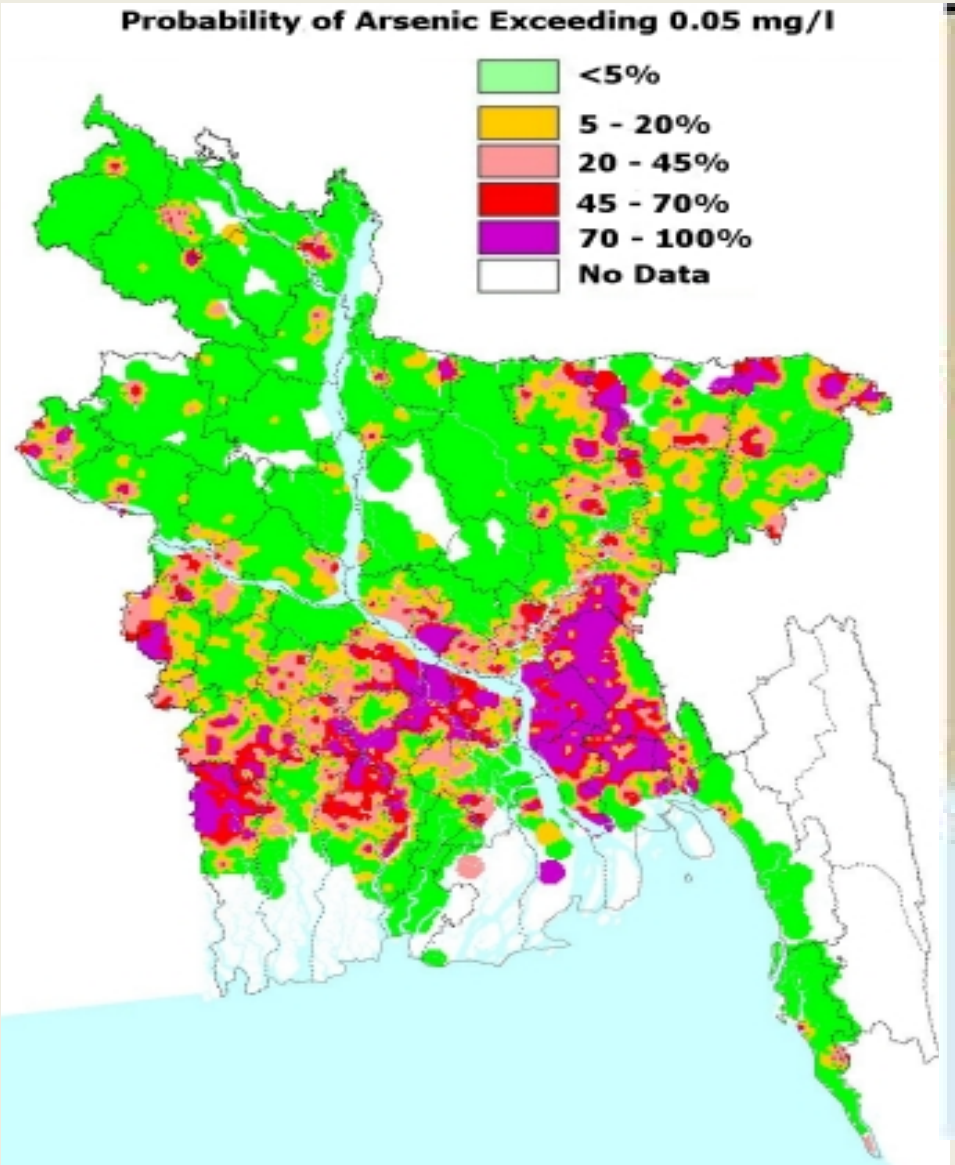

Probability of Arsenic Exceeding 0.05 mg/l
<5%
5 - 20%
20 - 45%
45 - 70%
70 - 100%
No Data


Arsenic contamination affects most of Bangladesh
Contamination level (ppb):
0–10
10–50
50–150
150–500
500–1,000
1,000–2,000
Source: Dainichi Consultant, Japan

Millions of tube-wells were dug beginning in the 1960s and 1970s financed by UNICEF and the World Bank in Bangladesh and West Bengal, India to provide water for agricultural purposes and to improve quality of drinking water that was causing fatal diarrhea The wells, however, were dug without testing for metal impurities.

The problems began appearing in the 1980s and included Arsenicosis which is the collective name for the symptoms of Arsenic Poisoning most notably lesions on the hands and feet . As of 2004, around 100,000 people were suffering from these lesions.

Cancer rates have started rising

This is thought to be the worst mass poisoning in history.

Skin lesions in Chronic Arsenic Poisoning

Following long-term exposure, the first changes are usually observed in the skin: pigmentation changes, and then hyperkeratosis.

Long-term exposure to arsenic via drinking-water causes cancer of the skin, lungs, urinary bladder, and kidney, as well as other skin changes

Some Events involving Toxic Chemicals

- **December 3, 1984:**
- Bhopal disaster in India is the largest industrial disaster on record. A faulty tank containing poisonous methyl isocyanate leaked at a Union Carbide plant and left nearly 4,000 people dead on the first night of the gas leak and at least 15,000 later from related illnesses. The disaster caused the region's human and animal populations severe health problems to the present.

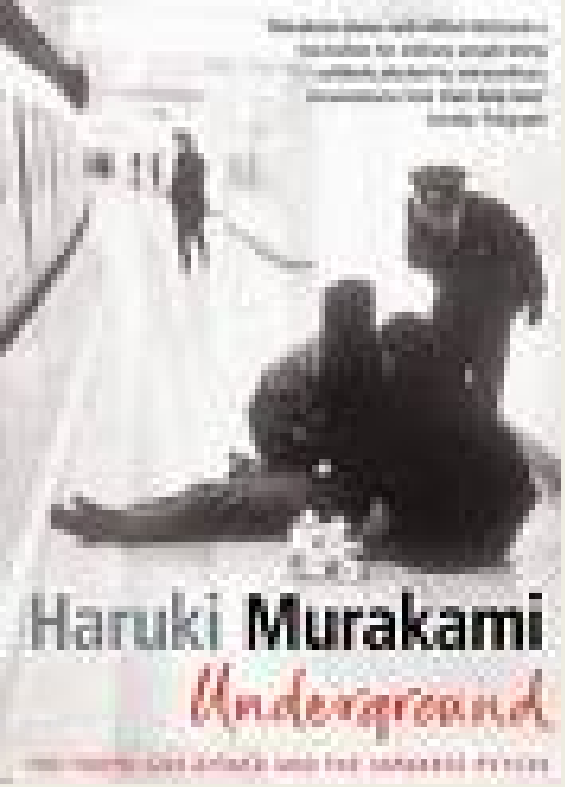
BHOPAL GAS DISASTER (DECEMBER,1984)

Chemicals which leaked at Union Carbide, Bhopal

METHYL ISOCYANATE

the gas cloud may have contained PHOSGENE, HYDROGEN CYANIDE, CARBON MONOXIDE, HYDROGEN CHLORIDE, OXIDES OF NITROGEN, MONOMETHYL AMINE (MMA) AND CARBON DIOXIDE, either produced in the storage tank or in the atmosphere.

Nearly 4000 dead and 100,000 having chronic ailments



Location	Tokyo, Japan
Date	(March 20, 1995) 7:00-8:10 a.m.
Attack type	Chemical warfare
Weapon(s)	Sarin
Deaths	12
Injured	1,034 (*50 severe; 984 temporary vision problems*)
Perpetrator (s)	Aum Shinrikyo

Chernobyl Disaster

- **April 26, 1986:** At the Chernobyl Nuclear Power Plant in the Ukraine, 31 people died and hundreds more injured from the nuclear fallout. The plume drifted over large parts of the western Soviet Union, Eastern Europe, Western Europe, and Northern Europe. Large areas in Ukraine, Belarus, and Russia had to be evacuated, with over 336,000 people resettled.

The nuclear reactor at Chernobyl after the disaster.

Thalidomide

- Introduced in 1956 as sedative (sleeping pill) and to reduce nausea and vomiting during pregnancy
- Withdrawn in 1961

- Discovered to be a human teratogen causing absence of limbs or limb malformations in newborns
- 5000 to 7000 infants effected
- Resulted in new drug testing rules

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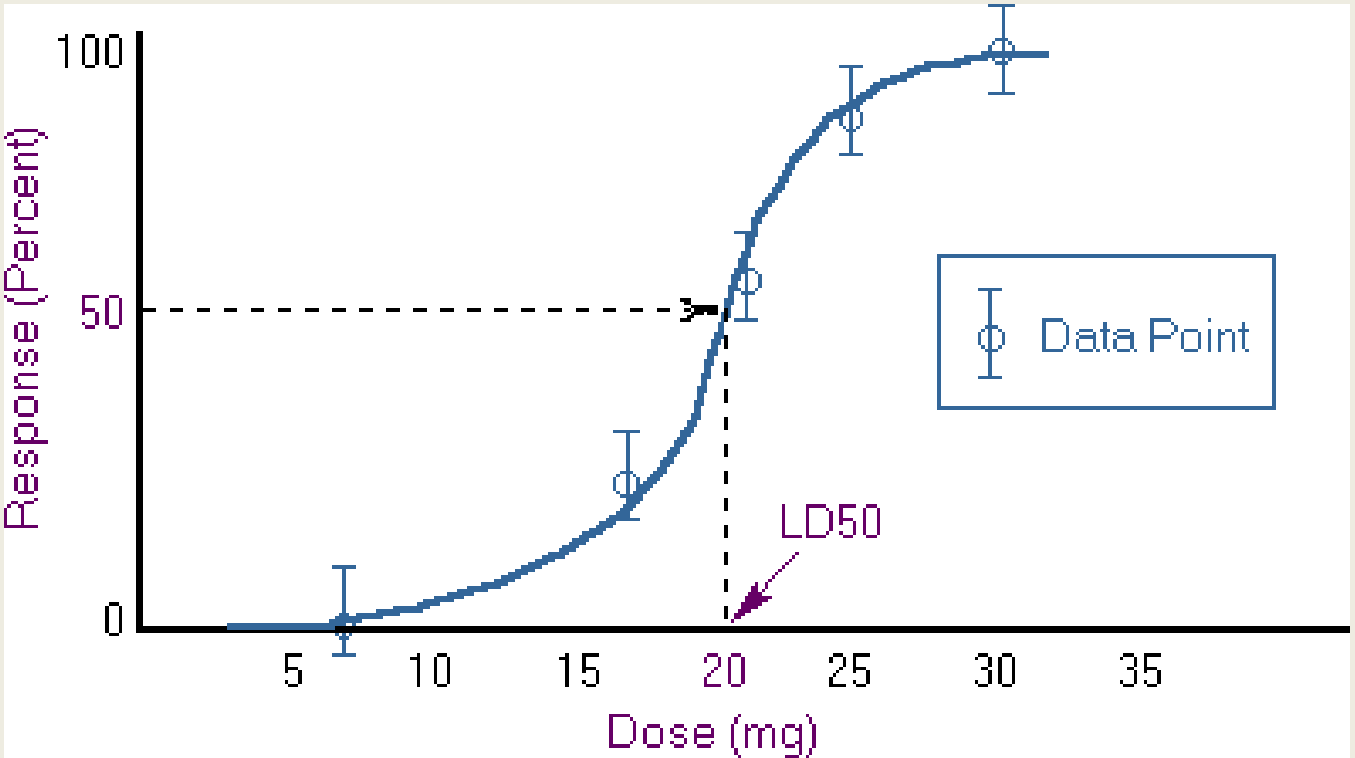


LD_{50} of Polonium 210 estimated at 10 (inhaled) to 50 (ingested) nanograms in humans makes this one of the most toxic substances known.

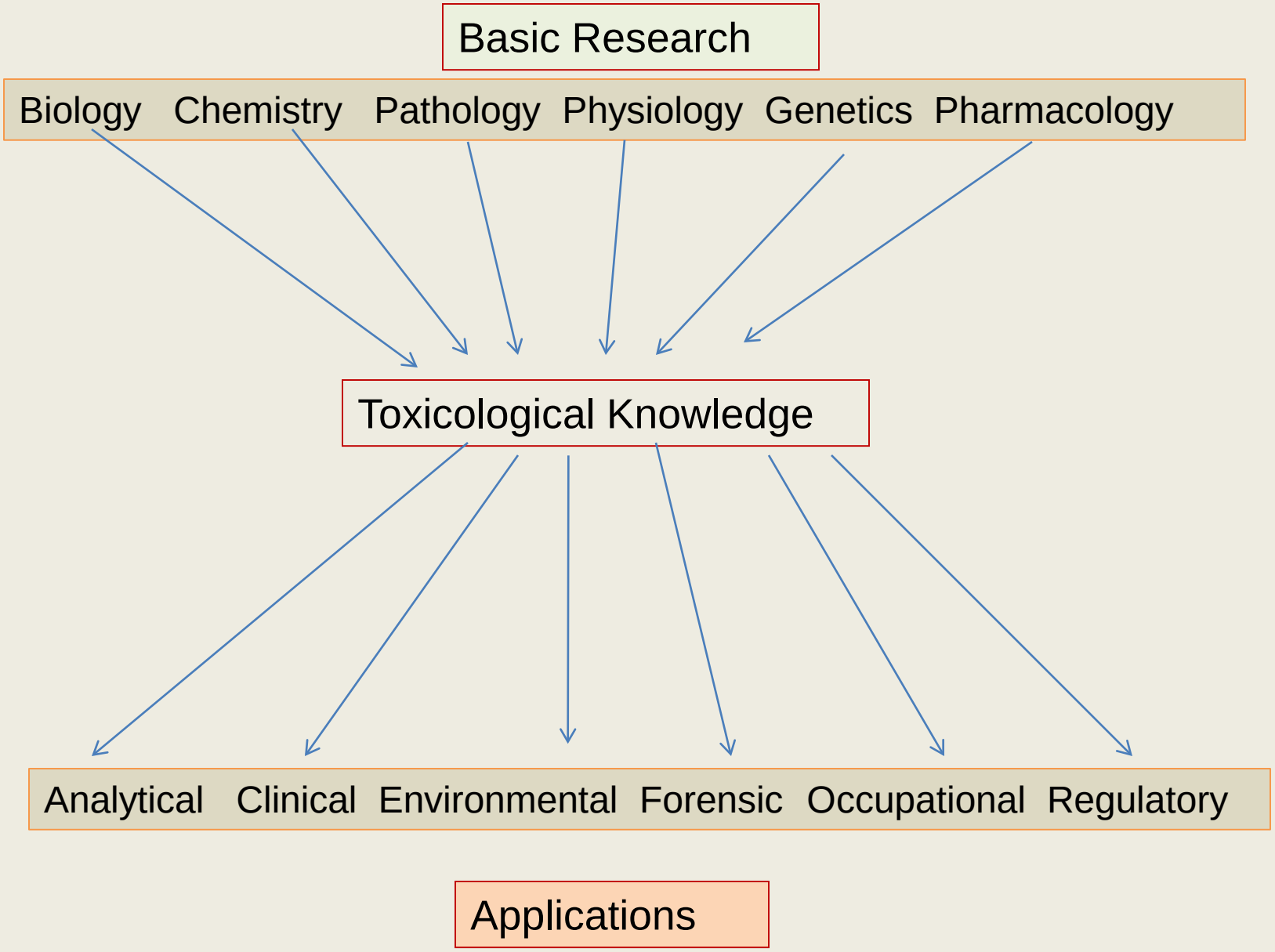
Theoretically One gram could poison 100 million people of which 50 million would die.

In 2006, Alexander Litvinenko, a former Russian spy, was fatally poisoned with Radioactive Polonium 210. The radioactive isotope was allegedly added to tea he drank at a London Hotel . He became the first confirmed victim of lethal Polonium-210 induced acute radiation syndrome

Unlike most common radiation sources, Polonium-210 emits only alpha particles that do not penetrate even a sheet of paper or the epidermis of human skin, thus being invisible to normal radiation detectors in this case

According to doctors, "Litvinenko's murder represents an ominous landmark: the beginning of an era of "nuclear terrorism"

Toxicology is a mixture of many disciplines and has many applications



Toxicologist..??

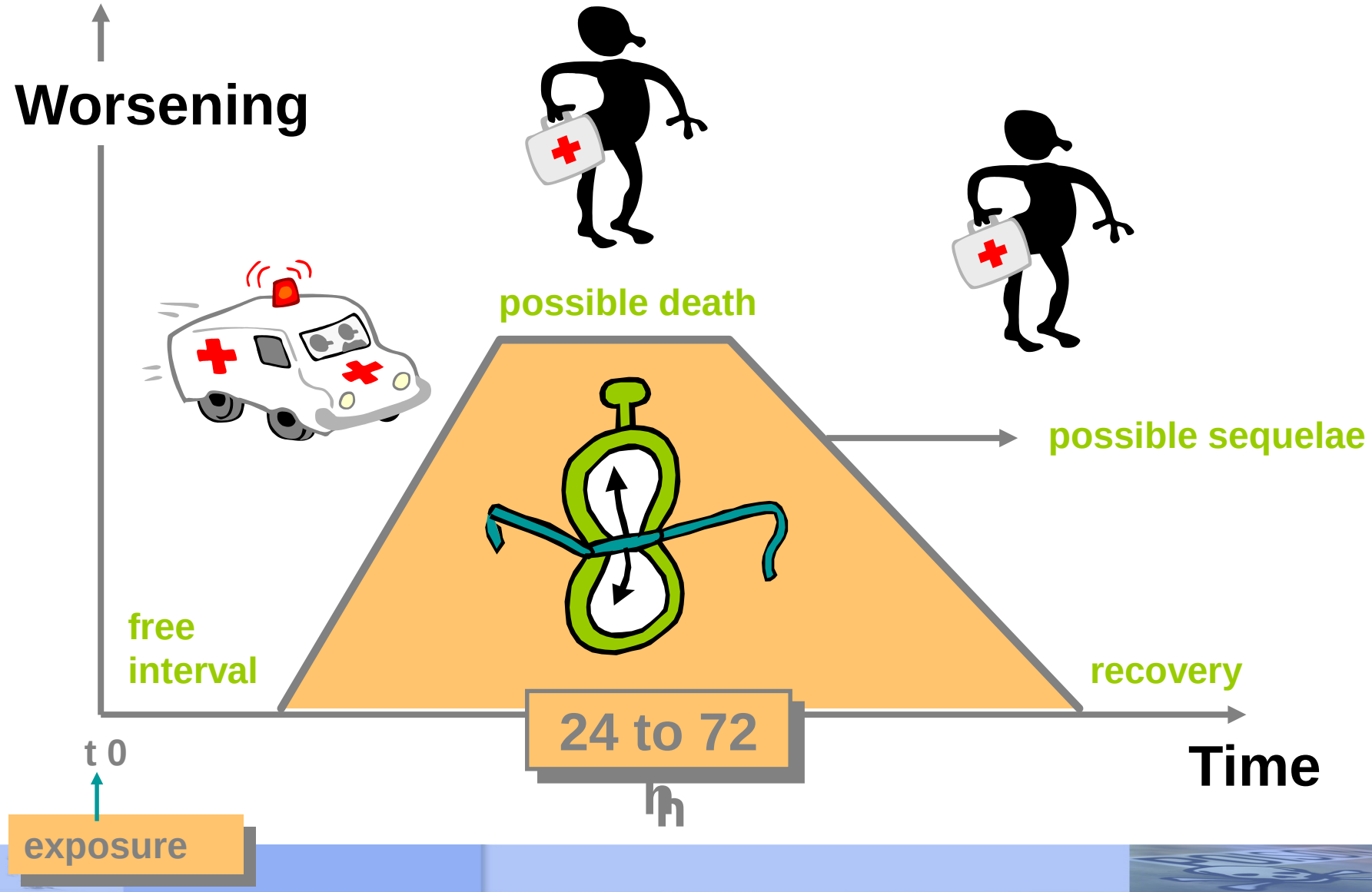
- in India, few specialist with a particular education
- Background in natural sciences + special knowledge which can be acquired in various ways – primarily by working with toxicological topics
- Veterinarian, biologist, pharmacist, medical doctor, human biologist, engineer

Background

One of the main challenges in managing poisoned patients is to identify this group as early as possible so that appropriate supportive, and if necessary, specific management steps can be instituted to prevent serious complications.’

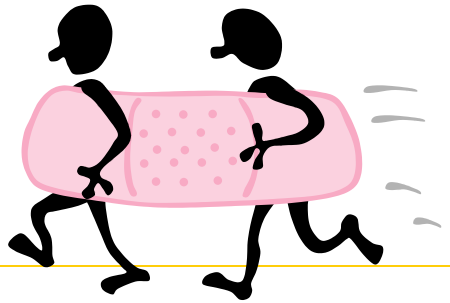
A L Jones, P I Dargan. Advances, challenges, and controversies in poisoning. Emerg Med J 2002;19:190–191

Acute poisoning, a dynamic process



Prehospital emergency care

- Decreasing the ‘free medical interval’
  - Diagnosis or approximation of diagnosis
  - Evaluation of severity, recognition of risk factors
  - Supportive treatment
  - Specific treatment? antidotes?
  - Prevention of early complications
  - Orientation (Hospital, ICU)
- As early as possible



When to send a Medical Emergency Care Unit ?

- Severity assessment
  - Toxicant(s), associations
  - Ingested dose / toxic dose
  - Formulation (slow release or not)
  - Patient (age, co morbidity)
  - Time from exposure, initial management?
  - Early complications

The French ETC score:

- Epidemiological
- Toxicological
- Clinical features

What can a toxicologist do?

- Make a scientifically based opinion about what can be expected to happen if a human being is exposed to a chemical substance
- Can calculate a ”safe” / ”dangerous” dose for human beings
- From data from animal experiments and human studies

Toxicology in our daily Life

Safety of food products e.g deliberate contamination with food colors, preservatives, artificial sweeteners etc.

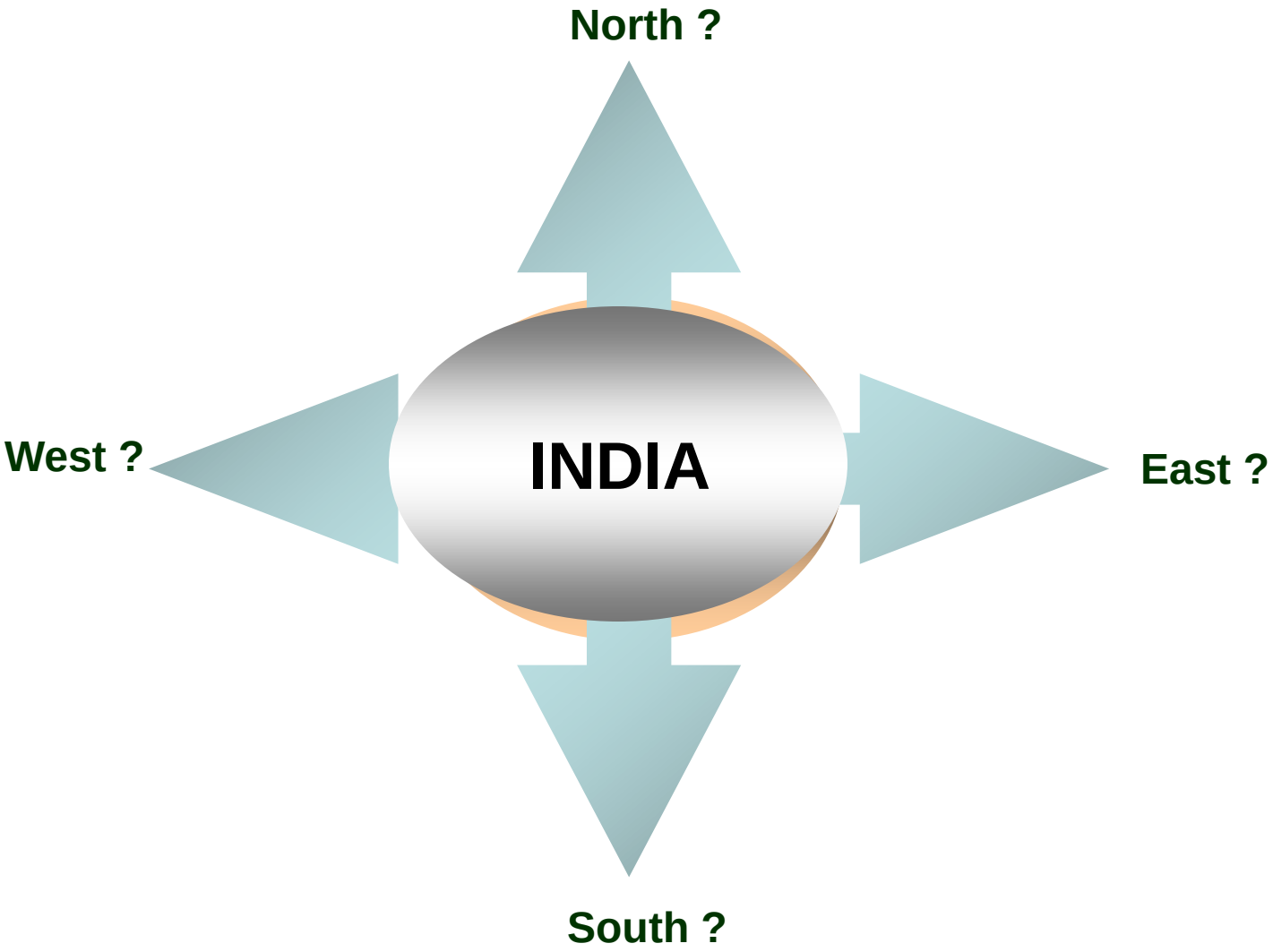
Consumer products, industrial chemicals

Pharmaceuticals, (toxicology research is critical in the development and production of pharmaceuticals. ensures that therapeutic benefits are not outweighed by unwanted side effects)

Poisoning Scenario
Developed *vs.* Developing countries

- Poisoning scenario in developed countries is quite different from developing countries.
- Case fatality with pesticides in developing countries is 10-30% compared to 0.5-1% with drugs in developed countries.
- Common poisonings in developed countries are due to pharmaceuticals, household chemicals, drugs of abuse etc.
- In countries like India and Sri Lanka, pesticide poisoning is commonest type of poisoning
- Intentional self-poisoning with pesticides is an important public health problem in the Asia- Pacific region with an estimated 300,000 deaths occurring each year.

POISONING IN INDIA



One year study of acute poisoning cases (excluding animal bites) at Civil Hospital, Ahmedabad, Gujarat, India.

Type of poison

	Frequency	Percent
Drugs	56	15.3
Household chemical	98	26.8*
Industrial chemical	11	3.0
Pesticide	124	33.9*
Plant	1	0.3
Unknown	76	20.8
Total	366	100.0

One year study of acute poisoning cases (excluding animal bites) at Civil Hospital, Ahmedabad, Gujarat, India.

- **Conclusion**
- **Our data supports other studies from India regarding Age and Sex distribution.**
- **However, compared to data reported from Poison information centre, NIOH, Ahmedabad, Household chemicals were encountered as the 2nd most common cause of poisoning.**
- **Of these Acid Ingestion accounted for 55.10% cases of household chemical cases.**
- **The prevention and treatment of poisoning due to pesticide and household poisoning should merit high priority in the health care of Gujarat population.**
- **There is also need for identifying unknown substances.**

Unlabelled pesticides???

- A large number of unlabelled pesticides are sold as powders or liquid formulations in the market as rat killers, insecticides meant for mosquitoes and cockroaches.

- It is difficult to decide about treatment guidelines in such cases.


MAHAK
SILVER
महक
सिल्वर
पान मसाला


ડાયમંડ
પાવડર નં.૧
SMD
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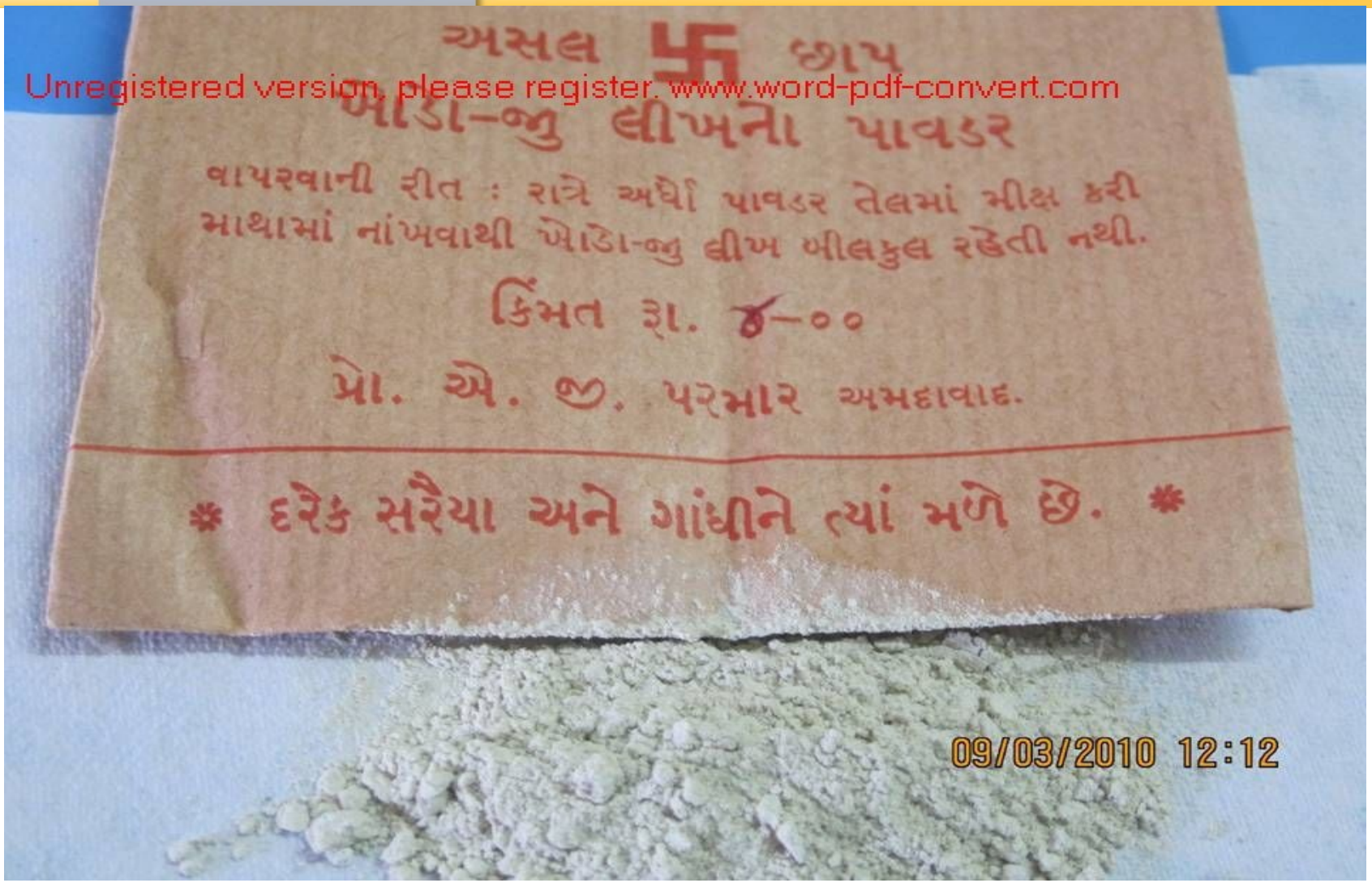
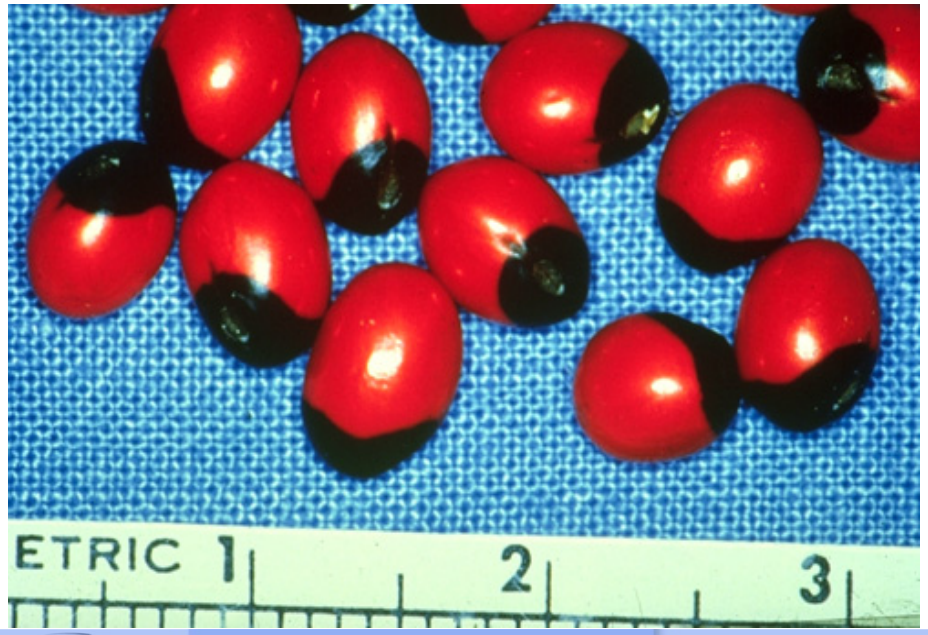


Abrus Precatorious

Ricin



Animal Bites and Stings

- Snake bite
- Scorpion bite
- Stings

Others

- Alcohol alone or in combination with pesticides and pharmaceuticals

- Drugs of Abuse – Cannabis, Opiates, Sedative Hypnotics, Cough syrups

Mixed ingestions: e.g. alcohol with drugs or pesticides

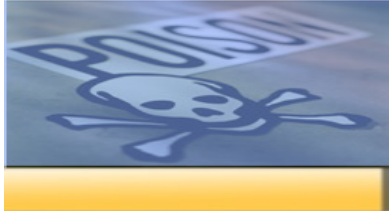
FUTURE……..????????

Toxicology Response Centre

Toxicology Research Center (Poison Information Center)

- The first Poison Information Centre was started in Chicago in 1953
- Poison Information Centres have been an integral part of emergency health care system in developed countries and in many of the developing countries.
- The most fundamental function of Poison Information Centers is to reduce morbidity and mortality from toxic exposures and to prevent poisoning

Functions and benefits of Toxicology Research Center



- Information Service: Toxicology Centers provide information and guidance to the public and healthcare professionals regarding acute and chronic poisoning due to any type of chemicals, pesticides, drugs, animal bites and stings and plant toxins.
- The expert advice gives reassurance to the public preventing unnecessary visits to the busy emergency departments in cases of minor and nontoxic exposures.
- The centers also help in better management of poisoning cases
- While suitably trained nurses, pharmacists, or other specialists may answer many routine enquiries, supervision by a physician trained in medical toxicology is essential.

Laboratory services

- Toxicology Centers may also provide analytical laboratory services for toxicological analyses and biomedical investigations, which are essential for the diagnosis and treatment of some types of poisoning
- Estimation of the drug or chemical involved in poisoning can help the treating physician to decide about the usefulness of antidotes and other therapeutic measures
- services of the laboratory can also be utilized for therapeutic drug monitoring
- Assessment of occupational chemical exposures can also be undertaken

Toxicovigilance

- This is an active process of identification and evaluation of toxic risks in the community.
- All enquiries addressed to a Toxicology center are regularly analyzed to determine the possible toxic agents and circumstances of poisoning
- Poison Centres can alert the regulatory or health authorities to take appropriate preventive measures, if poisoning related to a banned or new product, improper packaging or wrong labeling is observed.

CBRN disasters

- Toxicology centers make an important contribution in the prevention and handling of chemical disasters by providing appropriate information at the time of an accident and by taking part in contingency planning.
- Poison centers can also serve as antidote banks for those antidotes which are not easily available in the region and country.

Teaching and Training of health professionals

- Toxicology centers can take part in teaching of medical toxicology to health professionals
- Educational programmes for the whole community or for certain high risk groups' e.g. prevention of poisoning in toddlers, safe use of pesticides for agricultural workers, dangers of self medication for the elderly, prevention of occupational chemical exposures may be undertaken through various information materials or campaigns.

Research in Toxicology

- Toxicology centers are a rich source of human toxicology data and they can undertake clinical toxicology research in those areas, which are of importance to the particular region.

Facilities required for setting up a Toxicology Research Centre:

Location of the Centre:

- When a Toxicology centre has to be started, especially in a developing country, existing medical facilities should be surveyed to determine where the centre can best be located and operated most effectively.
- The most important thing to remember is that it is essential for a centre to have a number of health care professionals interested in human toxicology.
- Whatever the location chosen, it should be the aim of the facility to operate 24 hours a day all year round.

Staff for a Toxicology Research Centre

- Toxicology centre needs a multidisciplinary team of poison information specialists
- Qualification of such staff may be MBBS MD or pharmacist.
- These members must acquire adequate knowledge of toxicology and related scientific disciplines and should also be in regular contact with analytical and treatment facilities.
- The medical members of the team should be involved in the treatment of poisoned patients.

Information and Laboratory Services

- The Poison Centre should have facilities for storage, retrieval and dissemination of information on all kinds of toxicants. Information is mostly derived from computerized databases or specialized books and journals and also based on the experience of the staff
- The laboratory should also have adequate staff and equipment to carry out the analyses that are essential in cases of poisoning within the region.
- Emergency laboratory services should be able to provide results within a short time which could guide the management of the patient.

Future: Toxicogenomics?

- ”Omics”: Genomics – Proteomics - Metabolomics

- **determine whether gene, protein or metabolite expression profiles or ”signatures” can serve as markers to predict toxicity**

Prehospital use of antidotes

- Quality of the first call medical assessment
- Early lifesaving value, with little or no alternative measure
- Distance and time interval to the hospital
- Clinical situation: great value of toxidromes!
- Probability of use,
  depending on local epidemiology and industrial activities
- Particular risk of mass casualties (strategic storage)
  (*hydroxocobalamin*, *atropine*, *pralidoxime*, …)

Prehospital use of antidotes

- Ease and safety of use, possible adverse effects
- Storage conditions, shelf life (*glucagon*, *fomepizole*, *hydroxocobalamine*, …)
- Cost, including waste of unused or outdated products (*hydroxocobalamin*, *digoxin antibodies*, *viper antivenom*, ..)
- Qualification and skill level of the prehospital emergency team (good knowledge of toxidromes)

- Activated Charcoal

- Pesticides ==== OP organo phosphorus

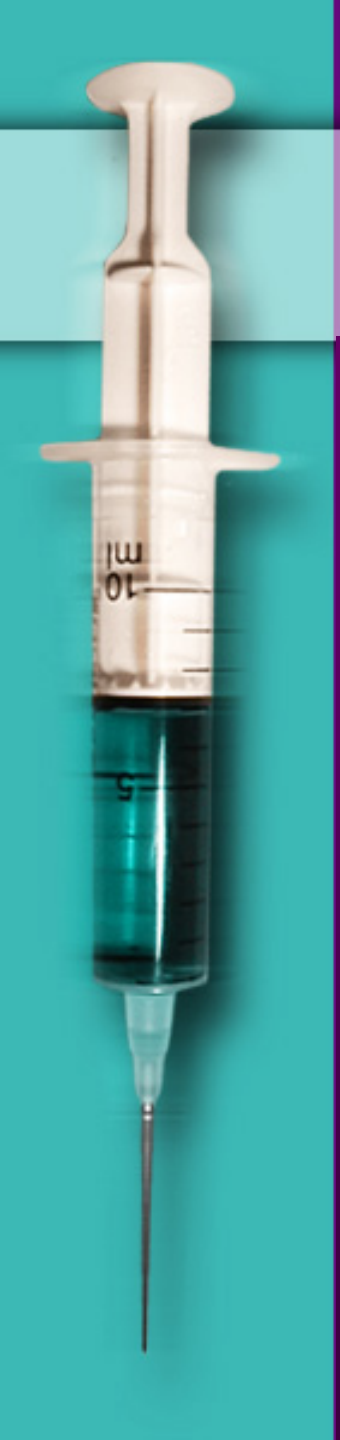
- PAM(Oximes)
- Atropine

Ethylene Glycol / Methanol

Ethylene Glycol

Methanol

Ethylene Glycol / Methanol



Methanol | **Ethylene Glycol**

Alcohol dehydrogenase

Formaldehyde | Glycoaldehyde

Aldehyde dehydrogenase

Formic acid | Glycolic acid

Folate → CO_2 & H_2O

Lactic Dehydrogenase Or Glycolic acid Oxidase

Glyoxylic acid & Oxalic acid

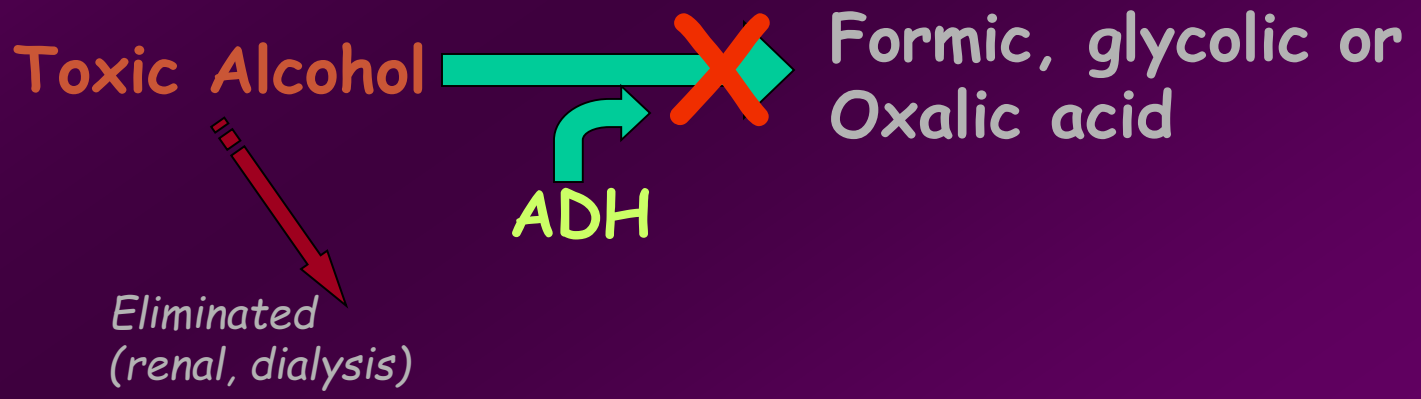
Th → A-OH-B ketoadipic acid

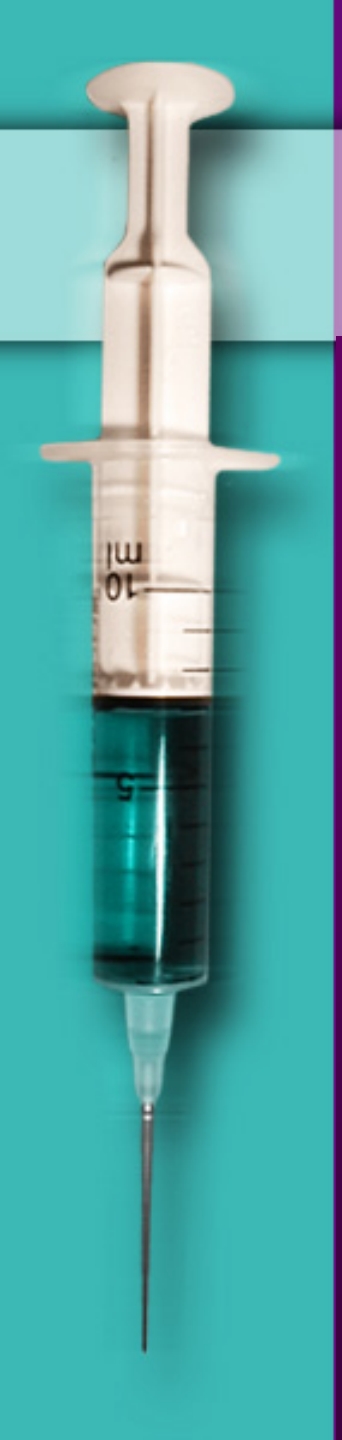
B_6 → Glycine and benzoic acid

Ethylene Glycol / Methanol

Goal of Specific Treatment:

1. Prevent further metabolism of toxic alcohol
2. Eliminate alcohol from circulation





Ethylene Glycol / Methanol

Lots of problems with Ethanol!!

1. Oral Absorption is erratic (and difficult)
2. IV preparations rarely shelved
3. Math is challenging (many reports of errors)
4. Kinematics vary between pts. and in same pt.
5. Causes even more profound CNS depression
6. Need large volumes (1120 cc bolus of 5% etoh)
7. Etoh intoxication can cause hypoglycemia, gastritis, pancreatitis
8. Use of Ethanol mandates hourly ethanol and glucose checks in ICU
9. Duration can take as long as 100 hrs (depending on dialysis)

Ethylene Glycol / Methanol

2. Fomepizole (4-methypyrazole)

- Introduced in 1986
- Competitive Inhibitor of Alcohol dehydrogenase
  - (*in vitro*: 80,000 times affinity for ADH than methanol)

Toxic Alcohol

ADH

Formic, glycolic or oxalic acid

Ethylene Glycol / Methanol

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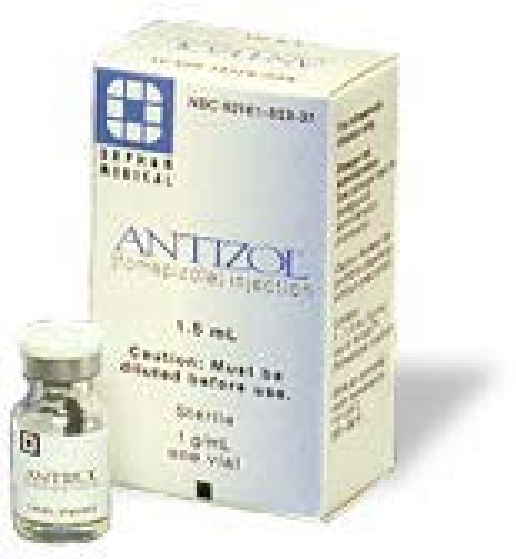
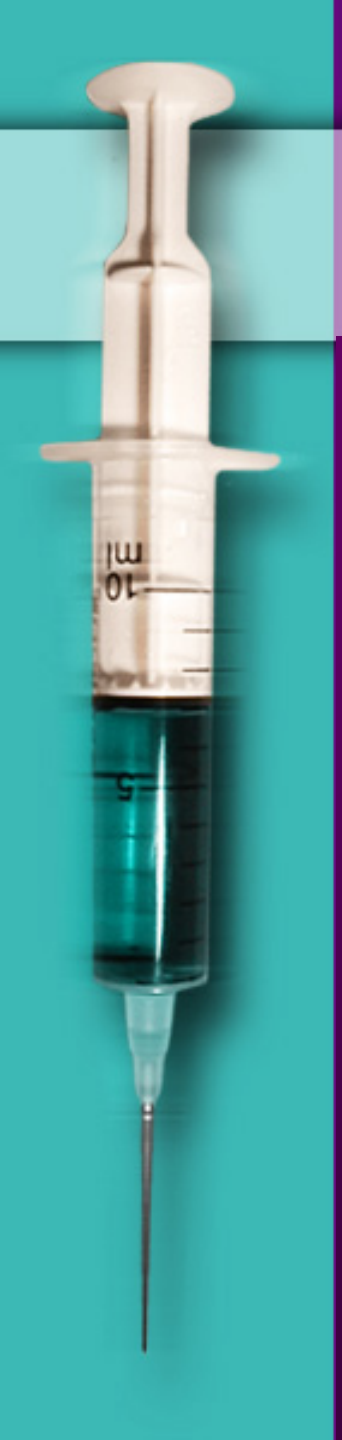
Ethylene Glycol / Methanol

Fomepizole (4-methypyrazole)

→ Approved by FDA for E.G. poisoning in 1997, and for methanol poisoning in 2000





Ethylene Glycol / Methanol

Fomepizole – Advantages:

1. Does not require separate preparations
2. Therapeutic levels are reliably achieved
3. No Change in mental status
4. No risk of hypoglycemia, hepatotoxicity
5. Hemodialysis not needed in subgroup of patients

<u>Main Disadvantage:</u> Cost!

Apr. $1000 US per 1500 mg vial

Suggested shelf life of drug ~ 3 yrs
U.S. Manufacturer (Orphan Medical) will replace drug at no charge

Cyanide antidotes

- Hydroxocobalamine +/- thiosulfate
  - Expensive
  - Very safe
  - First choice if uncertain CN poisoning or smoke exposure: any sign of tissue hypoxia
- Dicobalt Edetate (Kelocyanor®)
  - Relatively cheap
  - Cardiovascular side-effects
  - Mass CN poisoning (industrial, terrorism) ?

CYANIDE ANTIDOTE KIT

This kit contains		
10 ml. Ampoules	- Sodium Nitrite Injection USP 300 mg. in 10 ml.	2 Amp.
50 ml. Vial	- Sodium Thiosulphate Injection I.P., 25 g. in 50 ml.	1 Vial
Durules	- Amyl Nitrite Inhalant, 0.3 ml.	12 Durules
Sterile 10 ml. Plastic Disposable Syringe with Needle		1
Stomach Tube		1
Sterile 50 ml. Plastic Disposable Syringe		1
Sterile Disposable Needle		1
Non - Sterile 50 ml. Syringe		1
Instructions for the Treatment of Cyanide Poisoning		1
Additional Information on Cyanide Antidote		1

CUSTOMER - open this kit immediately upon receipt to make sure all contents are intact. Repeat inspection periodically. Prior to emergency, personnel should be instructed in the use of this kit.

Store in a cool place

M.R.P. Rs. 14,000/-
L.T. Extra

Troikaa Pharmaceuticals Ltd.
Thal - 382 729, Gujarat, India

Acute Methemoglobinemia

Acetanilid	Hydroxylamine	Nitroprusside
Alloxan	Lidocaine	Paraquat/Diquat
Aniline(dyes, ink)	Menadione	Phenacetin
Antipyrine	Metoclopramide	Phenazopyridine
Arsine	Methylene blue	Phenol
Benzene derivatives	Naphthalene	Phenylhydrazine
Benzocaine	Nitrates*	Phenytoin
Chlorates	Nitric oxide	Prilocaine
Chlorobenzene	Nitrites	Primaquine
Chloroquine	Nitroalkanes	Smoke inhalation
Dapsone	Nitrochlorobenzene	Sulfonamide antibiotics
Dinitrophenol	Nitrofuran	Trinitrotoluene
Dinitrotoluene	Nitroglycerin	

Many chemicals may have oxidizing properties and this list is not complete.
*Chemical and food sources.

Acute Methemoglobinemia

Meth-Hb levels	Signs and Symptoms
20-30%	Headache, fatigue, nausea
30-45%	Dyspnoea on exertion, lethargy & tacchycardia
50-70%	Arrhythmias, coma, seizures, resp. distress, lactic acidosis
>70%	Cardiovascular collapse, death

Anemic patients have symptoms at lower Meth-Hb levels

Acute Methemoglobinemia

Treatment:

-Supportive Tt. like O_2, decontamination of skin,

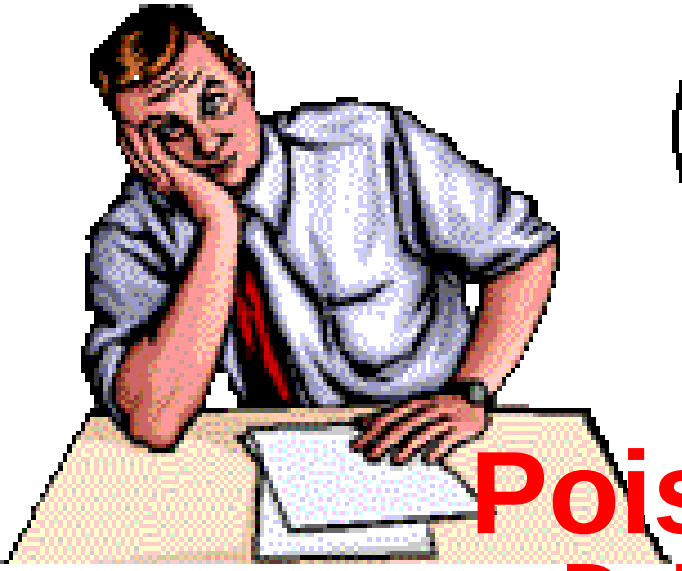
- Antidote : Methylene blue is indicated if Meth-Hb levels are more than 30% or patient is showing s/s of anoxia

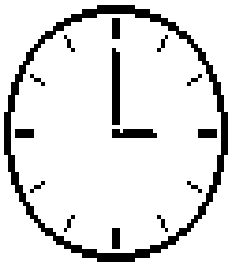
Dose: 1mg/kg body wt of 1% solution slowly over a period of 5 minutes. Repeat after 1 hour if patient is still symptomatic. Some chemicals may need many doses but do not exceed 7 mg/kg

Conclusion

- In most acute poisoning conditions, primary care of the patient is mainly supportive
- Early medical intervention (MECU) gives the opportunity to start specific treatments
- Antidotes used in the prehospital settings are a subset of those used in ED
- Main conditions are:
  - ✓ good phone call assessment of the situation
  - ✓ well trained medical teams
  - ✓ a clear history and a well defined toxidrome
- Risk of mass casualties must be anticipated

Any Questions ?





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Poison Help Line

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THANK YOU