Toxicology – an introduction
At the core of Risk Assessment

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Overview

▲ Applications for toxicology in IH / OH
▲ What is toxicology?
▲ Essentials
  – Toxicokinetics
  – Toxicodynamics
▲ Toxicology & Risk Assessment
▲ Dose & Response
▲ Occupational Disease versus adverse effect
Toxicology is fundamental to risk assessment
Strategy for assessing and managing occupational exposures (AIHA).

**Purpose/Goals**
Collect and organize available information on the workplace, workforce, agents, historical exposure data, biological monitoring data, etc.

**Tools**
- Workplace characterization
  - Process/operation description
  - Chemical, physical, and biological agent inventory
- Work force characterization
  - Job title description
  - Task analysis
  - Number of workers

- Characterization of agents
  - Health effects data
  - Occupational exposure limits (OELs)
- Characterization of existing controls
- Past assessments/results
- Historical exposure data
- Environmental emission data
- Past biological monitoring data

**Outcome**
Complete summary of available essential information on workers, tasks, agents, potential exposures, and potential health effects.
Concept “Risk”

Risk = (HARMFULNESS OF HAZARD) X EXPOSURE
RISK = TOXICITY X DOSE

Factors modulating the risks include:
• The environmental conditions in which the exposure takes place
• Host factors that influence response to exposure
# A “Risk Matrix”

## Risk Assessment Matrix

<table>
<thead>
<tr>
<th>Hazard Consequence Criteria</th>
<th>Types of Impact</th>
<th>Increasing Probability Score Left</th>
<th>Increasing Probability Score Right</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Score</strong></td>
<td>Human Health &amp; Safety (Generic)</td>
<td>Environment</td>
<td>Financial</td>
</tr>
<tr>
<td>0</td>
<td>None (No toxic, harmful, corrosive, irritant or asphyxiant effects) (Chemicals: AGCHN As carcinogens, Radioisotopes: None)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>1</td>
<td>Minor injuries (Lost time Or Reversible Health Effects (eg. joint pain)</td>
<td>Local Off-Site Effects, Reversible (6 months)</td>
<td>Local</td>
</tr>
<tr>
<td>2</td>
<td>Moderate injuries (Lost Time) Or Reversible Significant Health Effects (eg. repetitive tasks)</td>
<td>Locally Significant Long-Term Effect (Reversible in 6 months)</td>
<td>City</td>
</tr>
<tr>
<td>3</td>
<td>Single Major Injury (Hospital) Or Multiple Disableing Injuries Or Irreversible Significant Health Effects (eg. Noise, poor manual handling)</td>
<td>Regionally Significant Long-Term Effect (Reversible in 6 months)</td>
<td>Region</td>
</tr>
<tr>
<td>4</td>
<td>Multiple Major Injuries/ Disabilities Or Life-threatening Health Effects (eg. Ionising radiation, avian flu)</td>
<td>National Significant Reversible (&gt;1 year)</td>
<td>National</td>
</tr>
<tr>
<td>5</td>
<td>Multiple Fatalities Or Extreme Health Hazard</td>
<td>Internationally Significant Effect (Irreversible)</td>
<td>International</td>
</tr>
</tbody>
</table>

## Notes:
- **Risk = Consequences x Probability (or Exposure) (out of 25)**
- Use “LIKELIHOOD” in Phase One of HRA (Hazard Identification).
- Use “EXPOSURE SCORE” (Freq x Duration x Intensity)3 in Phase Two of HRA (Detailed HRA).
- Use MEASURED TWA instead of “Exposure Score”, if the value has been measured.

## Likelihood:
- Unlikely Ever
- 1 Incident / 10Yr
- 1 Incident / Year
- 1 Incident / Month
- 1 Incident / Week

## Exposure Frequency:
- Once A Year
- Quarterly
- Monthly
- Weekly
- Daily

## Exposure Duration:
- < 1 Hours / Week
- 1-5 Hours / Week (10%)
- 5-10 Hours / Week (10-50%)
- 10-20 Hours / Week (50-100%)
- > 20 Hours / Week (> 100%)

## Exposure Intensity:
- Enclosed Process, Fixed Location, Fixed Work Environment
- (Manual Work With Local Exhaust)
- (Manual Operation, Protected (PPE))
- (Manual Operation, Unprotected)

## Measured TWA Exposure (Where known):
- As per Table, Or < 56% of Prescribed Limits
- As per Table, Or 50-75% of Prescribed Limits
- As per Table, Or 75-100% of Prescribed Limits
- As per Table, Or >101-200% of prescribed limits
- As per Table, Or >200% of prescribed limits
The Safety Data Sheet (SDS)

1. Identification
2. Hazard(s) identification
3. Composition/information on ingredients
4. First-aid measures
5. Fire-fighting measures
6. Accidental release measures
7. Handling and Storage
8. Exposure controls/personal protection
9. Physical and chemical properties
10. Stability and reactivity
11. Toxicological information
12. Ecological information
13. Disposal considerations
14. Transport information
15. Regulatory information
16. Other information

▲ Key resource for toxicological material on chemicals
▲ Note new terminology due to GHS
WHAT IS TOXICOLOGY?
What is “toxicology”?

Definitions:

▲ "the study of the adverse effects of chemicals or physical agents on living organisms” (EU)

▲ the study of the adverse physicochemical effects of chemical, physical or biological agents on living organisms and the ecosystem, including the prevention and amelioration of such adverse effects (Society of Toxicology)
Founders of toxicology

Philippus Theophrastus Aureolus Bombastus von Hohenheim PARACELSUS (Einsiedeln, Zürich, 1493 - Salzburg, 1541)

Mathieu Joseph Bonaventure Orfila (1787–1853)

“All substances are poisons; it is the dose that makes the poison”

The first great 19th-century exponent of forensic medicine. Orfila was the first to establish a systematic correlation between the chemical properties and biological effects of poisons. Using autopsy results, he was able to link the presence of particular poisons with specific damage to tissues and organs.
Six applied areas

▲ **Clinical**: the diagnosis and treatment of human poisoning

▲ **Forensic**: the medical-legal aspects of clinical poisoning

▲ **Analytical**: the identification and quantification of toxic chemicals in biological materials.

▲ **Environmental & occupational**: deal with toxic hazards in the environment and in the workplace

▲ **Regulatory**: the regulation of potentially toxic substances
Toxic agent
Substance that can produce an adverse biological effect. Toxic agents may be:
▲ chemical ("hazardous chemical agents"),
▲ physical (such as radiation)
▲ biological ("hazardous biological agents", pathogenic organisms (viruses, bacteria, fungi, parasites, etc) or venoms (snake, bee, fish, etc) or plant toxins.

Toxic substance is simply material which has toxic properties.
TOXICOKINETICS & TOXICODYNAMICS
What we do to the chemical  What the chemical does to us
Toxicokinetics

The biochemical pathways that agents follow in the biological system of interest (human, animal, environment). ("What our bodies do with the chemical")

Stages include: ("ADME")
- **Absorption** (*route of entry*),
- **Distribution** (*body tissues*)
- **Metabolism** (*biotransformation* – *often the liver*).
- **Excretion** (exit from the body – air, faeces, urine)

These kinetics play an important role in modulating (reducing or aggravating) the health effects of the agents (toxicodynamics).
Overview of Toxicokinetics

[Diagram showing the process of toxicokinetics including absorption, distribution, metabolism, and excretion with specific pathways and organs involved.]
Toxicokinetics & biological monitoring

▲ “Biological monitoring of exposure” means a planned programme of periodic collection and analysis of biological media including body fluid, tissues, excreta or exhaled air, in order to measure the concentration of a chemical determinant - the substance itself or one or more metabolites - of those exposed, as an indicator of the uptake of a substance.

▲ The **Biological Exposure Index (BEI)** is a reference value for assessing biological monitoring results, intended as a guideline for the likelihood of adverse health effects and generally represents the level of determinants that are most likely to be observed in specimens collected from healthy employees who have been exposed to chemicals with inhalation exposure at the Occupational Exposure Limit.

**A basic understanding of the toxicokinetics of a substance is essential to interpret outcomes of biological monitoring.**
Biological Monitoring

▲ Expression of exposure
▲ Does NOT represent illness or effect
▲ Equivalent meaning to air monitoring

Biological Effect Monitoring

▲ May be related to exposure, but also to other things (susceptibility)
▲ Represents an expression of tissue impact (illness)
▲ Is related to air monitoring values, but may be quite disconnected to air monitoring if other pathways
▲ Eg. full blood count, liver function test, spirometry
Toxicodynamics

The biological effects that agents exert in the biological system of interest (human, animal, environment). ("What the chemicals do with our bodies")
More details about assessing risk
Risk Factors

Primary factors that determine the risk (of disease) include:

- Intrinsic toxicity (harmfulness)
- Dose (exposure)

Factors modulating the risks include:

- The environmental conditions in which the exposure takes place
- Host factors that influence response to exposure

These factors are the core issues to be considered in risk assessments (qualitative & quantitative)
Harmfulness & Intrinsic Toxicity (1)

Chemical properties
- molecular structure & functional groups
- solubility - insolubility
- volatility
- stability (light, water, acids, enzymes, …)
- reactivity

Physical properties
- gas (density, …)
- liquid (vapour pressure, …)
- solid (crystal structure, size, shape, …)
Target organ properties

- Irritation (corrosion)
- Allergy (skin, respiratory)
- Reproductive toxins (teratogens, genotoxins (mutagens))
- Direct toxicity (organ systems)
- Carcinogens (eg IARC categories 1-3, GHS)
- Other:
  - Developmental effects
  - Immunological effects
Exposure & Dose

▲ The quantity of a substance to which the target receptor (person) is exposed. (eg. mg/kg/day)

▲ Parameters needed to characterize the exposure include:
  - **Frequency** (times per second/hour/day/week/month/year)
  - **Duration** (acute, sub-acute, chronic)
  - **Intervals** between exposure
  - **Intensity** (concentration, eg mg/m^3^)

▲ Sub-sets of “dose” include:
  - **Exposure dose** (the amount encountered)
  - **Absorbed (internal) dose** (the amount in the body)
  - **Target organ (biologically effective) dose** (the amount that actively exerting effects)
Modulators of Risk
Modulators - exposure conditions

- Routes of exposure
- Pattern of exposure (intervals between exposure)
- Mixed exposures
- Environmental circumstances
- Host circumstances
Routes of exposure

- Inhalational
- Dermal
- Oral
- (parenteral)
- (peritoneal)
Mixed exposures

- **Additive** (1+1=2)
- **Synergistic** (1+1=4)
  - Toxicokinetic effects: improved penetration by solvents
  - Toxicodynamic effects: smoking + air pollutants; solvents + noise
- **Antagonistic** (1+1=1)
Environmental circumstances
- Heat, cold, wind, rain
- Enclosure
- Long work shifts

Host circumstances
- Level of exertion
Host factors:
Variations in susceptibility because of
- Age
- Sex
- Genetic factors
- Pregnancy
- Underlying disease
- Nutritional status
- History of previous exposures.
Persistent Pollutants

(Some) Metals and Organochlorines

General Characteristics:

- Lipophilic
- Bioaccumulate
- Resistant to metabolism
- Travel long distances in environment
- Linked to adverse effects on human health and wildlife

Bioaccumulation and biomagnification of DDT
DOSE AND RESPONSE
A fundamental and essential concept in toxicology.

It correlates exposures and the spectrum of induced effects.

Generally, the higher the dose, the more severe the response.

Based on observed data from experimental animal, human clinical, or cell studies.
Our knowledge of the effects of chemicals stems mainly from

▲ **clinical and occupational toxicology**
  - relatively high doses, limited number of agents

▲ **epidemiology**
  - complex exposures, rarely “causal” associations

▲ **animal experiments**
  - high doses, single chemicals, species differences, statistical limitations
Knowledge of the dose-response relationship:

▲ establishes causality that the chemical has in fact induced the observed effects
▲ establishes the lowest dose where an induced effect occurs – the threshold effect
▲ determines the rate at which injury builds up - the slope for the dose response.

Within a population, the majority of responses to a toxicant are similar; however, a wide variance of responses may be encountered, some individuals are susceptible and others resistant. Sources of variation include age and sex, pregnancy, underlying disease, nutritional status, and history of previous exposures.
Shifting Mean and Variance

Increase in mean

(a) Previous

Less Modest Effect

More Modest Effect

Clinical Outcome

Average

Clinical Outcome

More Extreme Effect

Increase in variance

(b) Previous

More Extreme Effect

More Modest Effect

Clinical Outcome

Average

Clinical Outcome

More Extreme Effect

Increase in mean and variance

(c) Previous

Less Modest Effect

Clinical Outcome

Average

Clinical Outcome

More Extreme Effect

Much More Modest Effect

Much More Extreme Effect
Dose-response curve (1)

The dose-response curve normally takes the form of a sigmoid curve. It conforms to a smooth curve as close as possible to the individual data points.

In the hypothetical curve above, no toxicity occurs at 10mg whereas at 35 mg 100% of the individuals experience toxic effects.

For most effects, small doses are not toxic. The point at which toxicity first appears is known as the threshold dose level. From that point, the curve increases with higher dose levels.
Knowledge of the shape and slope of the dose-response curve is extremely important in predicting the toxicity of a substance at specific dose levels.

Major differences among toxicants may exist not only in the point at which the threshold is reached but also in the percent of population responding per unit change in dose (i.e., the slope).

Toxicant A has a higher threshold (effects later) but a steeper slope (higher rate of toxic progression) than Toxicant B.
Dose-response curves are used to derive dose estimates of substances.

A common dose estimate for acute toxicity is the LD50 (Lethal Dose 50%) - a statistically derived dose at which 50% of the individuals will be expected to die. (other estimates include LD0 & LD10, etc) and reflects the potency of the substance.

For inhalation toxicity, air concentrations are used for exposure values. Thus, the LC50 is utilized which stands for Lethal Concentration 50%, the calculated concentration of a gas lethal to 50% of a group. Occasionally LC0 and LC10 are also used.

“Toxic Dose” indicates the dose that causes toxic effects (TD50, TD0, TD10, etc.)
Two terms often encountered are No Observed Adverse Effect Level (NOAEL) and Low Observed Adverse Effect Level (LOAEL). They are the actual data points from human clinical or experimental animal studies.

Sometimes the terms No Observed Effect Level (NOEL) and Lowest Observed Effect Level (LOEL) may also be found in the literature. NOELs and LOELs do not necessarily imply toxic or harmful effects and may be used to describe beneficial effects of chemicals as well.

The NOAEL, LOAEL, NOEL, and LOEL have great importance in understanding the toxicity of substances, and in conducting risk assessments.
**Occupational Exposure Limits** (air) and **Biological Exposure Indices** (BEIs) are derived by setting a point along the dose response curve based on the following:

- Beyond that point, the elevated risk of adverse effects becomes unacceptably high for that society.
- The agent can be reliably measured at that point (note – limits of detectability).
- It is “reasonably practicable” to be able to control the exposures to that limit value.
An illness which is **DIRECTLY** attributable to workplace exposure:

- Noise induced hearing loss
- Lead poisoning
- Contact dermatitis
- Asthma
- Repetitive strain injuries
- Post traumatic stress disorder
An illness which is **INDIRECTLY** attributable to workplace exposure:

▲ **Contributory**
  - Smoking + dust
  - House dust + chemical

▲ **Aggravating**
  - Pre-existing allergy /
  - medical condition aggravated by exposure
Every dose response curve of exposure versus effect has a transition from normal to abnormal.

This transition begins with subclinical metabolic effects, and progress eventually to serious impairment even, potentially, to death.

At what point does this transition become a reportable occupational disease?
Adverse effect vs occupational disease (2)

- Recurring chemical contact
- Relapsing mild reversible irritation (self medication)
- Chronic low grade eczema (first aid)
- More severe eczema (doctor)
- Severe allergic reaction requiring hospitalisation

- Noise exposure
- Mild reversible loss (TTS)
- Early notch at 4kHz
- Deeper notch at 4kHz
- PLH >10%
Take-Home Messages

▲ No chemical agent is entirely safe and no agent is entirely harmful

▲ Toxicology assesses the likelihood of the occurrence of adverse effects

▲ Toxicology can provide insights into the nature and mechanisms (modes) of adverse effects

▲ Toxicity is a function of:
  – Toxicodynamic factors (the intrinsic toxicity, dose, exposure conditions and response of host (host factors)
    Modulated by
  – Toxicokinetic factors (absorption, distribution, metabolism, excretion).

▲ Challenge you to consider the principles of toxicology to non-chemical exposures
QUESTIONS / DISCUSSION
The host response may lead to:

▲ Detoxification - metabolism of the substance results in less toxic metabolites

▲ Bioactivation - metabolism of the substance results in more toxic metabolites
OTHER SLIDES
The *predictive value* of detecting adverse effects is dependent on the **background prevalence**; the lower the prevalence, the greater the sample size needs to be to avoid missing cases.
Biotransformation / Metabolism

**Lipophilic** (parent compound)

1. **Decrease biological activity**
2. **Increase excretability**

**Hydrophilic** (metabolite)

**Phase I** (oxidative)

- Bioactivation
- Detoxification

**Metabolites**

- polarity
- functionality

**Phase II** (synthetic)

- Detoxification

**Metabolites**

- size
- ionization
- water solubility
- Increase excretability

Chemistry Influences Toxicity