Risk Assessment

TRAINING FOR THE HEALTH SECTOR

Introduction to Risk Assessment

Children's Health and the Environment

CHEST Training Package for the Health Sector

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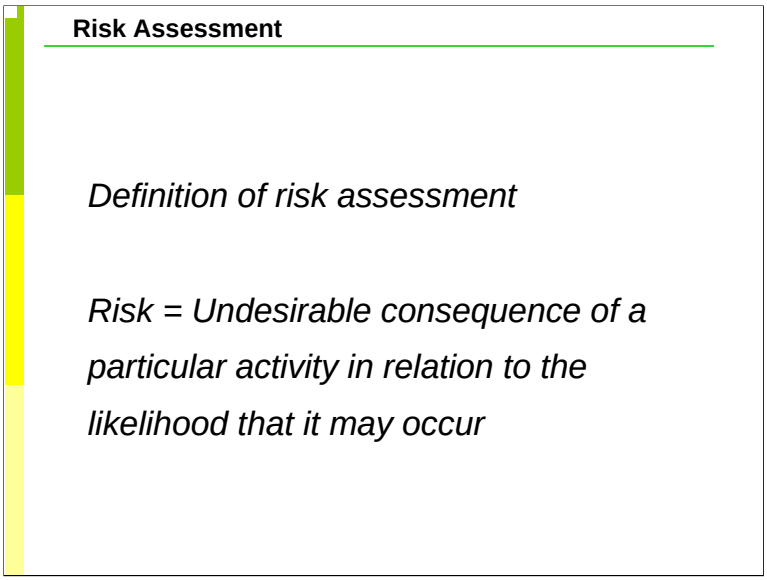


Risk assessment is an estimate of the likelihood of adverse effects that may result from exposure to certain health hazards, esp. pollutants in the environment.

Ref. *Webster's New Millennium™ Dictionary of English, Preview Edition (v 0.9.5), 2004 Lexico Publishing Group, LLC (http://dictionary.reference.com/search?q=risk+assessment&r=67)*

In 1983, the National Academy of Sciences (NAS) published standard terminology and concepts for risk assessments.

Risk management decisions follow the identification and quantification of risk which are determined by risk assessments. During the regulatory process, risk managers may request that additional risk assessments be conducted to justify the risk management decisions. As indicated in the figure above, the risk assessment and risk management processes are intimately related.

This section will describe only the risk assessment process. Risk assessments may be conducted for individual chemicals or for complex mixtures of chemicals. In cases of complex mixtures, such as hazardous waste sites, the process of risk assessment itself becomes quite complex. This complexity results from:

- simultaneous exposure to many substances with the potential for numerous chemical and biological interactions
- exposures by multiple media and pathways *(e.g., via water, air, and soil)*
- exposure to a wide array of organisms with differing susceptibilities *(e.g., infants, adults, humans, animals, environmental organisms)*

Question: The definition of risk is:

O the capacity of a substance to cause an adverse effect in a specific organ or organ system
O the probability that a hazard will occur under specific exposure conditions
O the weighing of policy alternatives and selection of the most appropriate regulatory actions

Answer: Risk assessment results in a statistically derived probability that an adverse effect will occur at a defined exposure level.

Risk Assessment

Hazard	Capability of substance to cause an adverse effect
Risk	Probability that the hazard will occur under specific exposure conditions
Risk Assessment	The process by which hazards, exposure, and risk are determined
Risk Management	The process of weighing policy altenatives and selecting the most appropriate regulatory action based on the results of risk assessment and social, economic, and policitical concerns

The following terms are routinely used in risk assessments:

Hazard

Risk

Risk assessment

Risk management

Risk Assessment

A risk is the chance that an adverse event will happen, multiplied by the extent of the effect

R = F x E

Risk is Frequency x Effect

This is a common way of defining risk.

Expression of risks

- **Non-threshold substances**
  probability of additional cases per unit of time in a specified population
  - e.g. 1.10^{-6} lifetime cancer risk

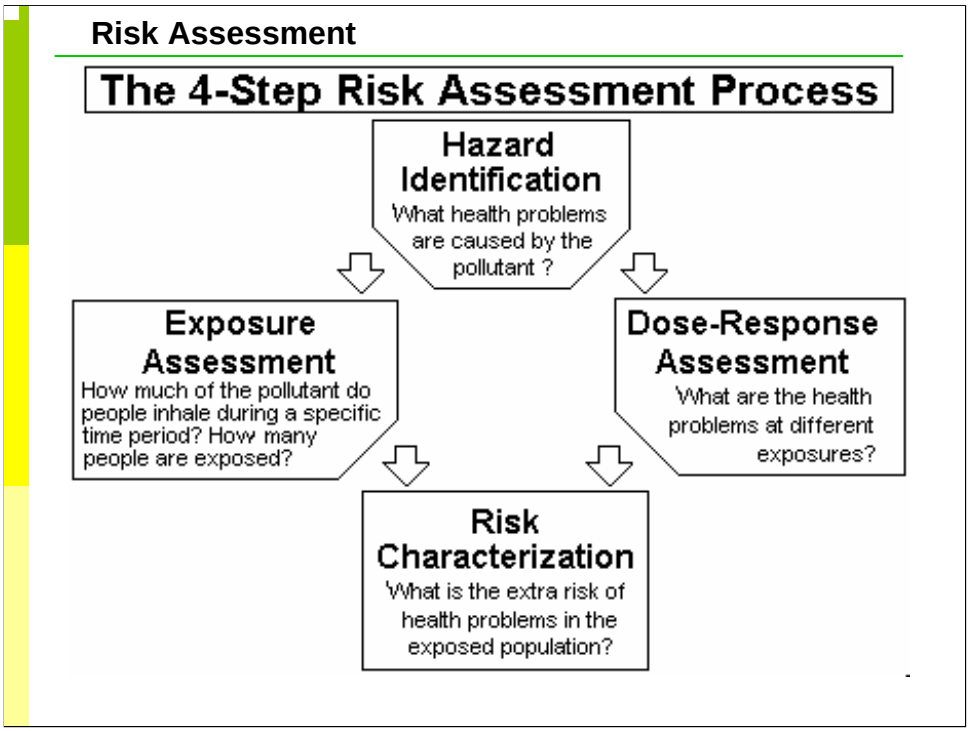
- **Threshold substances**
  Exposure/no-effect level ratio for a specified population or ecosystem;

1.10^{-6} lifetime cancer risk means that there is one additional case of cancer during a lifetime in a population of a million persons.

Potential human carcinogenic risks associated with chemical exposure are expressed in terms of an increased probability of developing cancer during a person's lifetime. For example, a 10^{-6} increased cancer risk represents an increased lifetime risk of 1 in 1,000,000 for developing cancer. For carcinogenicity, the probability of an individual developing cancer over a lifetime is estimated by multiplying the cancer slope factor *(mg/kg/day)* for the substance by the chronic *(70-year average)* daily intake *(mg/kg-day)*.

Threshold substances

There is a need for exposure above a certain level before effects can be observed. For each compound a exposure/no-effect levele ration should exist.



Four basic steps in the risk assessment process as defined are:
Hazard identification: characterization of innate adverse toxic effects of agents

Dose-repsonse assessment; characterisation of the realtion between doses and incidences of adverse effects in epxosed populations

Exposure assessment; measurement or estimation of the intensity, frequency, and duration of human exposures to agents

Risk characterisation; estiamtion of the incidence of health effects under the various conditions of human exposure

Risk Assessment – 4 phases

- **Hazard identification** – requires insight and understanding of the system in question
- **Dose-Response assessment** – costs time and money for hard science – positive findings require action
- **Exposure assessment** – can be very expensive and, for human exposure, complex
- **Risk characterisation -** depends totally on the 1st three steps

Hazard and risk are not the same thing. If you cross the road you could be hit by a bus. That is a potential hazard. The probability of being hit by a bus whenever you cross the road is related to the the risk. There are many factors that would need to be known in estimating that risk. What is the frequency of buses, is it day or night, dry or wet, etc etc. To discover those facts would require research.

Thus there are a series of steps in a risk assessment that are required. Hazard identification is clearly crucial. For those hazards identified there needs to be an assessment or characterisation. This requires hard science, which costs money. If there is an adverse outcome from any investigations then there is a need for action, one of which might be to ban the technology.

Hazard Identification

The hazard identification process determines whether exposure to a chemical can increase the incidence of a particular adverse health effect and determines the likelihood of occurrence in humans.

Hazard identification: in this initial step, the potential for a xenobiotic to induce any type of toxic hazard is evaluated.

Information is gathered and analyzed in a **weight-of-evidence approach**. The types of data usually consist of:
- human epidemiology data
- animal bioassay data
- supporting data

Based on these results, one or more toxic hazards may be identified *(such as cancer, birth defects, chronic toxicity, neurotoxicity)*. The **primary hazard of concern** is one in which there is a serious health consequence *(such as cancer)* that can occur at lower dosages than other serious toxic effects. The primary hazard of concern will be chosen for the dose-response assessment.

Question: In the risk assessment process, the hazard identification step performs which of the following functions?
- characterizes the relation between doses and incidences of adverse effects in exposed populations
- measures or estimates the intensity, frequency, and duration of human exposures to agents
- characterizes the innate adverse toxic effects of agents

Answer:Hazard identification is the first step in the risk assessment process.

Hazard Identification data

- Human epidemiology data
- Animal bioassay data
- Supporting data

Human epidemiology data are the most desirable and are given highest priority since they avoid the concern for species differences in the toxic response. Unfortunately, reliable epidemiology studies are rarely available. Even when epidemiology studies have been conducted, they usually have incomplete and unreliable exposure histories. For this reason, it is rare that risk assessors can construct a reliable dose-response relationship for toxic effects based on epidemiology studies. More often, the human studies can only provide qualitative evidence that a causal relationship exists.

In practice, **animal bioassay data** are generally the primary data used in risk assessments. Animal studies are well-controlled experiments with known exposures and employ detailed, careful clinical, and pathological examinations. The use of laboratory animals to determine potential toxic effects in humans is a necessary and accepted procedure. It is a recognized fact that effects in laboratory animals are usually similar to those observed in humans at comparable dose levels. Exceptions are primarily attributable to differences in the pharmacokinetics and metabolism of the xenobiotics.

Supporting data derived from cell and biochemical studies may help the risk assessor make meaningful predictions as to likely human response. For example, often a chemical is tested with both human and animal cells to study its ability to produce cytotoxicity, mutations, and DNA damage. The cell studies can help identify the mechanism by which a substance has produced an effect in the animal bioassay. In addition, species differences may be revealed and taken into account.

Question: What data are most desirable to identify the primary hazard in the hazard identification step?

O animal bioassay data
O supporting data from cell and biochemical studies
O human epidemiology data

Answer: Human data are the most desirable to identify the primary hazard in the hazard identification step and are given highest priority since there may be species differences in toxic response. Unfortunately, human epidemiology data are not often available.

Prediction of Hazard

- **Structure-activity relationship (SAR)**

A chemical's toxicity may be predicted based on its similarity in structure to that of chemical for which the toxicity is known. This is known as a **structure-activity relationship (SAR)**. The SAR has only limited value in risk assessment due to exceptions to the predicted toxicity.

Question: The structure-activity relationship (SAR) has value in risk assessments in that it:
O can often be used to predict possible toxicity
O is used to design cell studies of the chemical's metabolism
O can identify damage to DNA by actual testing of its chemical activity and biochemical structure
Answer: The structure-activity relationship (SAR) has value in risk assessments in that it can often be used to predict possible toxicity. In the absence of actual test data for a chemical, its potential toxicity can often be predicted by comparing its chemical structure to structures of chemicals whose toxicity has been characterized.

Dose-Response Assessment

The dose-response assessment describes the relationship between the magnitude of exposure and the appearance and duration of adverse effects.

The dose-response assessment step quantitates the hazards which were identified in the hazard evaluation phase. It determines the relationship between dose and incidence of effects in humans. There are normally two major extrapolations required. The first is from high experimental doses to low environmental doses and the second from animal to human doses.

The procedures used to extrapolate from high to low doses are different for assessment of carcinogenic effects and non-carcinogenic effects. **Carcinogenic effects** are not considered to have a threshold and mathematical models are generally used to provide estimates of carcinogenic risk at very low dose levels.

Noncarcinogenic effects *(e.g. neurotoxicity)* are considered to have dose thresholds below which the effect does not occur. The lowest dose with an effect in animal or human studies is divided by Safety Factors to provide a margin of safety.

Cancer risk Assessment

- **Qualitative evaluation**
- **Quantitate the risk**

Cancer classification schemes

- EPA
- IARC

Cancer risk assessment involves two steps. The first step is a qualitative evaluation of all epidemiology studies, animal bioassay data, and biological activity *(e.g., mutagenicity)*. The substance is classified as to carcinogenic risk to humans based on the weight of evidence. If the evidence is sufficient, the substance may be classified as a definite, probable or possible human carcinogen.

The second step is to quantitate the risk for those substances classified as definite or probable human carcinogens. Mathematical models are used to extrapolate from the high experimental doses to the lower environmental doses.

The two primary cancer classification schemes are those of the Environmental Protection Agency (EPA) and the International Agency for Research on Cancer (IARC). The EPA and IARC classification systems are quite similar.

The EPA's cancer assessment procedures have been used by several Federal and State agencies. The Agency for Toxic Substances and Disease Registry (ATSDR) relies on EPA's carcinogen assessments.

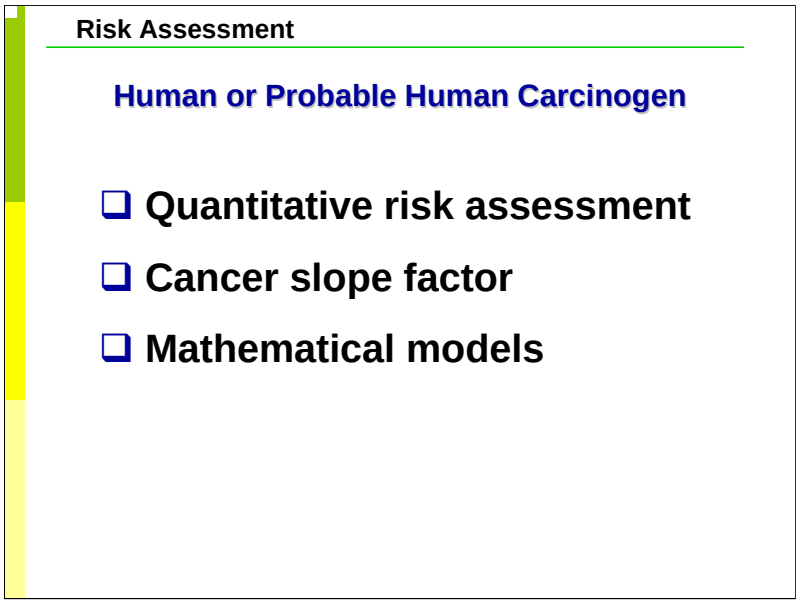
Cancer risk Assessment

- Sufficient human evidence
- Limited evidence in humans
- Inadequate evidence in humans

The EPA's cancer assessment procedures uses several categories as shown below:

The basis for **sufficient human evidence** is an epidemiology study that clearly demonstrates a causal relationship between exposure to the substance and cancer in humans. The data are determined to be **limited evidence in humans** if there are alternative explanations for the observed effect. The data are considered to be **inadequate evidence in humans** if no satisfactory epidemiology studies exist.

An increase in cancer in more than one species or strain of laboratory animals or in more than one experiment is considered **sufficient evidence in animals**. Data from a single experiment can also be considered sufficient animal evidence if there is a high incidence or unusual type of tumor induced. Normally, however, a carcinogenic response in only one species, strain, or study, is considered as only **limited evidence in animals**.



An agent can be classified as a Human or Probable Human Carcinogen. It cab be subjected to a **quantitative risk assessment**. For those designated as a Possible Human Carcinogen, the risk assessor can determine on a case-by-case basis whether a quantitative risk assessment is warranted.

The key risk assessment parameter derived from the EPA carcinogen risk assessment is the **cancer slope factor**. This is a toxicity value that quantitatively defines the relationship between dose and response. The cancer slope factor is a plausible upper-bound estimate of the probability that an individual will develop cancer if exposed to a chemical for a lifetime of 70 years. The cancer slope factor is expressed as mg/kg/day.

Mathematical models are explained on the next slide.

Question: The EPA classification of a substance as a "Probable Human Carcinogen" requires that the substance meets the following criteria:

- inadequate evidence of cancer in humans and sufficient evidence of cancer in animals
- limited evidence of cancer in animals
- sufficient human evidence for a causal association between exposure and cancer

Answer: Inadequate evidence in humans means that no satisfactory epidemiology study exists. With sufficient evidence in animals *(positive test results in more than one species or study)*, the substance can be considered as a Possible Human Carcinogen.

Question: The primary toxic effect which determines the type of procedure to be used in conducting a risk assessment is:

O lethality in laboratory animals
O evidence that the chemical is carcinogenic
O the ability of the chemical to cause eye irritation

Answer: The primary toxic effect which determines the type of procedure to be used in conducting a risk assessment is evidence that the chemical is carcinogenic. The risk assessment for carcinogens is quite different from that of noncarcinogens. Carcinogenic effects are viewed as non-threshold effects and non-carcinogenic effects are considered to have dose thresholds.

Risk Assessment

Mathematical models

One hit model	A conservative model. It assumes that there is a single stage for cancer and that one molecular event induces a cell transformation.
Multi hit model	One of the least conservative models. It assumes several interactions are needed before a cell can be transformed.
Probit model	This model assumes log normal distribution (Probit) for tolerances of exposed population. While sometimes used, it is generally considered inappropriate for the assessment of cancer risk.
Physiologically Based Pharmacokinetic Models (PB-PK models)	This model incorporates pharmacokinetic and mechanistic data into the extrapolation process. It requires extensive data and is becoming commonly used.

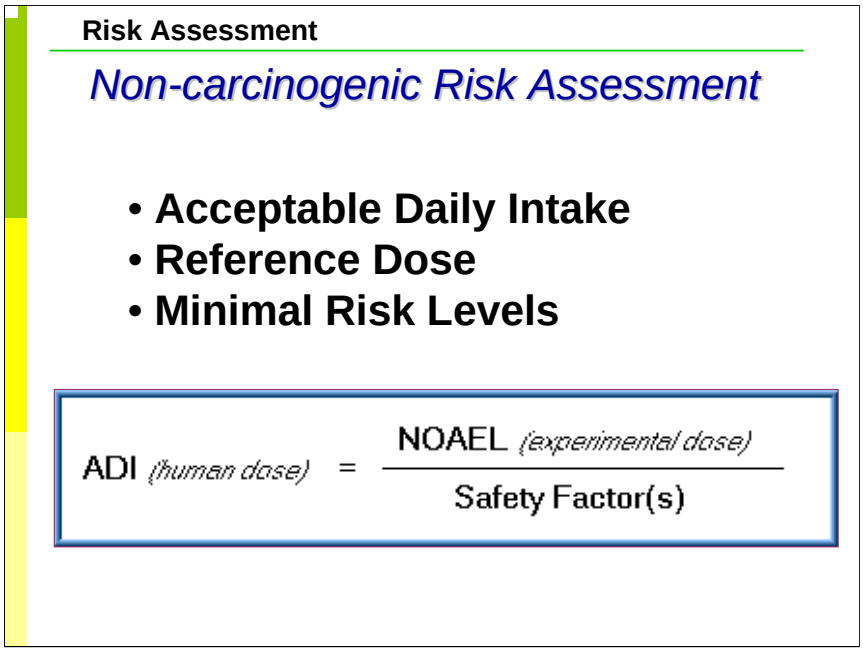
Mathematical models are used to extrapolate from animal bioassay or epidemiology data to predict low dose risk. Most assume linearity with a zero threshold dose.

EPA uses the **Linearized Multistage Model (LMS)** illustrated above to conduct its cancer risk assessments. It yields a cancer slope factor, known as the q1* *(pronounced Q1-star)* which can be used to predict cancer risk at a specific dose. It assumes linear extrapolation with a zero dose threshold from the upper confidence level of the lowest dose that produced cancer in an animal test or in a human epidemiology study.
Other models that have been used for cancer assessments include:
1) one hit model; 2) multi hit model; 3) probit model; and 4) Physiologically based Pharmacokinetic Models.

Estimated drinking water concentrations for chlordane that will cause a lifetime risk of one cancer death in a million persons, derived from different cancer risk assessment models, vary as illustrated below:

one hit model: 0,03 microgram per litre
multi hit model: 2 microgram per litre
probit model: 50 microgram per litre
linearised multistage model; 0,07 microgram per litre.

PB-PK models are relatively new and are being employed when biological data are available. They quantitate the absorption of a foreign substance, its distribution, metabolism, tissue compartments, and elimination. Some compartments store the chemical *(bone and adipose tissue)* whereas others biotransform or eliminate it *(liver or kidney)*. All these biological parameters are used to derive the target dose and comparable human doses.



Non-carcinogenic Risk Assessment

The **Acceptable Daily Intake (ADI)** procedure has been used to calculate permissible chronic exposure levels for humans based on non-carcinogenic effects. The ADI is the amount of a chemical to which a person can be exposed each day for a long time *(usually lifetime)* without suffering harmful effects. It is determined by applying safety factors *(to account for the uncertainty in the data)* to the highest dose in human or animal studies which has been demonstrated not to cause toxicity *(NOAEL)*.

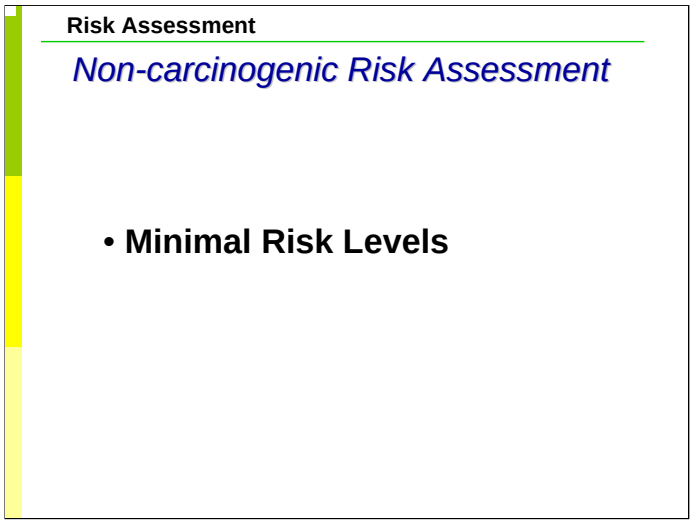
The EPA has slightly modified the ADI approach and calculates a **Reference Dose (RfD)** as the acceptable safety level for chronic non-carcinogenic and developmental effects. Similarly the ATSDR calculates **Minimal Risk Levels (MRLs)** for noncancer end points.

The **critical toxic effect** used in the calculation of an ADI, RfD, or MRL is the serious adverse effect which occurs at the lowest exposure level. It may range from lethality to minor toxic effects. It is assumed that humans are as sensitive as the animal species unless evidence indicates otherwise.

In determining the ADIs, RfDs or MRLs, the **NOAEL** is divided by safety factors *(uncertainty factors)* in order to provide a margin of safety for allowable human exposure.

Question: The ADI is calculated by the following procedure:
- dividing the NOAEL by safety factors
- linear extrapolation from the LOAEL to the zero intercept
- multiplying the RfD by a modifying factor

Answer: The ADI is determined by applying safety factors *(to account for the uncertainty in the data)* to the highest dose in human or animal studies which has been demonstrated not to cause toxicity *(NOAEL)*. ADI *(human dose)* = NOAEL *(experimental dose)* / Safety Factor(s).



Non-carcinogenic Risk Assessment continued (optional slide for countries where MRLs are used)

The EPA has slightly modified the ADI approach and calculates a **Reference Dose (RfD)** as the acceptable safety level for chronic non-carcinogenic and developmental effects. Similarly the ATSDR calculates **Minimal Risk Levels (MRLs)** for noncancer end points.

The **critical toxic effect** used in the calculation of an ADI, RfD, or MRL is the serious adverse effect which occurs at the lowest exposure level. It may range from lethality to minor toxic effects. It is assumed that humans are as sensitive as the animal species unless evidence indicates otherwise.

While ATSDR does not conduct cancer risk assessments, it does derive **Minimal Risk Levels (MRLs)** for noncancer toxicity effects *(such as birth defects or liver damage)*. The MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects over a specified duration of exposure. For inhalation or oral routes, MRLs are derived for acute *(14 days or less)*, intermediate *(15-364 days)*, and chronic *(365 days or more)* durations of exposures.

The method used to derive MRLs is a modification of the EPA's RfD methodology. The primary modification is that the uncertainty factors of 10 may be lower, either 1 or 3, based on scientific judgment. These uncertainty factors are applied for human variability, interspecies variability *(extrapolation from animals to humans)*, and use of a LOAEL instead of NOAEL. As in the case of RfDs, the product of uncertainty factors multiplied together is divided into the NOAEL or LOAEL to derive the MRL.
In determining the ADIs, RfDs or MRLs, the **NOAEL** is divided by safety factors *(uncertainty factors)* in order to provide a margin of safety for allowable human exposure.

Question: Which of the following statements best describes the derivation of Minimal Risk Levels?
- The method used to derive MRLs is similar to that for the RfD, except that the uncertainty factors of 10 may be lower.
- MRLs for dermal exposure are derived by multiplying the dermal penetration by the NOAEL.
- The MRL is derived by multiplying the cancer slope factor by the lowest exposure dose.
Answer: The method used to derive MRLs is similar to that for the RfD, except that the uncertainty factors of 10 may be lower. The ATSDR applies uncertainty factors of 1, 3, or 10 for human variability, interspecies variability, and use of a LOAEL instead of NOAEL.

Risk Assessment

Dose (concentration) - response (effect) assessment

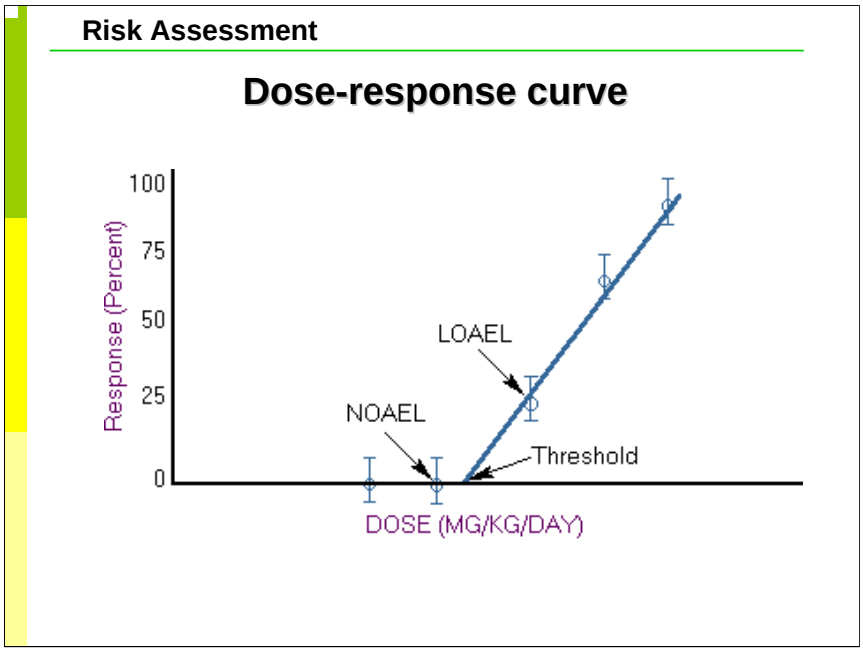
The estimation of the relationship between dose, or level of exposure to the substance and the incidence of the severity of the effect

- NOAEL - No observed adverse health effect
- LOAEL - Lowest observed adverse health effect

LOAEL to be set, if NOAEL is not possible

Lowest Observed Adverse Effect Level (LOAEL): The lowest dose of chemical in a study, or group of studies, that produces statistically or biologically significant increases in the frequency or severity of adverse effects between the exposed population and its appropriate control
No Observed Adverse Effect Level (NOAEL): The dose of chemical at which there were no statistically or biologically significant increases in the frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

When a NOAEL is not available, a LOAEL can be used to calculate the RfD. An additional safety factor is included if an LOAEL is used. A Modifying Factor of 0.1-10 allows risk assessors to use scientific judgment in upgrading or downgrading the total uncertainty factor based on the reliability and quality of the data. For example, if a particularly good study is the basis for the risk assessment, a modifying factor of < 1 may be used. If a poor study is used, a factor of >1 can be incorporated to compensate for the uncertainty associated with the quality of the study.



A dose response curve for non-carcinogenic effects is illustrated in the slide which also identifies the NOAEL and LOAEL. Any toxic effect might be used for the NOAEL/LOAEL so long as it is the most sensitive toxic effect and considered likely to occur in humans.

Risk assessments are also conducted to derive permissible exposure levels for acute or short term exposures to chemicals. Health Advisories (HAs) are determined for chemicals in drinking water. HAs are the allowable human exposures for one day, ten days, longer-term, and lifetime durations. The method used to calculate HAs is similar to that for the RfD's using uncertainty factors. Data from toxicity studies with durations of length appropriate to the HA are being developed.

Animal doses must be converted to human dose equivalents. The **human dose equivalent** is based on the assumption that different species are equally sensitive to the effects of a substance per unit of body weight or body surface area.

Historically, FDA used a ratio of body weights of humans to animals to calculate the human dose equivalent. EPA has used a ratio of surface areas of humans to animals to calculate the human dose equivalent. The animal dose was multiplied by the ratio of human to animal body weight raised to the 2/3rd power *(to convert from body weight to surface area)*. FDA and EPA have agreed to use body weight raised to the 3/4th power to calculate human dose equivalents in the future.

The last step in risk assessment is to express the risk in terms of allowable exposure to a contaminated source. Risk is expressed in terms of the concentration of the substance in the environment where human contact occurs. For example, the unit risk in air is risk per mg/m^3 whereas the unit risk in drinking water is risk per mg/L.
For carcinogens, the media risk estimates are calculated by dividing cancer slope factors by 70 kg *(average weight of man)* and multiplying by 20 m^3/day *(average inhalation rate of an adult)* or 2 liters/day *(average water consumption rate of an adult)*.

Risk Assessment

Safety factors

10X	human variability
10X	extrapolation from animals to humans
10X	use of less than chronic data
10X	use of LOAEL instead of NOAEL
0.1 - 10X	modifying factor

The **Uncertainty Factors or Safety Factors** used to derive an ADI or RfD are shown in the table on the slide.

The modifying factor is used only in deriving EPA Reference Doses. The number of factors included in calculating the ADI or RfD depend upon the study used to provide the appropriate NOAEL or LOAEL.
The general formula for deriving the RfD is:

$$RfD = \frac{\text{NOAEL or LOAEL}}{UF1 \times UF2 \times \ldots}$$

The more uncertain or unreliable the data becomes, the higher will be the total uncertainty factor that is applied. An example of an RfD calculation is provided below. A subchronic animal study with a LOAEL of 50 mg/kg/day was used. Thus the uncertainty factors are: 10 for human variability, 10 for an animal study, 10 for less than chronic exposure, and 10 for use of an LOAEL instead of a NOAEL.
A discussion has been held to add an additional safety factor for children, eg. For pesticides or for air pollution to correct for higher respiration rate. No conclusive deciosion has been made to do this.

$$RfD = \frac{50 \text{ mg / kg/ day}}{10 \times 10 \times 10 \times 10} = 0.005 \text{ mg / kg/ day}$$

In addition to chronic effects, RfDs can also be derived for other long term toxic effects, including developmental toxicity.

Human parameters

- Age and weight of little child or a grown-up?
- How much drinking water per day?
- How much soil intake / playing day by a child?
- Vegetable intake?
- Child food intake compared to grown-up?
- Cubic meters inhalation per day? Child/Grown-up?
- Intake is not uptake, % uptake?
- How many outdoor playing days per year for a child?

To assess the real exposure different parameters have to be taken into account for children.

Different organisations have set fixed data for child parameters. Risk assessment methodologies by EPA has set such parameters.

Risk Assessment

Scenario for exposure via the environment

- Adult, 70 kg, 20 m^3/day
- Intake media: air, drinking water, root/ leaf crops, fish, meat, dairy products
- Entire food basket sourced from vicinity of local point source or region
- Highest country-average intake rate per food product
- Concentrations/ intakes constant in time
- No further spatial differentiation

The last step in risk assessment is to express the risk in terms of allowable exposure to a contaminated source. Risk is expressed in terms of the concentration of the substance in the environment where human contact occurs. For example, the unit risk in air is risk per mg/m^3 whereas the unit risk in drinking water is risk per mg/L.

For carcinogens, the media risk estimates are calculated by dividing cancer slope factors by 70 kg *(average weight of man)* and multiplying by 20 m^3/day *(average inhalation rate of an adult)* or 2 liters/day *(average water consumption rate of an adult)*.

Question: The primary method used to predict movement of substances in environmental media is:

O actual measurements of air and water pollutants at various places in the environment

O by use of exposure models

O tagging pollutants with radioactive tracers and measuring the radioactivity at various times and locations within the environmental media

Answer: Exposure models are the primary method used to predict movement of substances in environmental media. Because actual measurements of environmental chemical exposure are often unavailable, exposure models are used. Models can predict future movement into areas that are currently free from contamination.

Risk Assessment

Exposure Assessment

- exposed populations *(general public or selected groups)*
- types of substances *(pharmaceuticals, occupational chemicals, or environmental pollutants)*
- single substance or mixture of substances
- duration of exposure *(brief, intermittent, or protracted)*
- pathways and media *(ingestion, inhalation, and dermal exposure)*

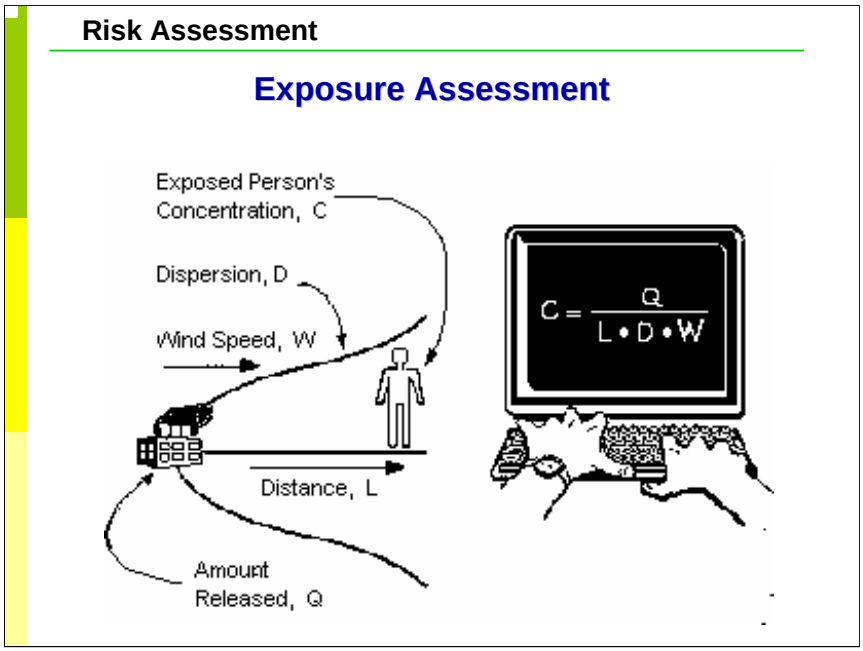
Exposure assessment is a key phase in the risk assessment process since without an exposure, even the most toxic chemical does not present a threat. All potential exposure pathways are carefully considered. Contaminant releases, their movement and fate in the environment, and the exposed populations are analyzed.

Exposure assessment includes three steps:

characterization of the exposure setting *(e.g., point source)*
identification of exposure pathways *(e.g., groundwater)*
quantification of the exposure *(e.g., microgram/L water)*

The main variables in the exposure assessment are:
exposed populations *(general public or selected groups)*
types of substances *(pharmaceuticals, occupational chemicals, or environmental pollutants)*
single substance or mixture of substances
duration of exposure *(brief, intermittent, or protracted)*
pathways and media *(ingestion, inhalation, and dermal exposure)*

For non-carcinogenic effects, the exposure level is compared with an ADI, RfD or MRL derived for similar exposure periods. Three exposure durations are considered: acute, intermediate, or chronic. For humans, acute effects are considered those that arise within days to a few weeks, intermediate effects are those evident in weeks to a year, and chronic effects are those that become manifest in a year or more.



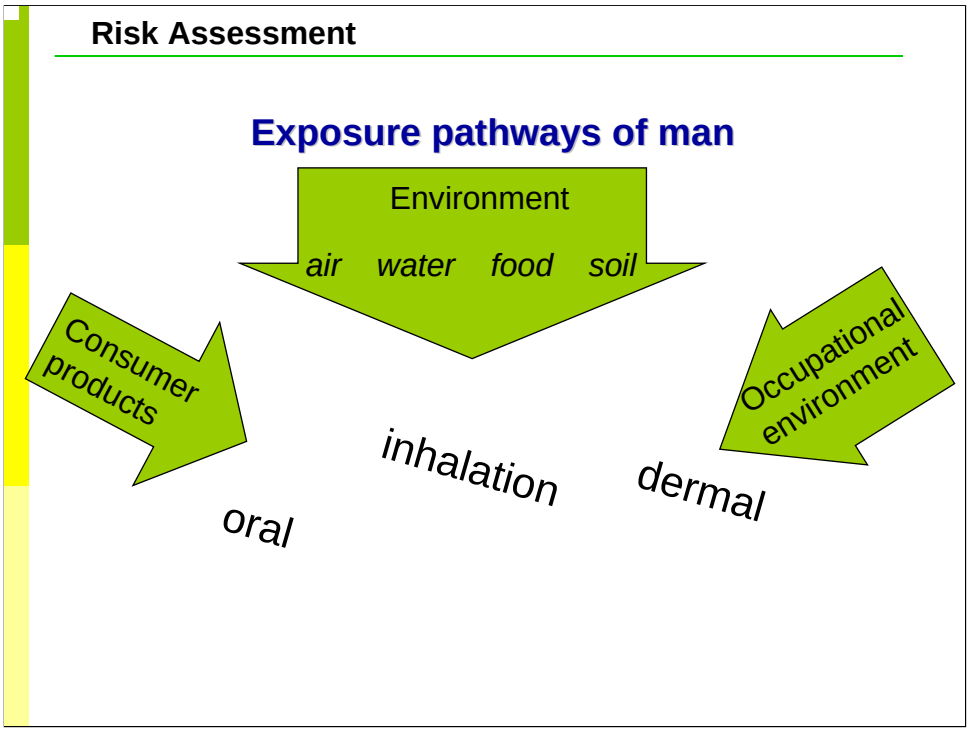
All possible types of exposure are considered in order to assess the toxicity and risk that might occur due to these variables.

The risk assessor first looks at the physical environment and the potentially exposed populations. The physical environment may include considerations of climate, vegetation, soil type, ground-water and surface water. Populations that may be exposed as the result of chemicals that migrate from the site of pollution are also considered.

Pollutants may be transported away from the source. They may be physically, chemically or biologically transformed. They may also accumulate in various media. Assessment of the chemical fate requires knowledge of many factors including:

organic carbon and water partitioning at equilibrium *(Koc)*
chemical partitioning between soil and water *(Kd)*
partitioning between air and water *(Henry's Law Constant)*
solubility constants
vapor pressures
partitioning between water and octanol *(Kow)*
bioconcentration factors

Question: A major aspect of the exposure assessment is to:
O determine the amount of exposure that must be reduced in order to comply with the acceptable risk level
O identify the exposure pathways
O measure the amount of a substance that is metabolized in the body
Answer: A major aspect of the exposure assessment is to identify the exposure pathways. All potential exposure pathways are carefully considered as well as contaminant releases, movement and fate in the environment and the exposed populations.



These factors are integrated with the data on sources, releases and routes of the pollutants to determine the exposure pathways of importance.

Exposure pathways may include:
groundwater
surface water
air
soil
food
breast-milk

Since actual measurements of exposures are often not available, exposure models may be used. For example, in air quality studies, chemical emission and air dispersion models are used to predict the air concentrations to downwind residents. Residential wells downgradient from a site may not currently show signs of contamination. They may become contaminated in the future as chemicals in the groundwater migrate to the well site. In these situations, groundwater transport models may estimate when chemicals of potential concern will reach the wells.

Exposure via the environment What's the challenge?

- Predicting exposure of humans via direct and indirect routes
- Problems:
  - many different subpopulations
  - many different scenarios
  - human behaviour and food sources are highly variable

Risk assessments may be conducted for individual chemicals or for complex mixtures of chemicals. In cases of complex mixtures, such as hazardous waste sites, the process of risk assessment itself becomes quite complex. This complexity results from:

simultaneous exposure to many substances with the potential for numerous chemical and biological interactions

exposures by multiple media and pathways *(e.g., via water, air, and soil)*

exposure to a wide array of organisms with differing susceptibilities *(e.g., infants, adults, humans, animals, environmental organisms)*

Subpopulations may be at greater risk due to a higher level of exposure or because they have increased sensitivity *(infants, elderly, pregnant women, and those with chronic illness)*.

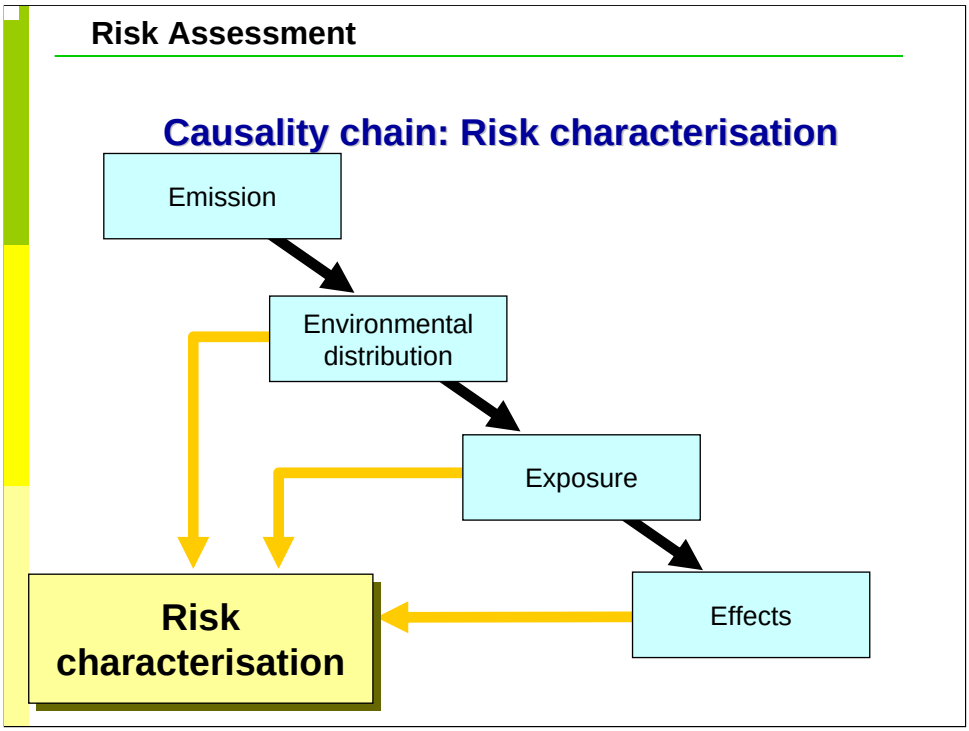
Risk Characterization

- ❑ Review toxicity and exposure assessment output
- ❑ Quantify risks
- ❑ Combine risks across all pathways
- ❑ Assess and present uncertainties
- ❑ Consider site-specific human studies, if available
- ❑ Summarize and present baseline risk assessment characterization results

This final stage in the risk assessment process involves prediction of the frequency and severity of effects in exposed populations. Conclusions reached concerning hazard identification and exposure assessment are integrated to yield probabilities of effects likely to occur in humans exposed under similar conditions.
Since most risk assessments include major uncertainties, it is important that biological and statistical uncertainties are described in the risk characterization. The assessment should identify which components of the risk assessment process involve the greatest degree of uncertainty.

In some complex risk assessments such as for hazardous waste sites, the risk characterization must consider multiple chemical exposures and multiple exposure pathways. Simultaneous **exposures to several chemicals**, each at a subthreshold level, can often cause adverse effects by simple summation of injuries.
The assumption of dose additivity is most acceptable when substances induce the same toxic effect by the same mechanism. When available, information on mechanisms of action and chemical interactions are considered and are useful in deriving more scientific risk assessments.
Individuals are often exposed to substances by **more than one exposure pathway** *(e.g., drinking of contaminated water, inhaling contaminated dust)*. In such situations, the total exposure will usually equal the sum of the exposures by all pathways.

Question: The process in which the dose-response assessment and exposure assessments are integrated to predict risk to specific populations is known as:
O risk management
O hazard identification
O risk characterization
answer: Risk characterization is the process in which the dose-response assessment and exposure assessments are integrated to predict risk to specific populations. It is the final stage in the risk assessment process and involves the prediction of the frequency and severity of effects in exposed populations.



The causality chain shows the linakge of the steps that lead to the risk characterisation.

Question: An increased cancer risk of 2.0 X 10^{-6} means that:

- it is likely that 2 persons in one million will develop the specific type of cancer in their lifetime due to exposure to the chemical.
- the xenobiotic for which the cancer risk assessment was performed is likely to cause cancer in 200 persons on a yearly basis.
- it is probable that 2 million persons will develop cancer if they are continuously exposed to the chemical for life.

Answer: An increased cancer risk of 2.0 X 10^{-6} means that it is likely that 2 persons in one million will develop the specific type of cancer in their lifetime due to exposure to the chemical.

Complex Systems

- Risk assessment is now being applied to very complex systems - such as ecosystems
- It is impossible to have comprehensive hazard data for such systems
- Missing data is often provided by ‘data models’, but these can be subjective
- Sometimes the whole risk assessment can be based solely upon data models

Risk assessment is now being applied to complex systems. Ecosystems could reasonably be described as unfathomably complex. Hazard identification in such systems is a major problem. For potential hazards that can be identified, the likelihood of being able to characterise them adequately must be regarded as low and prohibitively costly to investigate. Under such circumstances it is not surprising that a whole new industry has evolved which addresses the modelling hazards.

•A former director of the US EPA said:

“We should remember that risk assessment can be likened to the captured spy: if you torture it long enough, it will tell you anything you want to know”

Difficult issues

- How would you sort out the incidence of disease related to toxicant exposure versus the background incidence?
- Should people who have both personal and occupational exposure to the same toxicants have different standards than those who don't? (e.g., should smokers have lower occupational formaldehyde exposure limits?)

Additional questions could raised, such as: Should pregnant women be excluded from jobs where reproductive toxicant exposure occurs?

This can be discussed among the participants.

Maternal Plasma Concentrations of Pesticides: Circumpolar Study 1994-1996 (Geometric means ug/kg lipid (ppt))

Country/ Pesticides	Canada [1] (n = 67)	Green-land [2] (n = 117)	Sweden [3] (n = 40)	Norway [4] (n = 60)	Iceland [5] (n = 40)	Russia [6] (n = 51)
β-HCH	9.3	18.5	9.2	8.1	32.1	222.5
α-chlordane	1.0	1.1	1.0	1.3	1.3	1.6
γ-chlordane	1.1	1.3	1.0	1.3	1.3	1.4
Cis-nonachlor	6.6	20.9	1.2	1.8	2.7	5.3
p,p'-DDE	133	407	84.0	79.4	113.2	411.9
p,p'-DDT	7.9	15.0	2.4	3.0	4.0	48.3
HCB	55.1	97.6	15.6	23.1	41.2	62.8
Mirex	4.5	9.1	1.1	1.4	1.9	1.4
Oxychlordane	27.8	60.8	1.9	3.7	6.6	3.3
Transnonachlor	30.5	110	3.8	6.8	12.2	11.5

[1] Inuit women from west/central NWT,
[2] women from Disko Bay region,
[3] women from Kiruna,
[4] women from Hammerfest and Kirkenes,
[5] women from Nikel.
Source: Gilman *et al.* 1997).

Everybody on the planet has hundreds of persistent bio-accumualtive fat soluble chemicals in their bodies which could not have been there 70 years ago, because they simply didn't exist on this planet, they are man made. One can ask the question "was this predictable?". Yes it could have been, even with the science that was available then.

Simply reacting to disasters was seen to be an inadequate approach. Man was clearly capable of causing changes to the environment and health on a global scale. There was a desire to adopt an anticipatory mode to try to avoid failures by using past experience to predict likely areas of hazard

The options available are:

Hazard assessment

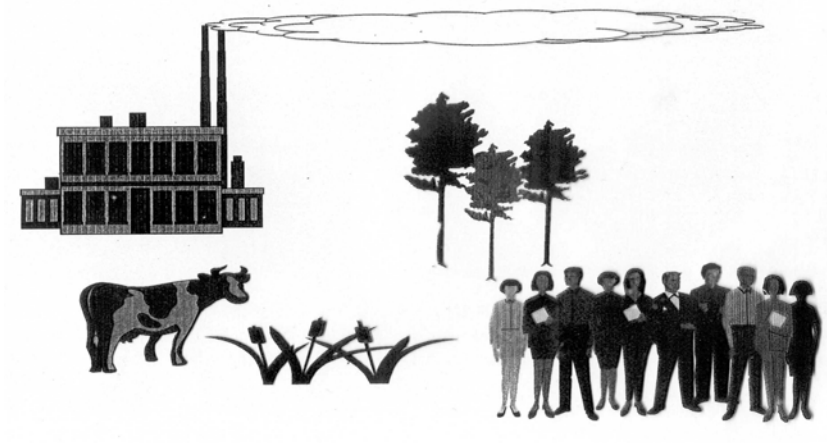
Risk assessment

Precaution

The disaster described above is a clear example of why regulators had to adopt a more anticipatory stance. The available options are hazard-based, risk-based and precaution –based.

Risk Assessment

If you ask the wrong question – you get the wrong answer



Let us examine an example where risk assessment has been suborned by the use of a ‘fact-free model’. When applications are made to license waste incinerators, a computer model is made of what might come out of the stack and then another computer model is made of the likely dispersion model over the local terrain. Then a ‘hypothetical person’ is stood at the ‘hypothetical maximal ground level concentration of the plume’ and his/her hypothetical intake of pollutant from plants grown at that point. Some hypothetical calculations are made. The result is compared with current exposure to the pollutant and a conclusion such as “that’s not very much, less than 3% of what is already being taken in now, it must be safe”. This is called an ‘incremental dose model’. Have you spotted the fatal model assumption? Well it is that the population to be polluted by this technological development have no pollutant inside them before they start! The data just presented must show the fallacy of that. The fact is that a proportion of the background population already have too much of certain pollutants in their bodies for the good of the next generation. This would radically change the outcome of any risk assessment.

Risk Assessment

How long are the reassurances offered in a risk assessment good for?

- A low probability
- Given enough time
- Becomes a racing certainty

This is a very important question. When a claim of safety is made in a risk assessment the question of “how long for” must always be asked. The normally un-stated implication is that it is in perpetuity. This is usually far from the truth. The concept of ‘waiting time’ needs to be considered. In a game of Russian roulette the ‘waiting time’ for an ‘event’, i.e. someone blowing their brains out, is rather short! As the likelihood of an event decreases , the ‘waiting time’ increases. However ‘waiting time’ is a statistical concept, the event could happen rather quickly or not for a very long time. The average waiting time is, however, linked to likelihood.

Standard format for risk assessments?

- Pro-forma listings of:
  - All hazards identified
  - Those hazards identified but not assessed
  - Those hazards not assessed but modelled
  - Areas of uncertainty identified
  - Levels of confidence in the results
  - Time scale over which the risk assessment can be considered to be valid

Risk assessments for processes that can effect the public through the environment should have a standard format imposed. This should give lists of topics mentioned in the slide and some statement of the confidence the authors have in the results and the time scale over which any assurances are deemed to be effective.

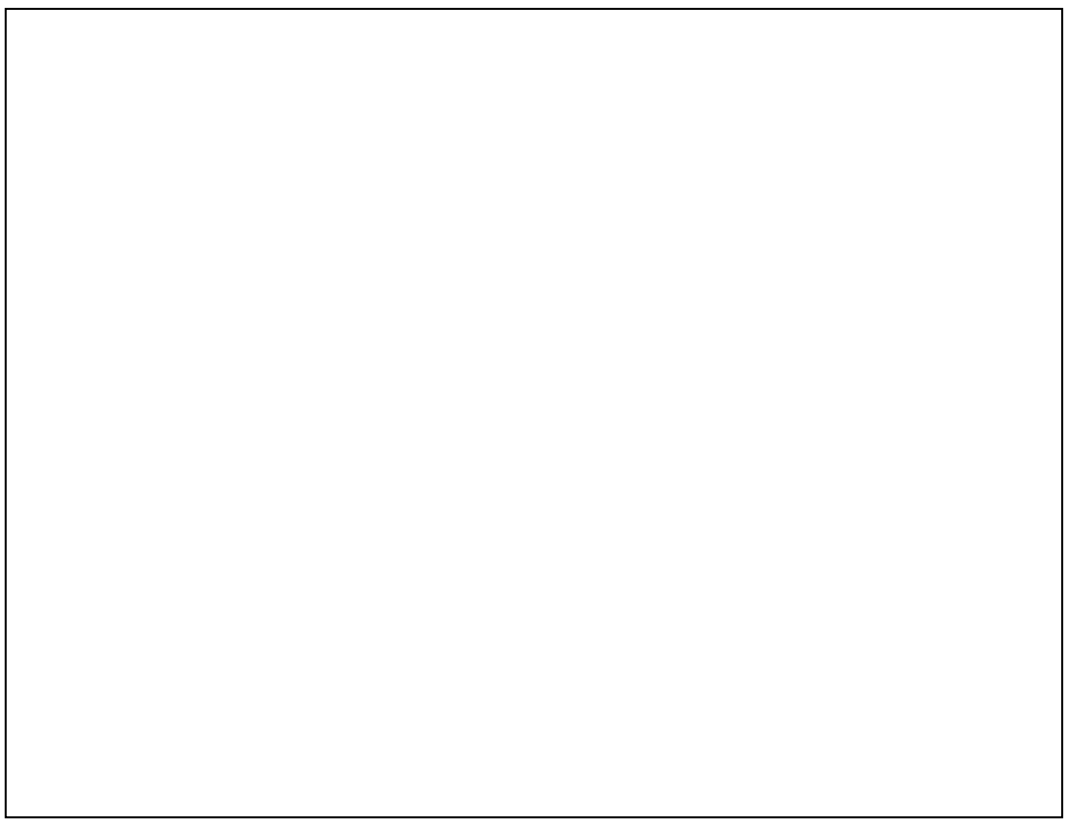
Simple

- What kind of pollution? (number of Chemical(s))
- Pollution concentration in air, soil, water, food? (C)
- Exposure routes: direct and indirect
- Exposure data (a lot of defaults) (Intake, I)
- Intake and absorption? (Total is $\sum$ (C x I))
- In case of air-polution compare to TCL or other
- Adverse effects? Compare $\sum$ with ADI or other
- Is medical examination necessary? Possible?

Some examples of listings that need to be considered in risk assessment practice.

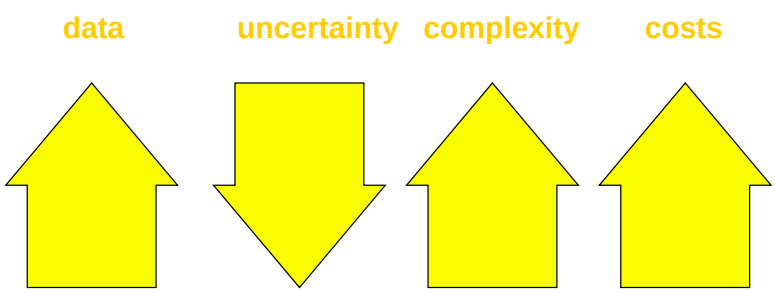
Variability and uncertainty

- Measurement errors
- Sampling errors
- Variability in natural systems
- Variability in human behaviour
- Limitations in model description
- Limitations in data
- Limitations in professional judgement



Risk Assessment

Correlations



Warning!

Always remember that the model is as good as what you put into it

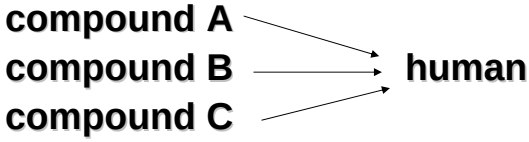
No model compares with reality

Don’t just fill in the model but always use your brains (too)!

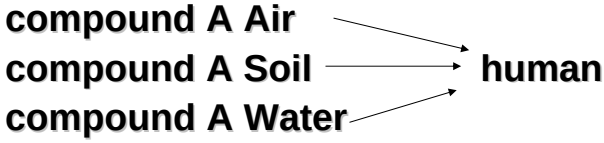
Some warnings about the use of models.

Combinations

1. Different compounds, same effect



2. One compound in more compartments



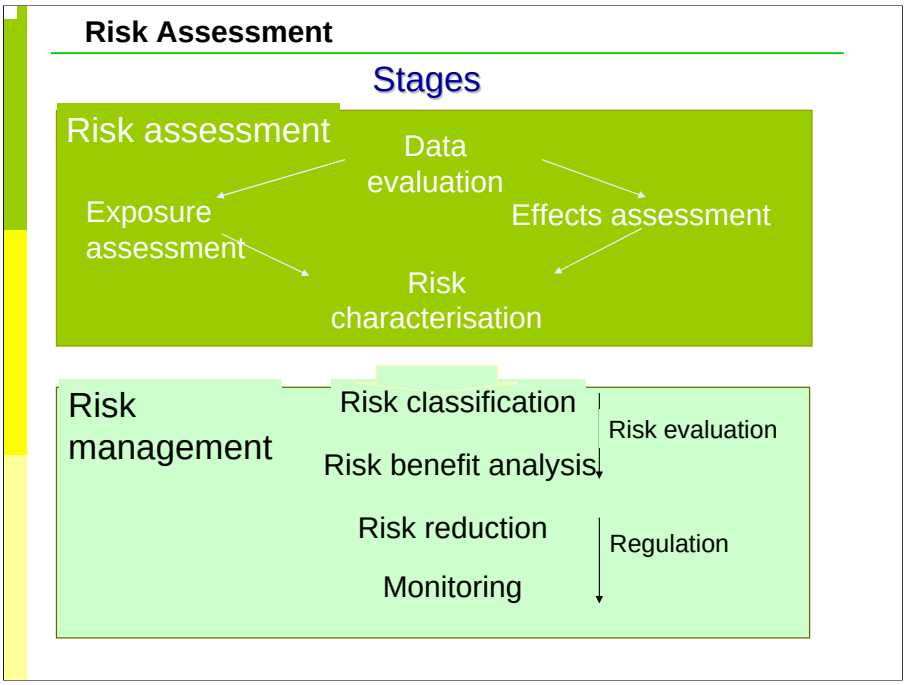
Some guidance of combination of effects. Different compounds can have the same effects. But also the same compound can be present in different environmental compartments and cause additive effects.

Risk Groups

1. **Higher exposure**
   - **living near industry, living under flight route**
   - **child eating soil,**
   - **running the marathon**

2. **More vulnerable**
   - **children, pregnant woman, elderly, COPD-patients**

Generally in risk assessment we consider different risk groups. The main risk groups are lsited in the slide.



This slide repeesents the different stages in risk assessment and risk management.

Features of risk assessment

- Data requirements
- Assessment stages
- Data availability
- Data quality and selection
- Protection goals
- Uncertainty
- Time scales
- Spatial scales

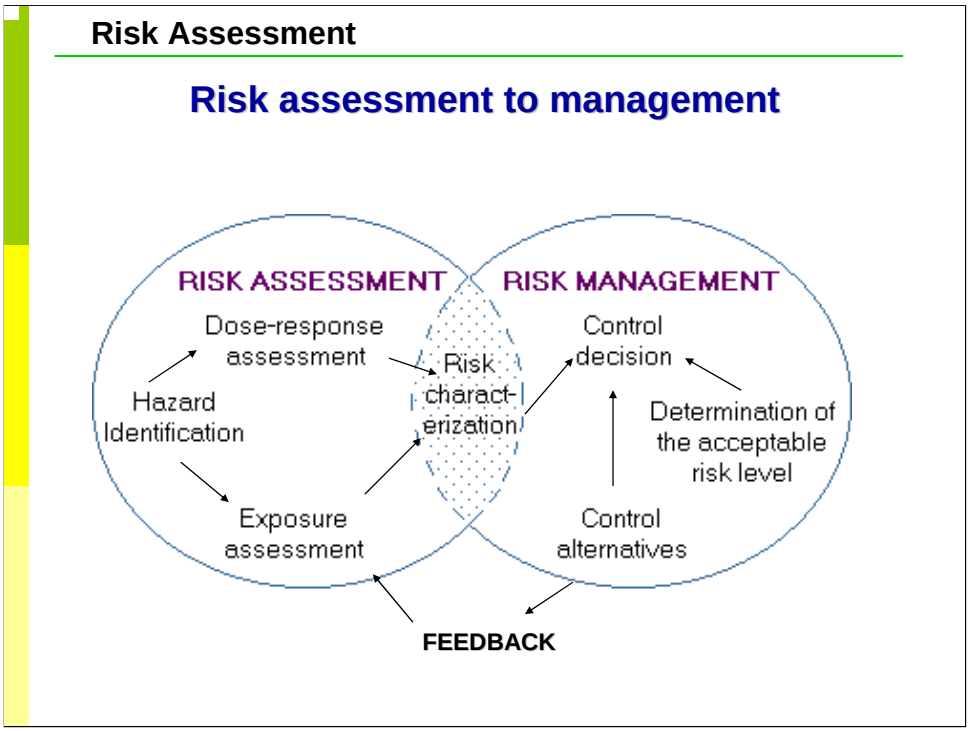
This slide summarizes the different features of risk assessment that need to be considered to do a good risk assessment.

Assessment stages (OECD)

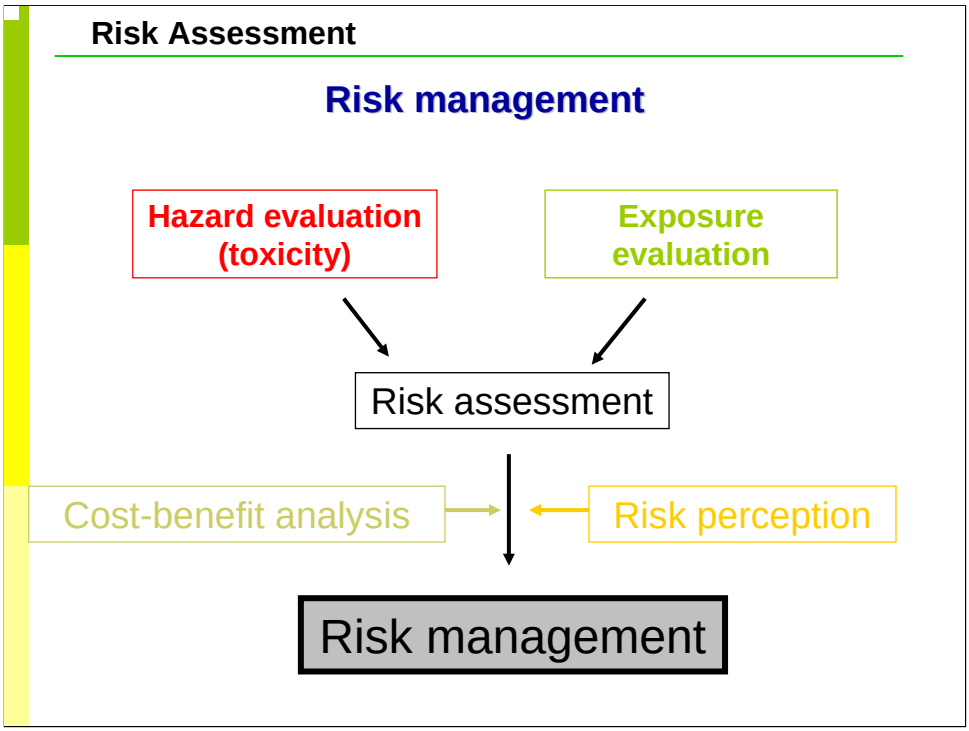
Assessment stage	Effects data
Initial (screening) stage	Acute toxicity
Intermediate (refined) stage	Chronic toxicity
Comprehensive stage	Field toxicity/ epidemiology

The OECD has developed some stages in which a risk assessment can be done.

In these stages the different data on effects have to be collected.



Risk management decisions follow the identification and quantification of risk which are determined by risk assessments. During the regulatory process, risk managers may request that additional risk assessments be conducted to justify the risk management decisions. As indicated in the figure above, the risk assessment and risk management processes are intimately related.



This graph shows an altenative way of the connection between risk assessment and risk management. In a simple way one can say that risk assessment is the tool that needs to be used to make some judgements that deals with managing the risk. This is very often a very difficult exercise! The scientific uncertainty (at low doses) and the non-scientific issues (economic, political) make the outcome of the risk management process not very predictable.

Methodological Issues

- Preventive policy: no "body counts"
- No human experimentation
- Ethical treatment of animals
- Short-term tests (*problem*: reductionism)
- Bioassays (*problem*: interspecies etc. extrapolation)
  - choice of test animals
  - routes of exposure
  - dose-response issues
- Epidemiology (*problem*: confounding factors)

Conducting scientifically sound risk assessments is of great importance. An error in undercalculating risk probabilities could lead to overexposure of the population. On the other hand, an overcalculation of risk could result in unwarranted costs to the public.

Risk Management Strategies

- Zero risk (no animal carcinogens in food)
- *De minimis* risk ($<10^{-6}$ lifetime cancer risk)
- Safety (no observable effect level or NOEL)
- Acceptable risk (regulatory standard)
- Risk tradeoffs
  - risks vs. benefits (disease vs. income, choice)
  - risks vs. risks (epidemic vs. drug reaction)

Generally speaking there are a few different management strategies. These range from no risk at all to accepting risks but trading these off with other aspects such as benefits.