The purpose of this lecture is to inform you of basic principles in hazard identification and dose response assessment.

It is a common (although not exclusive) practice in risk assessment to distinguish between cancer and non cancer health endpoints.

Thus, this lecture will be divided into these two areas.
DISCUSSION POINTS:

PART 1: NONCANCER RISK ASSESSMENT

Expert work groups throughout the world support the use of a "safe" dose concept in noncancer risk assessment, and define terms and conditions for its use.

This safe or subthreshold dose often goes by different names, such as WHO's Tolerable Intake (TI); U.S. ATSDR's Minimum Risk Level (MRL); U.S. FDA's Acceptable Daily Intake (ADI); and U.S. EPA's Reference Dose (RfD) or Reference Concentration (RfC).

For example, the U.S. EPA uses the terms Reference Dose (RfD) for oral and Reference Concentration (RfC) for inhalation exposures. These terms are defined on the adjacent slide.

Many of the underlying assumptions, judgements on critical effect, and choices of uncertainty factors (or safety factors) to estimate these various subthreshold doses are similar.

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The estimation of these subthreshold doses involves several judgments such as:

- the choice of the most appropriate No Observed Adverse Effect Level (NOAEL) of the critical effect, usually from animal data, and
- the choice of the appropriate uncertainty factors based on a review of the entire database.
DISCUSSION POINTS:
All toxicity data are reviewed in order to determine the critical effect.

The critical effect is the first adverse effect(s) or its know precursor(s) that occurs as dose rate increases.

Some effects are clearly not adverse, nor precursors; other are clearly adverse or precursors; many effects are of uncertain adversity.

The judgement of what effects are adverse is often difficult and often depends on the spectrum of effects seen in the chosen study or other studies in the data base.

For definitions of the EPA terms used on the adjacent slide, please see a separate handout. Also note that health organizations throughout the world use similar terms. This listing is only one example of how to define the concept of critical effect.

NOEL = No Observed Effect Level
NOAEL = No Observed Adverse Effect Level
LOAEL = Lowest Observed Adverse Effect Level
FEL = Frank Effect Level
UF = Uncertainty Factor, MF = Modifying Factor

DISCUSSION POINTS:
Uncertainty Factors are necessary reductions in the dose to account for missing data.

Health organizations throughout the world treat these areas of uncertainty somewhat differently. Some, like the U.S. EPA on the slide, call out explicit areas.

So what is ideal data to determine a protective value? When would an uncertainty factor not be needed?
DISCUSSION POINTS:

The composite UF is a judgement regarding the strengths and weaknesses of the entire database.

As UF's increase in number, the composite "protectiveness" of the resulting value (e.g., ADI) generally increases. This implies that as more data are brought into the database for the determination of the ADI, fewer uncertainty factors would be needed and the value of the ADI should increase. This is generally what occurs.

Most agencies that estimate these values recognize this composite "protectiveness" and roll several areas of uncertainty together.

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DISCUSSION POINTS:

These estimates of subthreshold dose rates are considered accurate.

However, the degree to which these dose rates are below the population threshold is not generally known.

Two examples of where such estimates were not below thresholds were colbalt in beer and the sedative thalidomide. In the former case, a population sensitive to the cardiomyopathy of colbalt appeared to have been missed (thus the uncertainty factor of 10 may not have been enough). In the latter case, the critical effect, developmental toxicity, was apparently not evident in the animal toxicity database.
DISCUSSION POINTS:

Subthreshold doses can only be as precise as their least precise component. In the case of most of these estimates, the least precise component is the uncertainty factor.

As the composite uncertainty factor grows larger, the imprecision of the resulting subthreshold doses also grows larger.

DISCUSSION POINTS:

Thus, as a result of this accuracy and precision, these subthreshold doses have an associated range.

For example, an RfD on EPA's Integrated Risk Information System (IRIS) of 1 mg/kg/day might have a range of 0.3 to 3 mg/kg/day, indicating a one-half order of magnitude both above and below the RfD.

This range might be larger or smaller depending how precise the NOAEL is and how many uncertainty factors are used to determine the subthreshold dose.

HOW PRECISE ARE THESE ESTIMATES?

Not very! Each uncertainty factor varies with ranges up to about 10-fold. Several factors are generally multiplied to estimate a subthreshold dose and some factors overlap, thereby increasing variability and decreasing precision.

If you play golf, precise drives are those that consistently land in one area of the fairway (or the creek).

RANGE OF THESE ESTIMATES

The resulting range of an RfD or RFC (a U.S. EPA term) has been defined as "perhaps an order of magnitude." This range is expected to differ amongst RfDs or RFCs, in part because of the use of different UF's.

What this means in general is that environmental exposures falling into the range of the subthreshold estimate cannot be scientifically distinguished from the estimate.
APPENDIX:
The following example on acrylamide is taken from U.S. EPA's Integrated Risk Information System (IRIS). This example shows summary information on an RfD. Also attached are definitions of some terms and additional readings. These are only a subset of terms and possible readings available for this area.

DISCUSSION POINTS:
The critical effect is considered to be nerve damage.

The left sciatic nerve was examined under light and electron microscope. No significant adverse effects were seen in the 0.05 or 0.2 groups, while the 5 and 20 mg/kg/d groups had frank nerve degeneration. In the 1 mg/kg/d group a slight, but significant, increase in peripheral axolemmal invaginations were observed under EM but not when using light microscopy.

Thus, the NOAEL was judged to be 0.2 mg/kg/day and the LOAEL was judged to be 1 mg/kg/day.
ACRYLAMIDE RFD
UNCERTAINTY AND MODIFYING FACTORS

UF = 1000. THE UF OF 1000 ALLOWS FOR UNCERTAINTY IN THE EXTRAPOLATION OF DOSE LEVELS FROM LABORATORY ANIMALS TO HUMANS, UNCERTAINTY IN THE THRESHOLD FOR SENSITIVE HUMANS, AND UNCERTAINTY IN THE EFFECT OF DURATION WHEN EXTRAPOLATING FROM SUBCHRONIC TO CHRONIC EXPOSURE. THE CHRONIC STUDY DID NOT ADEQUATELY ADDRESS THE LATTER UNCERTAINTY BECAUSE OF THE LACK OF A SENSITIVE MEASUREMENT OF THE CRITICAL EFFECT.

MF = 1.

STUDY: HIGH
DATA BASE: MEDIUM
RFD: MEDIUM

Below are some common definitions used in noncancer risk assessment. These definitions are for illustration only. Other terms are used in different organizations and countries.

**Acceptable Daily Intake** – An estimate of the dose resulting from daily exposure to a toxicant that is likely to be without deleterious effect even if continued exposure occurs over a lifetime.

**Acute Exposure** – One dose or multiple dose exposure occurring within a short time (<24 hours).

**Adaptive Effect** – Effects that enhance an organism’s performance as a whole and/or its ability to withstand a challenge (i.e., homeostatic mechanism). An increase in hepatic smooth endoplasmic reticulum is an example of an adaptive effect, if hepatic metabolism reduces the chemical’s toxicity.

**Adverse Effect** – A biochemical change, functional impairment, or pathological lesion which impairs performance and reduces the ability of the organism to respond to additional challenge.

**Chronic Exposure** – Multiple or continuous exposures occurring over an extended period of time, or a significant fraction of the animal’s or the individual’s lifetime.

**Compensatory Effect** – Effects that maintain overall function without enhancement or significant cost. Increased respiration due to metabolic acidosis is an example of a compensatory effect.

**Critical Effect** – A chemical often elicits more than one toxic effect, even in one species, or in tests of the same or different duration. The critical effects are the first adverse effects or their known precursors that occur as dose rate increases. The critical effects may change among toxicity studies of different durations, may be influenced by toxicity in other organs, and may differ depending on the availability of data on the shape of the dose-response curve.

**Frank-Effect Level (FEL)** – The exposure level which produces unmistakable adverse effects, such as reversible or irreversible functional impairment or mortality, at a statistically or biologically significant increase in frequency or severity between an exposed population and its appropriate control.
Health Hazard (types of) (Adapted in part from Klaasen et al., 1986) -

1. **Acute Toxicity** – Another term used to describe immediate toxicity (see below). Its use is associated with toxic effects that are severe (e.g., mortality) in contrast to the term "subacute toxicity", which is associated with toxic effects that are less severe. The term "acute toxicity" is often confused with that of acute exposure.

2. **Allergic Reaction** – Adverse reaction to a chemical resulting from previous sensitization to that chemical or to a structurally similar one.

3. **Chronic Toxicity** – The term "chronic toxicity" refers to effects that persist over a long period of time whether or not they occur immediately or are delayed. The term "chronic toxicity" is often confused with that of chronic exposure and is often used to describe delayed toxicity (see below).

4. **Idiosyncratic Reaction** – A genetically determined abnormal reactivity to a chemical.

5. **Immediate versus Delayed Toxicity** – Immediate effects occur or develop rapidly after a single administration of a substance, while delayed effects are those that occur after the lapse of some time. These effects have also been referred to as acute and chronic, respectively.

6. **Reversible versus Irreversible Toxicity** – Reversible toxic effects are those that can be repaired, usually by a specific tissue's ability to regenerate or mend itself after chemical exposure, while irreversible toxic effects are those that cannot be repaired.

7. **Local versus Systemic Toxicity** – Local effects refer to those that occur at the site of entry (e.g., lungs, stomach) of a toxicant into the body; systemic effects are those that are elicited after absorption and distribution of the toxicant from its entry point to a distant site.

**Lowest-Observed-Adverse-Effect Level (LOAEL)** – The lowest exposure level at which there are statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control group.
Address adequately all possible adverse outcomes in man.

rather than NOEL data, and (5) the inability of any single study to
lesser-than-nominal exposure. (4) the uncertainty in using NOEL data
unfortunately in extrapolating from data obtained in a study that is of
the uncertainty in extrapolating animal data to the case of humans; (2)
the uncertainty among the members of the human population; (2)
mental data, LIFS are intended to account for (1) the variation in
used in operationally defining the reference dose (RfD) from expert-

Uncertainty Factor (UF) — One of several, generally 10-fold, factors
usually over 3 months.

Subchronic Exposure — Multiple or continuous exposures occurring
appreciable risk of deleterious effects during a lifetime.

Reference dose (RfD) — An estimate (with uncertainty spanning a

lifetime).

Reference Concentration (RfC) — An estimate (with uncertainty spanning a

appropriate control

No-Observed-Effect Level (NOEL) — An exposure level at which there

exposure without adverse effect.

No-Observed-Adverse-Effect Level (NOAEL) — An exposure level at

(e.g., the number of animals tested), the default value for the MF is 1.
How Toxicity Data are Used in the Process of Hazard Identification and Dose-Response Assessment

Part 2: Cancer Risk Assessment

Cancer Risk Assessment - Critical Issues

- Confidence chemical is an animal/human carcinogen
- Extrapolation across species (animal to human)
- Extrapolation within species (human to human)
- Extrapolation from high to low doses
Confidence Chemical Is an Animal/Human Carcinogen

- EPA 1986 Scheme - Weight of Evidence
  A (definite) > B (probable) > C (possible) > D (not known) > E (not)
  Based on number of species, tumor sites, etc.
  Limited consideration of mechanisms
  Unintended consequences

- IARC/NTP - strength of evidence

Alternative Classification Approaches

- Ashby et al. (1990)
  - 8 categories - in-depth consideration of mechanisms
  - Allows for carcinogenicity in animals, not in humans

- Harvard Center for Risk Analysis (1992)
  Focuses on dose-response
  - Probabilistic description of dose-response relationships
    (including no response)
Predicted Cancer Incidence at 2.28 ppb Formaldehyde

Percentages

Cumulative Percentages

(HCRA, 1992)
Extrapolation Issues

(Conolly and Andersen, 1991)

Extrapolation Across Species

Body weight vs. body weight $^{23}$ vs. body weight $^{3/4}$ (EPA/CPSC/FDA workgroup)

- Physiologically based pharmacokinetic (PBPK) models to estimate integrated dose of toxic metabolite
- Species-specific responses - e.g., male rat kidney tumors (d-limonene, unleaded gasoline)
Use of PBPK Model - Plausible Upper Limit Estimate on Potency (mg/kg/d)$^{-1}$

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Standard Method</th>
<th>PBPK Model</th>
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<tbody>
<tr>
<td>Ethylene oxide</td>
<td>0.028</td>
<td>0.019</td>
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<tr>
<td>Butadiene</td>
<td>0.098</td>
<td>0.032</td>
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<tr>
<td>Perchloroethylene</td>
<td>0.0033</td>
<td>0.013</td>
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</table>

(Hattis, 1991)

Extrapolation Within Species

- Inter-human variability in susceptibility - prior exposure, gender, genetics
- Poorly addressed in cancer risk assessment
Extrapolation from High to Low Dose

- PBPK model - saturation of activating/deactivating pathway
- Dose-dependent mechanisms - e.g., proliferation and genotoxicity at high doses vs. genotoxicity at low doses
- Use of biologically based models vs. default models (i.e., LMS)

Biologically Based Model for Carcinogenesis

\[ S = \text{normal stem cell} \]
\[ D = \text{differentiated or dead cell} \]
\[ I = \text{intermediate cell} \]
\[ M = \text{malignant cell} \]

\[ \mu_1, \mu_2, \delta_2, \beta_2 = \text{rate constants} \]

(Moolgavkar, 1986)
Use of Biologically Based Model for Chloroform Risk Assessment

**Daily Human Dose Associated with 10^{-6} Cancer Risk**
*Virtual Safe Dose (VSD)*

<table>
<thead>
<tr>
<th>Assumed Mechanism</th>
<th>Exponential Model VSD (mg/d)</th>
<th>Geometric Model VSD (mg/d)</th>
<th>Linearized Multistage Model VSD (mg/d)</th>
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<tbody>
<tr>
<td>Promotion only</td>
<td>950</td>
<td>730</td>
<td>-</td>
</tr>
<tr>
<td>Mutation only</td>
<td>0.011</td>
<td>0.011</td>
<td>0.30</td>
</tr>
</tbody>
</table>

(Bogen, 1990)
Additional Reading:


Society of Toxicology 1993