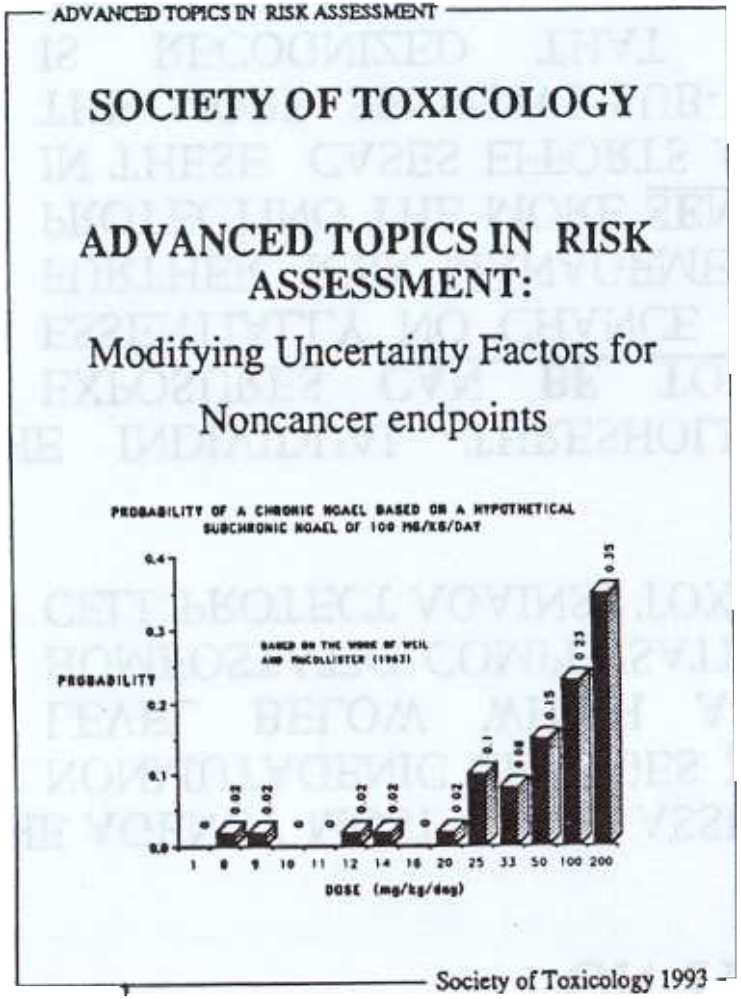
Dourson, M. L., 1993. Modifying Uncertainty Factors for Noncancer Endpoints. In: Advanced Topics in Risk Assessment. Society of Toxicology Continuing Education Course #10, 32nd Annual Meeting, New Orleans, Louisiana, March 14.



DISCUSSION POINTS:

The purpose of this lecture is to inform you of recent ideas and discussions on uncertainty factors used in the determination of "safe" (or subthreshold) doses, and to elicit your thoughts on the subject.

This area is still under development and can be improved by additional thought, publications, debates and discussions.

Basic principles in hazard identification and dose response assessment will only briefly be mentioned.

ON THRESHOLDS

THE AGENCY MOST OFTEN ASSUMES THAT NONCARCINOGENIC AND/OR NONMUTAGENIC CHANGES **HAVE A THRESHOLD,** THAT IS, A DOSE LEVEL BELOW WHICH A RESPONSE IS UNLIKELY, BECAUSE HOMEOSTATIC, COMPENSATION AND ADAPTIVE MECHANISMS IN THE CELL PROTECT AGAINST TOXIC EFFECTS.

THE INDIVIDUAL THRESHOLD HYPOTHESIS HOLDS THAT SOME EXPOSURES **CAN BE TOLERATED** BY AN ORGANISM WITH ESSENTIALLY NO CHANCE FOR EXPRESSION OF A TOXIC EFFECT. FURTHER, RISK MANAGEMENT DECISIONS FREQUENTLY FOCUS ON PROTECTING THE MORE **SENSITIVE MEMBERS OF A POPULATION**. IN THESE CASES EFFORTS ARE MADE TO KEEP EXPOSURES BELOW THE MORE SENSITIVE SUB-POPULATION THRESHOLD, ALTHOUGH IT IS RECOGNIZED THAT HYPERSENSITIVITY AND CHEMICAL IDIOSYNCRASY MAY EXIST AT YET LOWER DOSES.

ADVERSE EFFECTS ARE EITHER BIOCHEMICAL CHANGE, FUNCTIONAL IMPAIRMENT, OR PATHOLOGIC LESION WHICH IMPAIRS PERFORMANCE AND REDUCES THE ABILITY OF AN ORGANISM TO RESPOND TO ADDITIONAL CHALLENGE.

AN **ADAPTIVE EFFECT** ENHANCES AN ORGANISM'S PERFORMANCE AS A WHOLE AND/ OR ITS ABILITY TO WITHSTAND A CHALLENGE. AN INCREASE IN HEPATIC SMOOTH ENDOPLASMIC RETICULUM IS AN EXAMPLE OF AN ADAPTIVE EFFECT, IF HEPATIC METABOLISM REDUCES THE CHEMICAL'S TOXICITY.

A **COMPENSATORY EFFECT** MAINTAINS OVERALL FUNCTION WITHOUT ENHANCEMENT OR SIGNIFICANT COST. INCREASED RESPIRATION DUE TO METABOLIC ACIDOSIS IS AN EXAMPLE OF A COMPENSATORY EFFECT.

THE **CRITICAL EFFECTS** ARE THE FIRST ADVERSE EFFECTS OR THEIR KNOWN PRECURSORS THAT OCCUR AS DOSE RATE INCREASES.

SEVERITY IS THE DEGREE TO WHICH AN EFFECT CHANGES AND IMPAIRS THE FUNCTIONAL CAPACITY OF AN ORGAN SYSTEM

ADVANCED TOPICS IN RISK ASSESSMENT

AS DEFINED BY EXPERT WORK GROUPS

...an estimate (with uncertainty spanning perhaps an **order of magnitude**) of

a **daily** (for RfD) **or continuous** (for RfC) exposure to the human population (including **sensitive** subgroups)

that is **likely to be without** an appreciable risk of deleterious effects during a lifetime.

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DISCUSSION POINTS:

Expert work groups throughout the world support the use of a "safe" dose concept, and define terms and conditions for 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's definition of the terms RfD for oral doses and RfC for inhalation exposures are shown on the adjacent slide.

Many of the underlying assumptions, judgements on critical effect, and choices of uncertainty factors (or safety factors) are similar with these expert work groups in estimating these various subthreshold doses.

ADVANCED TOPICS IN RISK ASSESSMENT

UNCERTAINTY FACTORS

FACTOR*		EXTRAPOLATION
H	10	AVERAGE HUMAN TO SENSITIVE HUMAN
A	10 or 3**	ANIMAL TO HUMAN
S	≤10	SHORT TERM TO LONG TERM EXPOSURE
L	≤10	LOAEL TO NOAEL
D	≤10	MINIMUM TO COMPLETE DATA BASE

*These factors are as used by the U.S. EPA. Other health organiztions use similar factors. In EPA, The maximum UF for any given data base is 10,000. Data bases weaker than this are judged too uncertain to estimate RfD/RfCs.

**For RfCs the default UF for area "A," animal to human, is 3.

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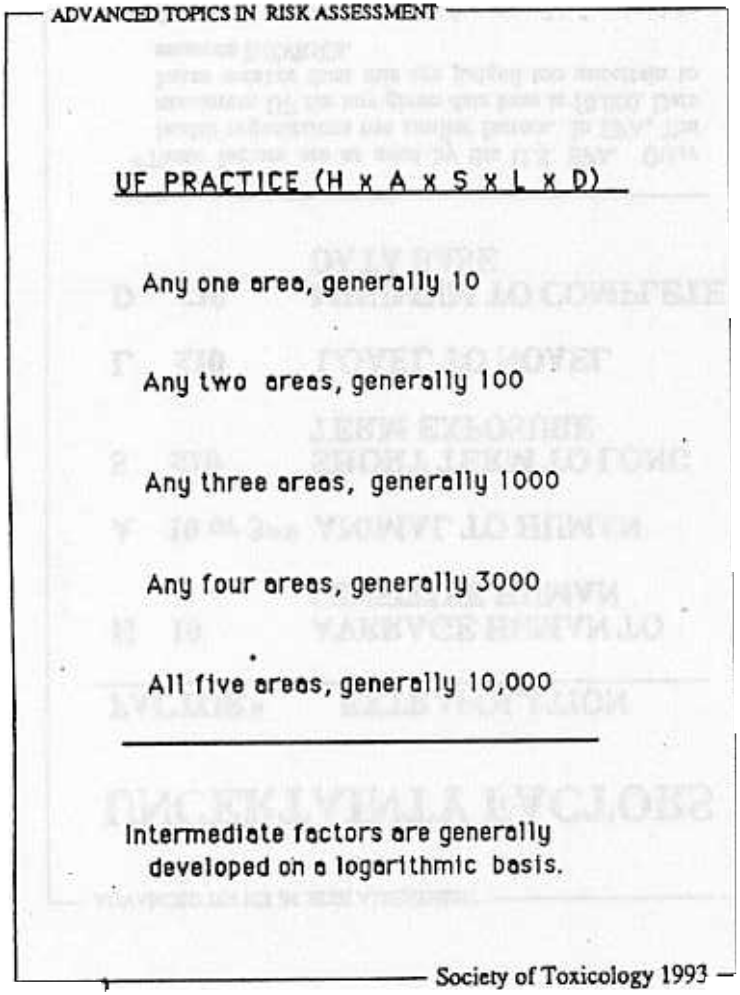
DISCUSSION POINTS:

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

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

Despited these differences, many similarities exist. In your opinion, what are ideal data to determine a protective value? When would uncertainty factors not be needed?



DISCUSSION POINTS:

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

As UFs increase in number, the composite "protectiveness" of resulting value (e.g., ADI) generally increases. This implies that as more data are brought into the data base 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 limitation and roll several areas of uncertainty together.

ADVANCED TOPICS IN RISK ASSESSMENT

Accuracy of an ADI

ADIs, MRLs, RfDs, RfCs or TIs are considered to be reasonable estimates of doses **below a toxicity threshold,** because they are based on a review of all toxicity data and individual uncertainty factors are considered to be somewhat protective. The use of several UFs can yield conservative estimates...

If you play golf, accurate drives are generally those that land in the fairway, although they may be scattered over a wide area.

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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 are cobalt in beer and the sedative thalidomide. In the former case, a population sensitive to the cardiomyopathy of cobalt 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 data base.

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).

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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.

Several areas of uncertainty are thought to overlap. For example, the dosimetric adjustments used in developing U.S. EPA's RfCs results in a reduction of the 10-fold factor from animal to human, to 3-fold. These adjustments may also impact the 10-fold factor for within human variability.

As the composite uncertainty factor grows larger, the imprecision of the resulting subthreshold dose also grows larger. This is due to a number of reasons, the primary one due to the underlying variability of the uncertainty factor.

RANGE OF THESE ESTIMATES

As a result of this accuracy and precision, these subthreshold estimates have an associated range. For example, 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 UFs.

What this means in general is that environmental exposures falling into the range of the subthreshold estimate **cannot be scientifically distinguished** from the estimate.

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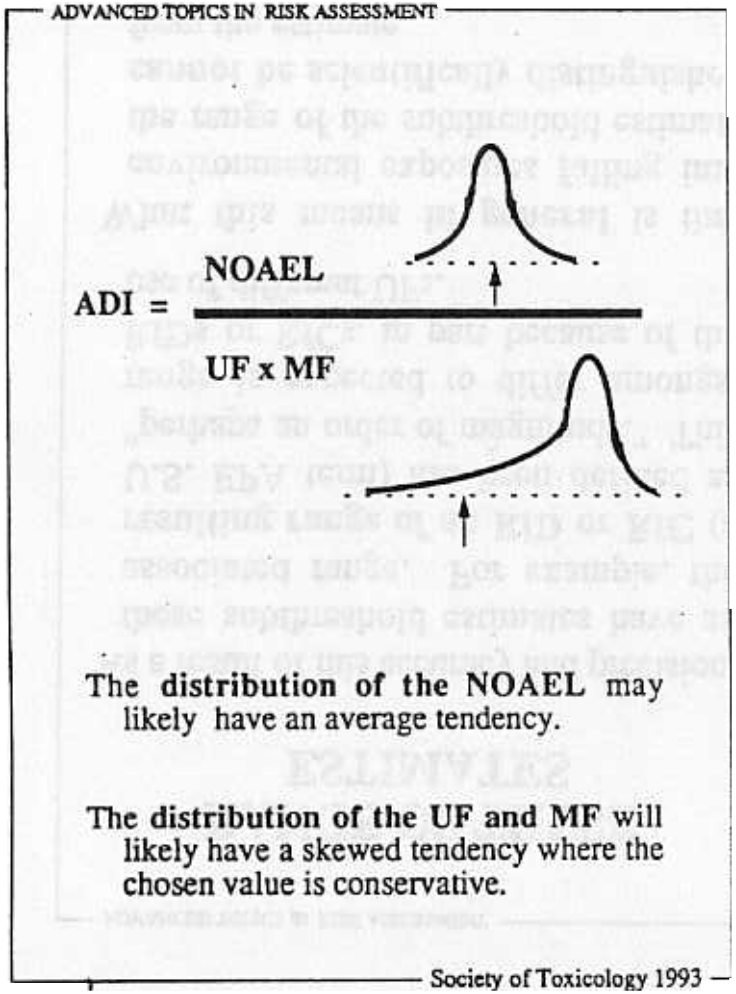
DISCUSSION POINTS:

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.

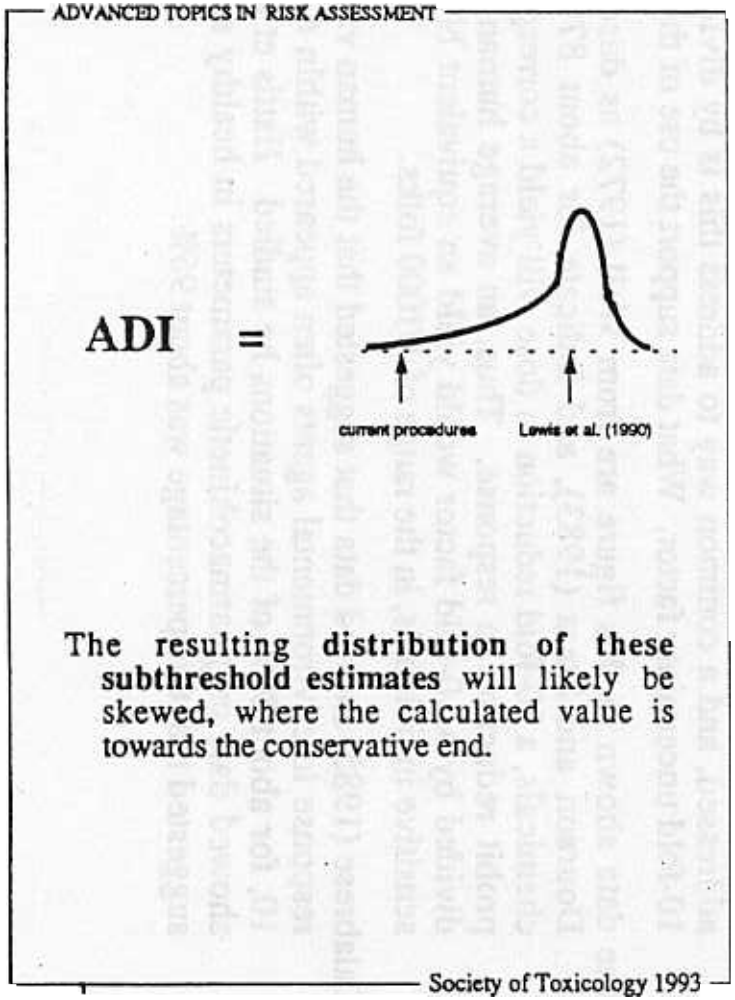


DISCUSSION POINTS:

One way to look at the estimation of these subthreshold doses is probabilistically.

The NOAEL is an experimental dose that does not show any adverse effects. As an experimental dose it may likely have a central tendency. For a discussion of the statistical uncertainty in NOAELs see Brown and Erdreich (1990) and Leisenring and Ryan (1992); for incidence of effects at the NOAEL see for example Gaylor (1992).

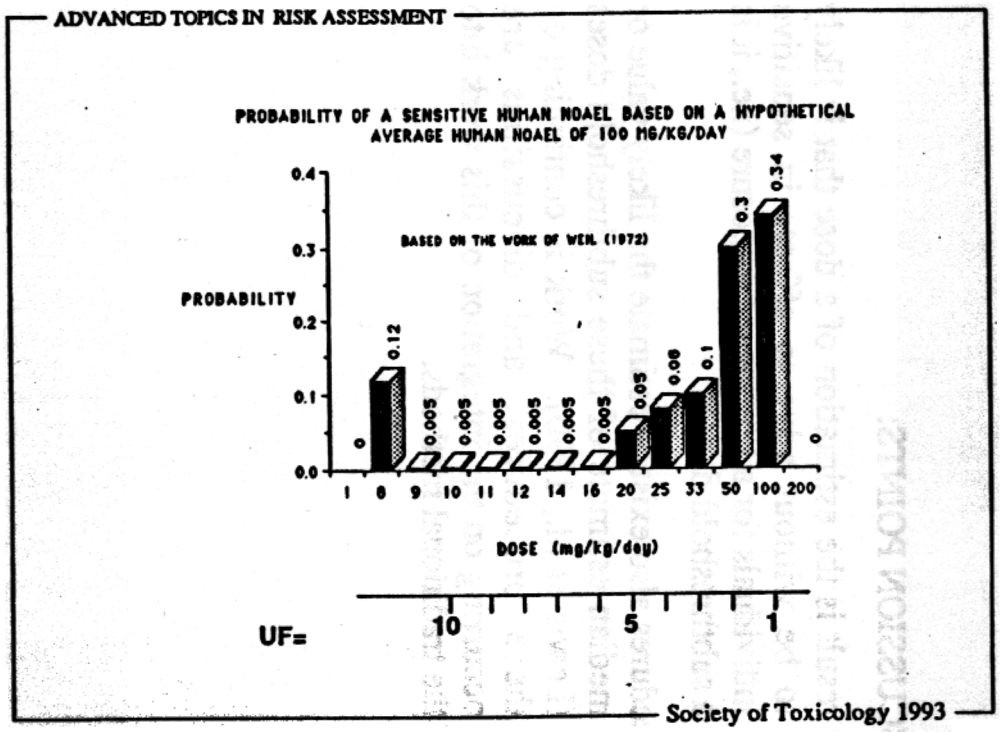
Uncertainty factors tend to be protective from the standpoint of the behavior of the average chemical (Dourson and Stara, 1983). Thus, composite uncertainty factors tend to be loose upper bound estimates. As discussed by Lewis et al. (1990), they are not average values.



DISCUSSION POINTS:

The result is the estimation of a dose that is likely to be without adverse effects in sensitive individuals for a lifetime of exposure (i.e., it is a subthreshold dose).

Procedures also exist to estimate the likely value or median estimate of these subthreshold doses (Lewis et al., 1990). Work is continuing on these procedures, and discussions are occurring on the integration of this work into the traditional methods.

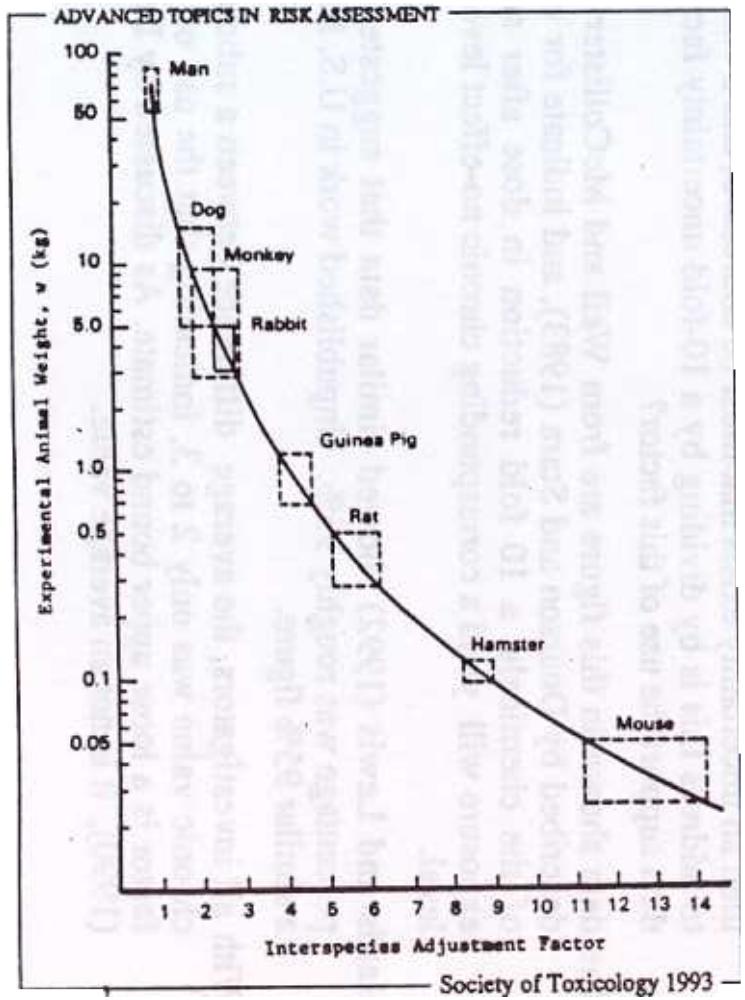


DISCUSSION POINTS:

If data in humans exist on which to base the estimation of a subthreshold dose, the question to ask is whether these data are in sensitive individuals. If not, then an uncertainty exists that must be addressed, and a common way to address this is by dividing by a 10-fold uncertainty factor. What data support the use of this factor?

The data shown in this figure are from Weil (1972) as described by Dourson and Stara (1983), and indicate for about 87% of the chemicals, a 10-fold reduction in dose will yield a corresponding 3 probit reduction in response. Thus, an average human NOAEL divided by a 10-fold factor would yield an equivalent NOAEL in sensitive individuals, in the range of 1/1000 folks.

Calabrese (1985) showed data that suggested that the human variation in response to environmental agents often appeared within a factor of 10, for about 80% of the situations he studied. Hattis et al (1987) showed data on pharmacokinetic parameters in healthy adults that suggested that this percentage was about 96%.



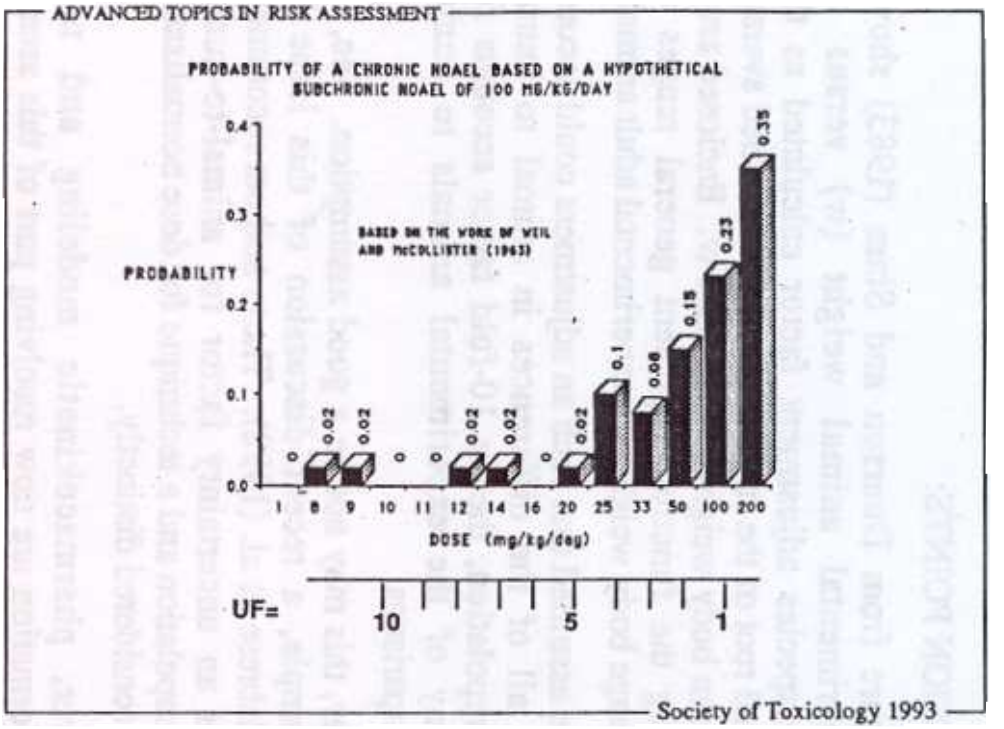
DISCUSSION POINTS:

This figure from Dourson and Stara (1983) shows experimental animal weight (w) versus an interspecies adjustment factor calculated as the cubed root of the ratio between the assumed average human body weight (70 kg) and w. Enclosed areas along the function represent general ranges of average body weights of experimental adult animals.

If it were assumed that such an adjustment could account for all of the differences in animal to human extrapolation, then a 10-fold factor accounts for many of the experimental animals to human comparisons.

However, this may not be a good assumption. See, for example, a recent discussion of this issue by Calabrese et al. (1992). These authors recommend that an uncertainty factor for animal-to-human extrapolation and a technique for dose normalization be considered distinctly.

Moreover, pharmacokinetic modeling and new information are now resolving part of this area of uncertainty. For example, in an earlier lecture in this course (A. Jarabek), the default uncertainty factor for animal to human when estimating RfCs has been reduced from 10 to 3 on the basis of known dosimetric adjustments between animals and humans.



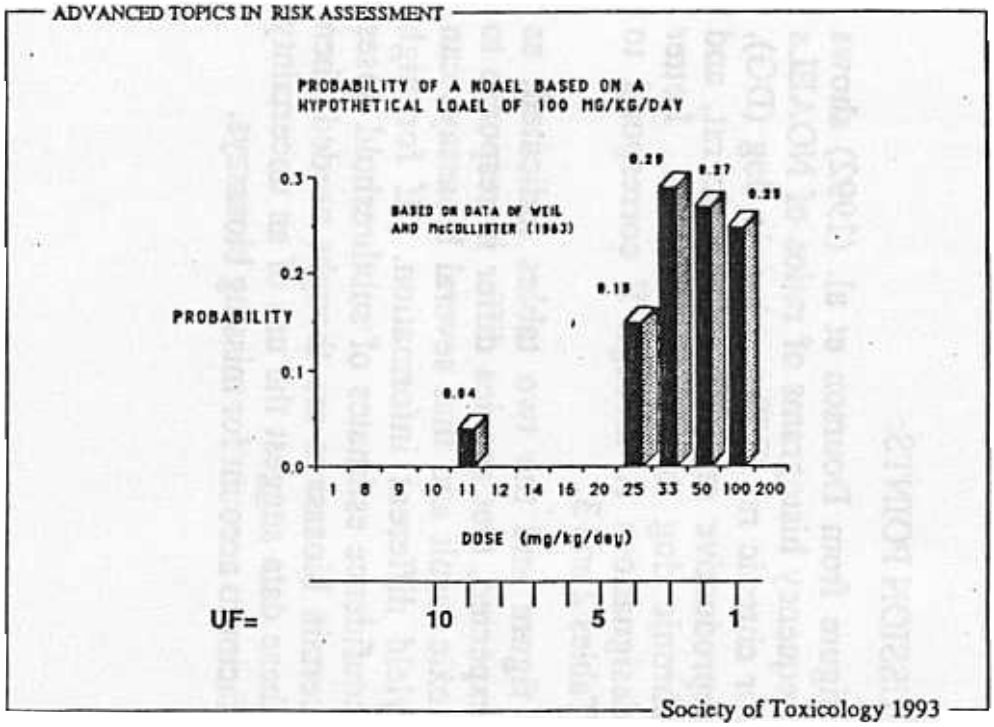
DISCUSSION POINTS:

If data in subchronic studies exist on which to base the estimation of a subthreshold dose, the question to ask is whether data in chronic studies would yield lower NOAELs. If so or if this is not known, then an uncertainty exists that must be addressed, and a common way to address this is by dividing by a 10-fold uncertainty factor. What data support the use of this factor?

The data shown in this figure are from Weil and McCollister (1963) as described by Dourson and Stara (1983), and indicate for about 96% of the chemicals, a 10 fold reduction in dose after subchronic exposure will yield a corresponding chronic no-effect level or effect level.

Hattis and Lewis (1992) showed similar data that suggested that this percentage was roughly 95%. Unpublished work in U.S. EPA shows a similar 95% figure.

With all investigators, the average difference between a subchronic and chronic value was only 2 to 3, indicating that the use of a 10-fold factor is a loose upper bound estimate. As discussed by Lewis et al. (1990), it is not an average value.



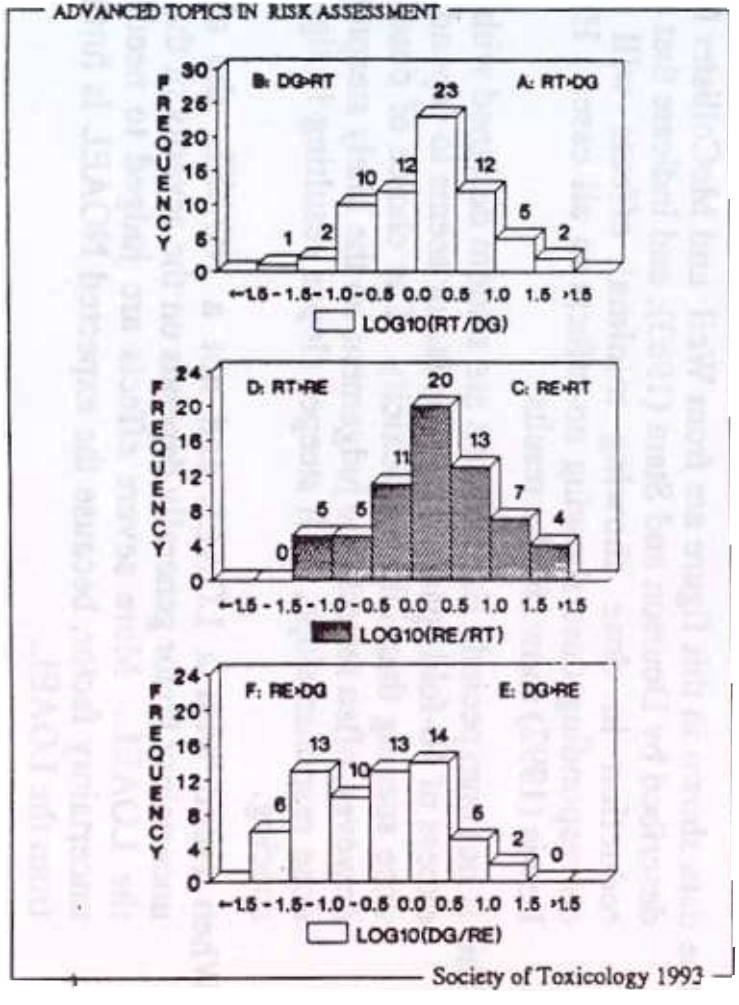
DISCUSSION POINTS:

If a LOAEL exists on which to base the estimation of a subthreshold dose, the question to ask is whether a 10-fold reduction would yield a NOAEL.

The data shown in this figure are from Weil and McCollister (1963) as described by Dourson and Stara (1983), and indicate that a 10 fold reduction in dose showing minimal effects will yield a corresponding dose showing no-effects in all cases. Hattis and Lewis (1992) show similar results.

This is not unexpected. Experiments are seldom designed with doses in excess of 10-fold apart. Thus, this factor seems to depend more on dose spacing than inherent toxicity. The choice of dose spacing, however, often reflects the judgement on the likely steepness of the dose response slope, with steeper slopes resulting in tighter dose spacing.

When faced with a LOAEL and not a NOAEL, the choice of uncertainty factor generally depends on the severity of the effect at the LOAEL. More severe effects are judged to need a larger uncertainty factor, because the expected NOAEL is further away from the LOAEL.



DISCUSSION POINTS:

This figure from Dourson et al. (1992) shows frequency histograms of ratios of NOAELs for chronic rat (RT) to chronic dog (DG), reproductive rat (RE) to chronic rat, and chronic dog to reproductive rat. Letter designations A through F correspond to Tables 2 and 3.

This figure and the two tables indicated, as expected, that species differ in response to toxic insult and that several bioassays can yield different information. If for high confidence estimates of subthreshold doses certain bioassays are thought needed, then these data suggest the use of an uncertainty factor to account for missing bioassays.

ADVANCED TOPICS IN RISK ASSESSMENT

TABLE 2
Probabilities for All Ratios
Event: $NOAEL_1 \geq NOAEL_2 * 10^k$

Event Label	$NOAEL_1$	$NOAEL_2$	Probability of Event $k = 0.5$	$k = 1.0$	$k = 1.5$
A	RT	DG	0.28	0.10	0.03
B	DG	RT	0.19	0.04	0.01
C	RE	RT	0.37	0.17	0.06
D	RT	RE	0.15	0.08	0.00
E	DG	RE	0.11	0.03	0.00
F	RE	DG	0.46	0.30	0.10
G	DG	MS	0.03	0.00	0.00
H	MS	DG	0.67	0.50	0.17
I	RT	MS	0.03	0.00	0.00
J	MS	RT	0.44	0.25	0.06
K	RE	MS	0.13	0.00	0.00
L	MS	RE	0.35	0.19	0.06
M	DG	DV	0.05	0.03	0.00
N	DV	DG	0.66	0.44	0.23
O	RT	DV	0.05	0.03	0.02
P	DV	RT	0.65	0.48	0.19
Q	RE	DV	0.13	0.02	0.00
R	DV	RE	0.50	0.37	0.10
S	MS	DV	0.16	0.09	0.00
T	DV	MS	0.38	0.22	0.06

RT = Chronic Rat, DG = Chronic Dog, RE = Reproductive Rat, MS = Mouse, DV = Developmental Toxicity

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DISCUSSION POINTS:

This table shows the probabilities associated with ratios of chronic toxicity dog, chronic toxicity rat, reproductive toxicity rat, chronic toxicity mouse and developmental toxicity rat NOAELs, one to another. These probabilities are listed for values of "k," which is the exponent to the value of 10.

The interpretation of this table is really straight-foward. For example, in the first line of the table the chronic rat and chronic dog NOAELs are compared. The value of k = 0.5 represents 10 raised to the 0.5 power, or a value of about 3. The probability of 0.28 listed for this event is the probability that the chronic rat NOAEL will exceed 3 times the chronic dog NOAEL.

This probability of 0.28 is compiled from the previous figure, event A: RT>DG (top chart), by adding frequencies of 12, 5 and 2 together and dividing this sum by the total frequency of 67.

TABLE 3
Combined Probabilities for the First Set of Ratios

Study Present	Events Occurring*	Probability Formula	Probability of Events Occurring by a Factor of 10^k		
			$k = 0.5$	$k = 1.0$	$k = 1.5$
RT	$A \cup D$	$P(A) + P(D) - P(A\|D)P(D)$	0.37	0.16	0.03
DG	$B \cup E$	$P(B) + P(E) - P(B\|E)P(E)$	0.24	0.06	0.01
RE	$C \cup F$	$P(C) + P(F) - P(C\|F)P(F)$	0.62	0.39	0.13
RT, DG	$D \cap E$	$P(D\|E)P(E)$	0.06	0.00	0.00
RT, RE	$A \cap F$	$P(A\|F)P(F)$	0.18	0.04	0.00
DG, RE	$B \cap C$	$P(B\|C)P(C)$	0.12	0.02	0.00
RT, DG, RE	None	—	0.00	0.00	0.00

*Events which must occur if the missing studies are to undercut the lowest NOAEL available. $\cap$ = intersection; $\cup$ = Union

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DISCUSSION POINTS:

This table shows the probabilities associated with combinations of the individual ratios' probabilities of the previous figure and table. These probabilities are also listed for values of "k," which is the exponent to the value of 10.

The interpretation of this table is less straight-foward than the first one. For example, suppose that the chronic rat is the only NOAEL available, out of a three study data base (the first line of this table). The probability of 0.37 listed for a "k" value of 0.5 is the probability that the chronic rat NOAEL would be undercut by 3-fold by either a dog or reproductive rat NOAEL, if these studies were available. This probability of 0.37 is compiled from the union of events A and D of the previous figure.

As a second study is added to the data base, the probabilities at each "k" value decrease. This is expected. As a second study is added, the probability that the remaining study can undercut the available two NOAELs also must decrease. A close study of this table also leads to certain conclusions about the sensitivity of the various studies.

MAJOR ASSUMPTIONS AND LIMITATIONS OF THESE MODELS

Major assumptions are...

a population threshold exists,

these estimates represents subthreshold doses, and

preventing the critical effect protects against all effects.

Major limitations are...

NOAEL of the critical effects ignores much of the data and often does not distinguish amongst better quality studies,

uncertainty factors are imprecise, and

risks above these estimates of subthreshold doses are not estimated.

THE MOST CRITICAL AREAS FOR RESEARCH AND DEVELOPMENT

Thresholds for toxic effect are demonstrable theoretically for many compounds on mechanistic grounds. It should be experimentally possible to determine the likely threshold dose in humans for certain effects (e.g., cyanide poisoning).

How can the **statistical variability** of any chosen NOAEL be determined?

What is the **within human variability** to toxic effects for any chosen class of chemicals?

What is the proper **scaling between animal and human** for dose and duration for any chosen class of chemicals?

Are **toxicokinetic/toxicodynamic** models generallizable to situations with less data?

How can the **overall uncertainty** in the risk assessment problem be addressed?

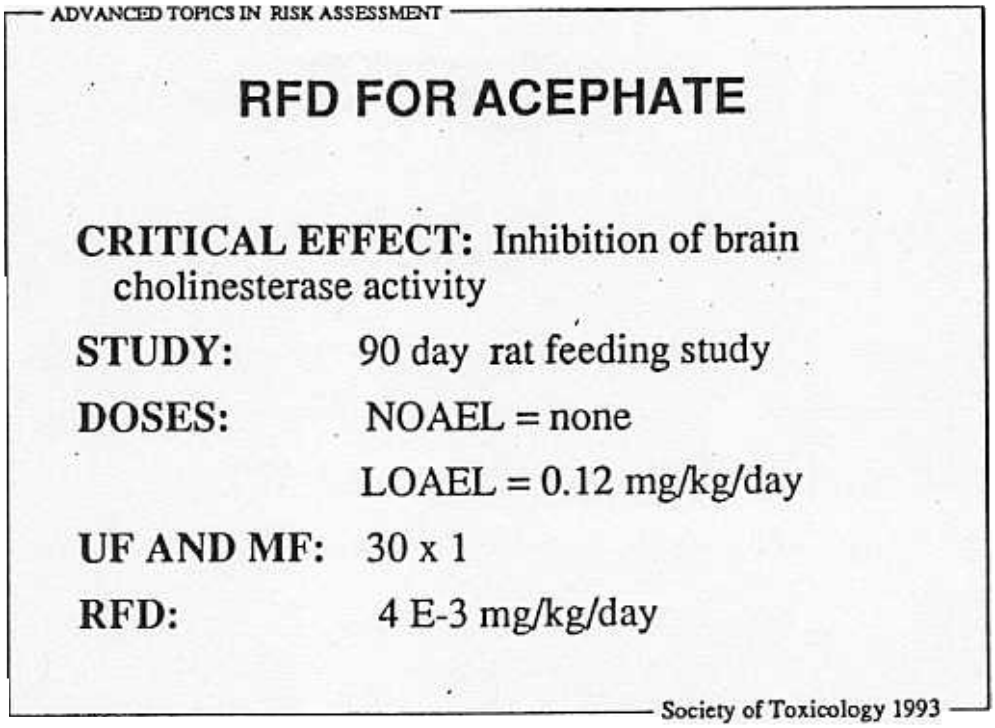
THE MOST CRITICAL AREAS FOR RESEARCH AND DEVELOPMENT

Develop **biologically-based** dose-response models for target organs of interest, e.g., liver.

Develop **hazard identification** guidelines for target organs of interest, e.g., immune system.

Integrate **comparative species** morphometrics, toxicokinetics and response into the present risk assessment process, e.g., inhalation RfC.

Experimentally **test the theoretical work** in this area of science described by a number of investigators.



APPENDIX:

The following examples on acephate, acrylonitrile and nitrate are taken from U.S. EPA's Integrated Risk Information System (IRIS). These examples show some of the types of data that are used to adjust the standard 10-fold uncertainty factors. These judgements occur quite often as indicated by a random search of EPA's IRIS.

ACEPHATE RFD: UNCERTAINTY AND MODIFYING FACTORS

UF = 30. The human study and the comparative in vitro studies were considered by the RfD/RfC Work Group when evaluating the data base for acephate. ...In vitro studies on the affinity of acephate to human brain, RBC and plasma ChE, show differences of less than 10-fold.

...Agency concluded that both the human study and the in vitro data could be used to support a modification of the customary 100-fold uncertainty faactor used for brain cholinesterase inhibition. This 100-fold factor was reduced to 10 (e.g., the 10-fold factor from animal to man was not considered necessary).

Furthermore, a 3-fold factor was used because a NOEL was not determined in the critical study. This intermediate factor of 3 was considered as more appropriate than 10 because the LEL dose was concluded to represent a threshold dose.

Finally, the 10-fold factor normally used to estimate an RfD using subchronic data was not considered necessary, since the results after subchronic exposure are similar in both severity and magnitude as for chronic studies.

MF = 1

STUDY: MEDIUM
DATA BASE: HIGH
RFD: HIGH

CONFIDENCE IN THE ACEPHATE RFD

The critical study is of adequate quality and given a medium confidence rating. Additional studies are also of good quality; therefore, the data base is given a high confidence rating. High confidence in the RfD follows.

RFC FOR ACRYLONITRILE

CRITICAL EFFECT: Degeneration and inflammation of nasal respiratory epithelium

STUDY:	2-year rat inhalation study
DOSES:	NOAEL = none
	LOAEL (HEC) = 1.9 mg/m3
UF AND MF:	1000 x 1
RFD:	2 E-3 mg/m3

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ACRYLONITRILE RFC: UNCERTAINTY AND MODIFYING FACTORS

UF = 1000. The uncertainty factor of 1000 reflects a factor of 10 to protect unusually sensitive individuals

and 3 to adjust from a minimally adverse LOAEL to a NOAEL.

An uncertainty factor of 3 for interspecies variability is used because the use of the dosimetric adjustments accounts for part of this area of uncertainty.

An additional factor of 10 is applied due to an incomplete data base, or more specifically, the lack of an inhalation bioassay in a second species, and the lack of reproductive data by the inhalation route with the existence of an oral study showing reproductive effects.

MF = 1

STUDY: MEDIUM
DATA BASE: MEDIUM
RFD: MEDIUM

CONFIDENCE IN THE ACRYLONITRILE RFD

The principal study is given medium confidence because although it was a well-conducted chronic study in an appropriate number of animal (100/sex/concentration), it was performed on only one species, did not identify a NOAEL, was confounded by the early sacrifice of rats with large mamary gland tumors and the target organ (nasal turbinates) was only examined at the end of the study in relatively few animals (10-12/sex/concentration).

Confidence in the data base can be considered medium to low due to a lack of chronic or subchronic inhalation data in a second species, the lack of reproductive data by the inhalation route and the existence of an oral study showing reproductive effects.

Confidence in the RfC can also be considered medium to low.

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RFD FOR NITRATE

CRITICAL EFFECT: Early clinical signs of methemoglobinemia in excess of 10%

STUDY: Human epidemiological surveys

DOSES: NOAEL = 1.6 mg/kg/day

LOAEL = 1.8-3.2 mg/kg/day

UF AND MF: 1

RFD: 1.6 mg/kg/day

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NITRATE RFD: UNCERTAINTY AND MODIFYING FACTORS

UF = 1. An UF of 1 was employed because available data define the no-observed adverse-effect level for the critical toxic effect in the most sensitive human subpopulation.

MF = 1.

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STUDY: HIGH
DATA BASE: HIGH
RFD: HIGH

CONFIDENCE IN THE NITRATE RFD

The studies of Bosch et al. (1950) and Walton (1951) provide convincing evidence that infantile methemoglobinemia does not occur at drinking water levels of 10 mg nitrate-nitrogen/L or less. These studies rate high confidence.

This is supported by a large number of additional epidemiological and case studies in humans (e.g., Cornblath and Hartman, 1948; Simon et al., 1964; Toussaint and Selenka, 1970; Craun et al., 1981; see U.S. EPA's Integrated Risk Information System for descriptions of additional studies. Thus, the data base rates high confidence.

High confidence in the RfD follows.

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READING LIST

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