Recent Innovations in IRIS Health Assessments

Joint Meeting of
The Environmental Health Committee and
The Integrated Human Exposure Committee
U.S. EPA Science Advisory Board

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September 6, 2006

Outline of Presentation

- *Introduction – IRIS Program*
- *Scientific advances in the IRIS Program*
- *Examples of recent scientific advances in IRIS assessments*
- *Examples of use of MOA data in IRIS cancer assessments*
- *Summary*

USEPA's Integrated Risk Information System (IRIS) Program

- *IRIS provides qualitative and quantitative health effects information on over 500 substances*
- *Many high-profile, first applications of risk assessment guidelines and science policy*
- *Reference Dose (RfD)/Reference Concentration (RfC): An estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral or inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.*
- *Cancer risk: Hazard characterization, oral slope factors and inhalation unit risks*
- *Improvements in transparency, consistency, and timeliness*
- *http://www.epa.gov/iris*

Major Recurring Issues and Advances in the IRIS Program

- *Use of data from human studies in health assessments*
- *Accounting for less-than-lifetime exposure durations*
- *Qualitative and quantitative use of mode of action data in noncancer and cancer assessments*
- *Benchmark dose modeling and selection of the benchmark response*
- *Evaluation and use of PBPK models*
- *Accounting for life-stage and subpopulation susceptibility in uncertainty factors*
- *Use of data-derived uncertainty factors*
- *Characterization of uncertainty in noncancer and cancer analysis*
- *Use of time-to-tumor modeling for cancer assessments*

Recent Advances in IRIS Assessments

Pilot Program for Assessing Hazard from Less-than-lifetime Exposure

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- *Pilot for IRIS assessments with less-than-lifetime exposure durations*
  - *Acute: <=24 hours*
  - *Short-term: >24 hours up to 30 days*
  - *Longer-term: up to 10% of life span*
  - *Chronic: Greater than 10% of life span*
- *Assessments in pilot*
  - *Two assessments for all four exposure durations*
    - *Dibutylphthalate*
    - *1,1,1-Trichloroethane*
  - *Four assessments for acute exposure only*
    - *Hydrogen sulfide*
    - *Hexachlorocyclopentadiene*
    - *Ethylene oxide (chronic cancer assessment also underway)*
    - *Phosgene (chronic assessment completed in 2005)*

Different Approaches for the Use of Human Data

Example: Toluene

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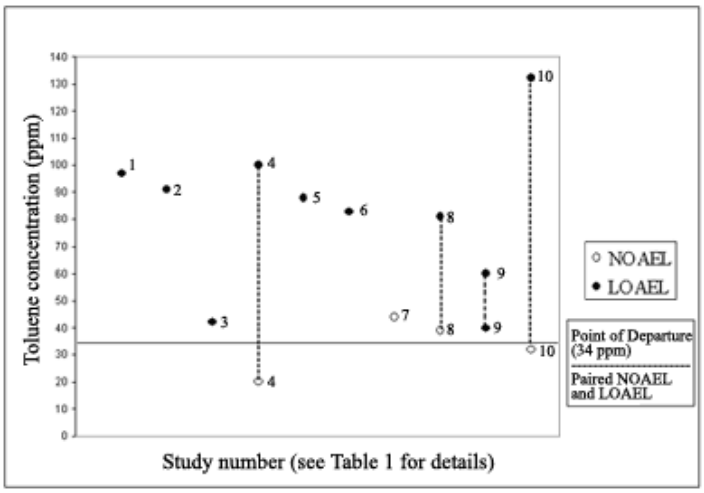
IRIS Summary: RfC for Toluene

--1.B.1. Inhalation RfC Summary

Critical Effect	Experimental Doses	UF	RfC
Neurological effects in occupationally-exposed workers Multiple human studies (see Table 1 and Figure 1)	NOAEL (average): 34 ppm (128 mg/m^3) NOAEL (ADJ)*: 46 mg/m^3	10**	5 mg/m^3

*The NOAEL (ADJ) is an 8-hour TWA occupational exposure adjusted to continuous exposure.
**UF(H)=10
Source: U.S. EPA (2005) IRIS Summary for Toluene. www.epa.gov/iris

Figure 1. Summary of NOAELs/LOAELs for neurological endpoints for a subset of occupational studies of chronic inhalation exposure to toluene.



Adjustment Factors

Example: Boron

IRIS Summary: RfD for Boron

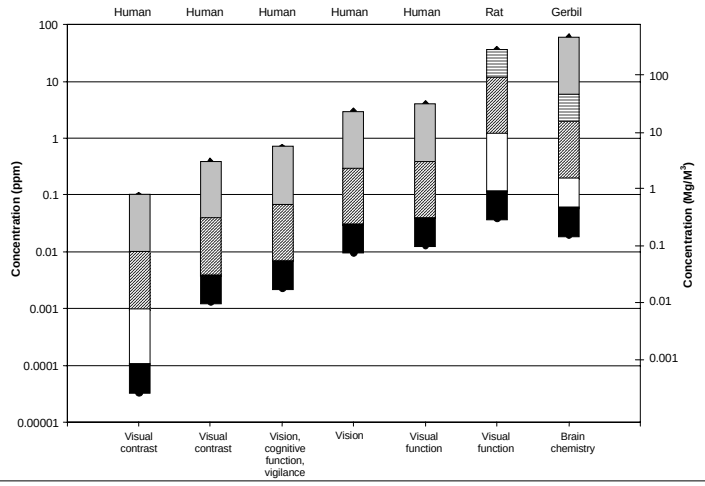
--1.A.1. Oral RfD Summary

Critical Effect	Experimental Doses	UF	RfD
Decreased fetal weight (developmental) Rat dietary gestational exposure to boric acid Price et al., 1996a Heindel et al., 1992	$BMDL_{05}$: 10.3 mg/kg-day	66*	2E-1 mg/kg-day

*The UF is data-derived and is based on variability and uncertainty in toxicokinetics and toxicodynamics.
Source: U.S. EPA (2004) IRIS Summary for Boron.
www.epa.gov/iris

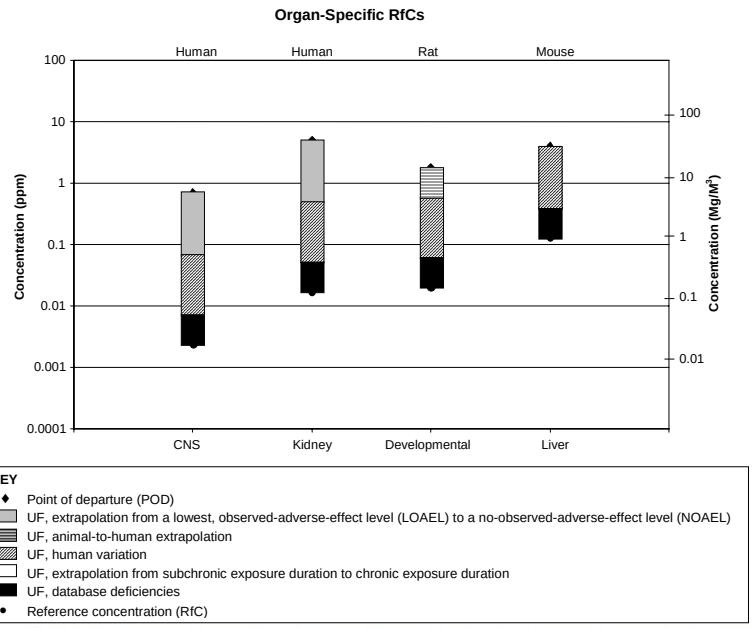
Data Arrays and Organ-Specific Reference Values

CNS Toxicity: Inhalation



KEY

- ♦ Point of departure (POD)
- UF, extrapolation from a lowest, observed-adverse-effect level (LOAEL) to a no-observed-adverse-effect level (NOAEL)
- UF, animal-to-human extrapolation
- UF, human variation
- UF, extrapolation from subchronic exposure duration to chronic exposure duration
- UF, database deficiencies
- • Reference concentration (RfC)



Use of Mode of Action Data in Cancer Assessment

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Key Features of Cancer Guidelines

- *Analyze data before invoking default options.*
- *Framework for mode of action.*
- *Weight-of-evidence narrative for human cancer potential replaces the previous alpha-numeric classification system*
- *Two-step dose-response process separates*
  1. *modeling the observed data, from*
  2. *extrapolation to lower doses.*
- *Linear and nonlinear extrapolations are considered.*
- *Differential risks to susceptible populations and life-stages are considered.*
- *Characterization of qualitative and quantitative uncertainty*
- *Evaluation of mutagenicity as a mode of carcinogenic action*

Mode of Action Framework

- *Summary description of the hypothesized mode of action (MOA)*
- *Identification of key events*
- *Strength, consistency, specificity of association*
- *Dose-response concordance*
- *Temporal relationship*
- *Biological plausibility and coherence*
- *Consideration of the possibility of other MOAs*

Conclusions about the MOA

- *Is the mode of action sufficiently supported in the test animals?*
- *Is the mode of action relevant to humans?*
- *Which populations or life-stages can be particularly susceptible to the mode of action?*
  - *Question is both qualitative and quantitative*
  - *Quantitative differences may be used in the dose-response assessment*

Current IRIS Cancer Assessments with a MOA Analysis

- Chloroform

  (oral assessment on IRIS in 2001)
  - *"available evidence indicates that chloroform-induced carcinogenicity is secondary to cytotoxicity and regenerative hyperplasia"*
  - *"cancer risk to the fetus or children would be a function of cytotoxic injury, like in adults, and protecting these life stages from sufficient cytotoxicity to elicit this response should protect against cancer risks"*
  - *the Agency relied on a nonlinear dose-response approach and the use of a margin-of-exposure analysis for cancer risk based on interim guidelines*

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Ongoing Cancer Assessments in the IRIS Program

- ~35 assessments underway for chemicals that induce tumor formation in animals
- most chemicals have limited MOA data
- more data-rich chemicals include acrylamide, arsenic, EGBE, carbon tetrachloride, acrylonitrile, benzo[a]pyrene, ethylene oxide
- MOA analysis being performed in each case

Major Issues Related to the Use of MOA Data

- Defining a key event
- Amount and type of data needed to support a MOA for qualitative and quantitative purposes
- Data needs for determining a mutagenic MOA

MOA Analysis for Carcinogenicity

Example: Draft Ethylene Oxide Assessment

Ethylene Oxide

- ***Hypothesis:*** *EtO carcinogenicity has a mutagenic mode of action that is presumed to apply to all of the tumor types*
- ***Key events:*** *DNA adduct formation resulting in genetic damage, including the formation of point mutations as well as translocations*
- ***Postulated Mode of Action:*** *Mutagenicity is a well-established cause of carcinogenicity*

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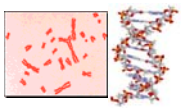
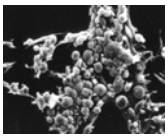
Postulated Mode Of Action for Ethylene Oxide

DNA adducts/
Chromosomal Damage



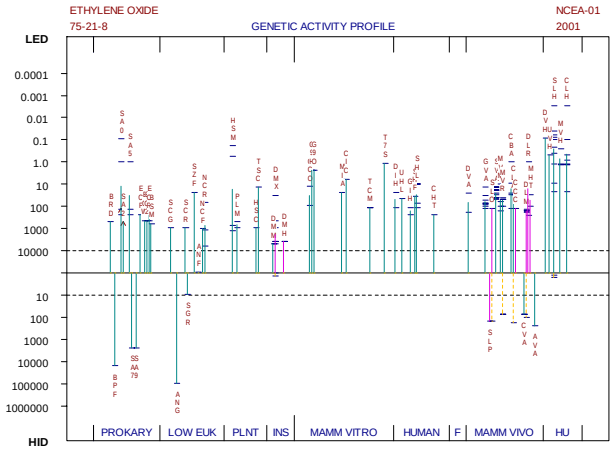
Key Events

Cell Proliferation



Tumor Development

Genetic Profile of EtO



IARC human carcinogen (group 1: human - limited, animal - sufficient)

Display of 203 datasets, including bacteria, fungi, plants, insects and mammals (in vitro and in vivo), measuring the full range of genotoxic endpoints (This is an updated version of the figure in IARC, 1994).

Is the hypothesized mode of action relevant to humans?

- *EtO is a systemic mutagen in test animals; thus, there is the presumption that it would also be a mutagen in humans.*
- *Several studies of humans have reported exposure-response relationships between hemoglobin adduct levels and EtO exposure levels.*
- *EtO causes chromosomal aberrations, SCEs, and micronucleus formation in human peripheral blood lymphocytes.*
- *There is strong evidence that EtO causes cancer in humans, including cancer types observed in rodent studies.*

Which populations or lifestages can be particularly susceptible to the hypothesized mode of action?

- *EtO acts through mutagenic mode of action for carcinogenicity*
- *A mutagenic mode of action is considered relevant to all populations and lifestages*
- *There may be increased susceptibility to early-life exposures for carcinogens with a mutagenic mode of action (EPA's Supplemental Guidance)*

MOA Analysis for Carcinogenicity

Example: Draft EGBE Assessment

Ethylene Glycol Monobutyl Ether (EGBE)

- ***Hypothesis:*** *EGBE increases the incidence of hemangiosarcomas and hepatocellular tumors in male mice and forestomach tumors in female mice. The formation of these tumors is specific for male and female mice and is not relevant to humans.*
- ***Key events:*** *Available mode of action data indicate species-specific hemolysis in male mice leading to oxidative damage in endothelial cells and species-specific retention of EGBE in the forestomach and subsequent formation of an irritant metabolite in female mice.*
- ***Postulated Mode of Action:*** *Hemolysis and subsequent oxidant damage in male mice and chronic irritation in female mice.*

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Ethylene Glycol Mono-butyl Ether (EGBE) MOA for Hemangiosarcomas & Hepatocellular Tumors in Male Mice

Event	Biological plausibility	WOE	Human Relevance
1. **EGBE metabolism to butoxyacetic acid (BAA) by alcohol dehydrogenase**	**Moderate** EGBE metabolized to BAA in rat and mouse, but tumor only seen in male mouse	Moderate/ Strong	High/ Moderate
2. **Red blood cell hemolysis by BAA**	**Moderate** Hemolysis is observed in rat and mouse, but tumor only seen in male mouse	Moderate/ Strong	Low
3. **Buildup of hemosiderin in Kupffer cells of liver**	**Moderate** Buildup in rat & mouse, but tumor only seen in male mouse; Consistent with other NTP studies	Moderate/ Strong	Not Likely
4a. **Production of reactive oxygen species by Fenton or Haber-Weiss reactions**	**High** $FeSO_4$ causes ox. Damage to SVEC4-10 mouse endothelial cells, SHE cells, rodent hepatocytes; EGBE & BAA do not	Weak/ Moderate	Not Likely
4b. **Kupffer cells activated and release cytokines**	**Moderate**	Moderate	Not Likely

EGBE MOA for Hemangiosarcomas & Hepatocellular Tumors in Male Mice

Event	Biological plausibility	WOE	Human Relevance
5. **Reactive oxygen species results in oxidative DNA damage to endothelial cells**	High More pronounced in male mouse than in female mouse or rat. Male mouse is more susceptible to liver tumors	Weak/ Moderate	Not Likely
6. **Modulation of endothelial cell gene expression**	Moderate EGBE & metabolites are not genotoxic	Weak	Not Likely
7. **Endothelial cell proliferation**	Moderate EGBE & metabolites are not genotoxic	Moderate/ Strong	Not Likely
8. **Promotion of initiated endothelial cells**	High	Weak	Not Likely
9. **Neoplasm formation**	High Reason for male sensitivity unknown	Moderate/ Strong	Not Likely

Summary

- *Advances in the development of IRIS assessments have led to the identification of emerging issues for consideration*
  - *less-than-lifetime toxicity values*
  - *use of human data*
  - *data-derived adjustment factors*
  - *data arrays and organ-specific toxicity values*
  - *use of mode of action data*

- *The IRIS Program is leading the advancement of the state of the science for health assessments.*