United States Environmental Protection Agency

U.S. EPA's Integrated Risk Information System (IRIS)

Xabier Arzuaga PhD
Integrated Risk Information System Program
National Center for Environmental Assessment
Office of Research and Development

US Environmental Protection Agency

- The mission of the Environmental Protection Agency is to protect human health and the environment.
- Since 1970, EPA has been working for a cleaner, healthier environment for the American people.
- EPA employs 17,000 people across the United States, including the headquarters offices in Washington, DC, 10 regional offices, and more than a dozen labs.
- EPA staff are highly educated and technically trained; more than half are engineers, scientists, and policy analysts.
- In addition, a large number of employees are legal, public affairs, financial, information management and computer specialists.

United States Environmental Protection Agency

What Is Risk?

- Hazard
  - Any potential source of harm
- Risk
  - The probability of adverse effects resulting from exposure to an environmental agent or mixture of agents.

United States Environmental Protection Agency

Definition of Risk Assessment for Exposure to Environmental Agents

Risk Assessment: The evaluation of scientific information on the hazardous properties of environmental agents (hazard identification), the dose-response relationship (dose-response assessment), and the extent of human exposure to those agents (exposure assessment). The product of the risk assessment is a statement regarding the probability that populations or individuals so exposed will be harmed and to what degree (risk characterization).

Risk assessment is used to facilitate the application of science to policy.

United States Environmental Protection Agency

Hazard Characterization

A description of the potential adverse health effects attributable to a specific environmental agent, the mechanisms by which agents exert their toxic effects (mode of action), and the associated dose, route, duration, and timing of exposure.

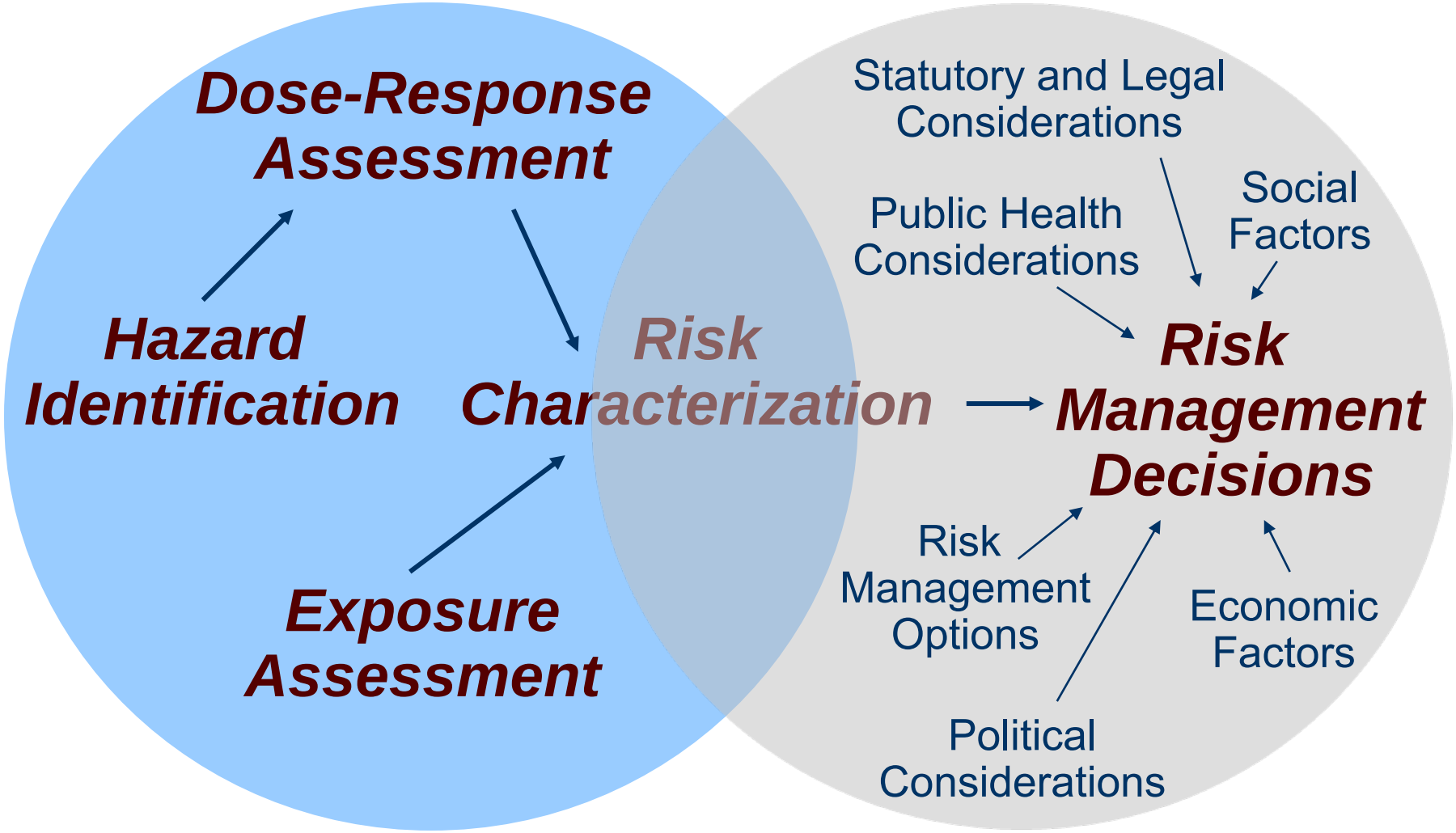
United States Environmental Protection Agency

Dose-Response Assessment

A determination of the relationship between the magnitude of an administered, applied, or internal dose and a specific biological response.

Response can be expressed as measured or observed incidence or change in level of response, percent response in groups of subjects (or populations), or the probability of occurrence or change in level of response within a population.

Risk Assessment / Risk Management



Risk Paradigm Alignment in EPA's Office of Research and Development

United States Environmental Protection Agency

National Health and Environmental Effects Research Laboratory

Research on mechanisms and susceptibility to identify hazards and dose-response

National Exposure Research Laboratory

Research to measure, characterize and assess exposures and to support compliance with environmental regulations and policies

National Risk Management Research Laboratory

Research and technology transfer to prevent, mitigate and control pollution

National Center for Computational Toxicology

Application of computational tools and models to improve understanding of toxicity and risks posed by environmental agents.

National Center for Environmental Assessment

Development of human health assessments, research on risk assessment methods, and guidance development

National Homeland Security Research Center

Research to help decision-makers prepare and respond to chemical and biological attacks

National Center for Environmental Research

Extramural program - grants, fellowships, and national centers of excellence - to complement ORD's in-house research program

United States Environmental Protection Agency

National Center for Environmental Assessment (NCEA)

NCEA occupies a critical position in EPA's Office of Research and Development between:

- The research labs (e.g. NHEERL) who are generating new findings and data on human health

AND

- The risk managers in the EPA program offices and regions who must make regulatory, enforcement, and remedial action decisions.

United States Environmental Protection Agency

Integrated Risk Information System

- Provides EPA scientific information on potential adverse health effects that may result from exposure to chemical substances found in the environment.
  - *Oral reference doses and inhalation reference concentrations for non-cancer endpoints.*
  - *A weight of evidence description (e.g., carcinogenic to humans), oral slope factors, and inhalation unit risks for cancer.*
- EPA risk assessors combine IRIS toxicity values with scenario-specific exposure values to estimate risk.
- IRIS provides a source of toxicity information to inform risk-based decision-making.
- IRIS is founded on EPA guidelines for health risk assessment.
- Fosters consistent risk assessments across EPA Programs and Regions.

United States Environmental Protection Agency

Integrated Risk Information System

- IRIS provides qualitative and quantitative health effects information for over 540 substances.
- IRIS users include:
  - *EPA Program Offices and Regional Offices*
  - *Other Federal agencies*
  - *State and local agencies*
  - *International agencies*
  - *Public - including academia, regulated industries, environmental organizations, individuals*
- New IRIS process established on May 21, 2009.
- IRIS database: www.epa.gov/iris

Assessment Development Process for New IRIS

United States Environmental Protection

Comprehensive Literature Search and Data Call-In

Completed lit searches posted on Web and announced in FRN

FRN requesting information about studies not in lit search and new research

1 Complete Draft IRIS Assessment

2 Internal Agency Review

3 Science Consultation on the Draft Assessment with other Federal Agencies and White House Offices

EPA coordinates Interagency review

4 Independent Expert Peer Review, Public Review and Comment, and Public Listening Session

Draft assessment and peer review charge posted on Web site

Public comment period and Listening Session announced in FRN

Peer review meeting announced in FRN

5 Revise Assessment

Address peer review and public comments; prepare response to comments document

6A Internal Agency Review and EPA Clearance of Final Assessment

6B EPA-led Interagency Science Discussion

Science feedback on final assessment from other Federal Agencies and White House offices

7 Post Final Assessment on IRIS

Includes IRIS summary, Toxicological Review and response to comments

IRIS Database Home Page

United States Environmental Protection Agency

Integrated Risk Information System (IRIS) | IRIS | US EPA - Windows Internet Explorer provided by EPA

http://www.epa.gov/ncea/iris/index.html

File Edit View Favorites Tools Help

Search 15 PDF

Integrated Risk Informati... | PubMed Home

Page Tools

U.S. ENVIRONMENTAL PROTECTION AGENCY

Integrated Risk Information System (IRIS)

Share

Recent Additions | Contact Us Search: All EPA IRIS Go

You are here: EPA Home » Research & Development » NCEA » Integrated Risk Information System (IRIS)

- IRIS Home
- Basic Information
- IRIS Process
- A to Z List of IRIS Substances
- Advanced Search
- Compare IRIS Values
- IRIS Guidance
- Download IRIS
- IRIS Track
- Site Help & Tools
  - Site Overview
  - IRIS Glossary
  - Frequent Questions
  - Tools & Databases
- Related Links

IRIS (Integrated Risk Information System) is a compilation of electronic reports on specific substances found in the environment and their potential to cause human health effects. IRIS was initially developed for EPA staff in response to a growing demand for consistent information on substances for use in risk assessments, decision-making and regulatory activities. The information in IRIS is intended for those without extensive training in toxicology, but with some knowledge of health sciences.

Getting Started with IRIS

- An overview of the web site
- What is IRIS?
- How does EPA decide which substances to add or update?

More frequent questions >>

Using the IRIS Database

- IRIS Process (2009 Update)
- Advanced Search in IRIS
- Compare IRIS Values
- Download IRIS

New Assessments and Reviews

The following documents are new assessments or under external peer review at this time:
More Recent Additions >>

Substance	Milestone	Meeting Date
Ethyl Tertiary Butyl Ether	External Peer Review Draft	TBD
Pentachlorophenol	External Peer Review Meeting	08/04/2009
1,4-Dioxane	External Peer Review Meeting	08/17/2009

Search IRIS by Keyword

go

IRIS Summaries/Toxicological Reviews

Entire IRIS Website

List of IRIS Substances >>

Ask Peter

I'm Peter, the IRIS Virtual Representative. I am an automated response system available weekdays 9 - 5 EST.

I can answer questions from the public about the IRIS Assessments from an extensive database of chemical risk information. Ask Peter

IRIS Track Status

Final Assessment	9
External Peer Review	11
Interagency Review	12
Agency Review	7
Draft Development	35

Detailed Status Report >>
About IRIS Track >>
IRIS Annual Agenda >>

Top of page

The IRIS Annual Agenda

- Nominations solicited from EPA Program and Regional Offices and the public

Criteria for selection

- Potential public health impact;
- EPA statutory, regulatory, or program-specific implementation needs
- Availability of new scientific information or methodology that might significantly change the current IRIS information
- Interest to other governmental agencies or the public and
- Availability of other scientific assessment documents that could serve as a basis for an IRIS assessment.

United States Environmental Protection Agency

IRIS Toxicity Values For Noncancer Effects

- **Oral Reference Dose (RfD) (mg/kg-day)**
  - An estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.

- **Inhalation Reference Concentration (RfC) (mg/m^3)**
  - An estimate (with uncertainty spanning perhaps an order of magnitude) of a daily inhalation exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.

Developing RfDs and RfCs

- Identify one or more principal studies and critical effects

- Identify point of departure (POD):
  - This point can be the lower bound on dose for an estimated incidence or a change in response level from a dose-response model or benchmark dose (BMDL),
  - or a No-Observed-Adverse-Effect Level (NOAEL),
  - or Lowest-Observed-Adverse-Effect Level (LOAEL) for an observed incidence, or change in level of response

- The POD is divided by uncertainty factors (UFs) to account for extrapolation from experimental data and gaps in the database.

Uncertainty Factors

- Intraspecies UF (UF_H) - to account for variations in susceptibility among members of the population.
- Interspecies UF (UF_A) - to account for uncertainty in extrapolating from laboratory animals to humans when human data are not available.
- Subchronic-to-Chronic-Duration UF (UF_S) - to extrapolate from subchronic to chronic exposure when a chronic study is not available.
- Database UF (UF_D) - to account for database deficiencies.
- LOAEL-to-NOAEL UF (UF_L) - to account for the extrapolation from a LOAEL to a NOAEL, when adverse effects are observed at the lowest dose tested.

United States Environmental Protection Agency

Cancer Assessments in IRIS

- Assign cancer descriptor
  - Weight-of-Evidence (WOE) for Carcinogenicity. The approach outlined in EPA's Guidelines for Carcinogen Risk Assessment (2005) considers all scientific information in determining whether and under what conditions an agent may cause cancer in humans, and provides a narrative approach to characterize carcinogenicity rather than categories.
  - Five standard weight-of-evidence descriptors are used as part of the narrative.
- Identify available key human studies and cancer bioassays.
- Attempt to identify carcinogenic mode(s) of action.
- Where data are sufficient, select and apply extrapolation methods to develop a slope factor and/or inhalation unit risk.
- For carcinogens with a mutagenic mode of action, the application of age-dependent adjustment factors is recommended as per the Supplemental Guidance for Early Life Exposures.

Weight of Evidence Descriptors from EPA Cancer Guidelines

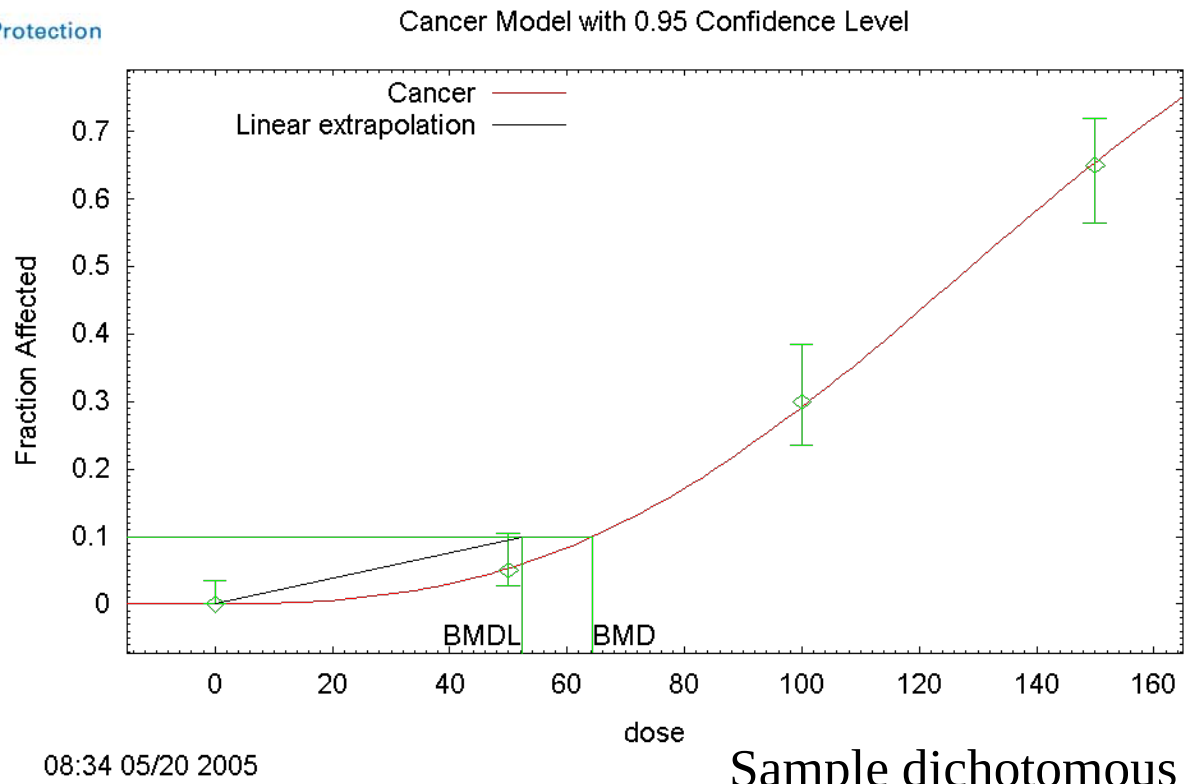
1986 Guidelines	1999 Interim Guidelines	2005 Guidelines
A: Human carcinogen	Carcinogenic to humans	Carcinogenic to humans
B1: Probable human carcinogen (limited human data)	Likely to be carcinogenic to humans	Likely to be carcinogenic to humans
B2: Probable human carcinogen (inadequate or no human data)	Suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential	Suggestive evidence of carcinogenic potential
C: Possible human carcinogen	Data inadequate for assessment of human carcinogenic potential	Inadequate information to assess carcinogenic potential
D: Not classifiable	Not likely to be carcinogenic to humans	Not likely to be carcinogenic to humans

United States Environmental Protection Agency

Quantitative estimates of risk for cancer

- **Linear low dose extrapolation**
  - **Oral Cancer Slope Factor (CSF):** An upper bound, approximating a 95% confidence limit, on the increased cancer risk from a lifetime exposure to an agent. This estimate, expressed in units of proportion (of a population) affected per mg/kg-day, is generally reserved for use in the low-dose region of the dose-response relationship.
  - **Inhalation Unit Risk (IUR):** The upper-bound excess lifetime cancer risk estimated to result from continuous exposure to an agent at a concentration of 1 $\mu g/m^3$ in air.
- **Non-linear extrapolation**
  - Nonlinear models (e.g. log probit)
  - RfD (if threshold)
  - RfC (if threshold)

BMD Example For Cancer



BMD	64
BMDL	52

Sample dichotomous cancer data

Dose	N	Response
0	100	0
50	100	5
100	100	30
150	100	65

Source: Adapted from Gift J and Howard A. Dose-Response Modeling; An IRIS Problem-Solving Workshop. Chemical Managers' Seminar Series, June 30, 2005.

United States Environmental Protection Agency

Identify carcinogenic mode(s) of action

- The *"mode of action"* is a sequence of key events and processes, starting with interaction of an agent with a cell, proceeding through operational and anatomical changes, and resulting in cancer formation.
- A *"key event"* is an empirically observable precursor step that is itself a necessary element of the mode of action or is a biologically based marker for such an element.
- Mode of action is contrasted with *"mechanism of action,"* which implies a more detailed understanding and description of events, often at the molecular level, than is meant by mode of action.
- Examples of possible modes of carcinogenic action include mutagenicity, mitogenesis, inhibition of cell death, cytotoxicity with reparative cell proliferation, and immune suppression.

Source: U.S. EPA Guidelines for Carcinogen Risk Assessment (2005).

United States Environmental Protection Agency

Use of Mode of Action Information in Cancer Dose-Response Assessment

- Linear extrapolation is used when the dose-response curve is expected to have a linear component below the point of departure
  - agents that are DNA-reactive and have direct mutagenic activity, or
  - agents for which human exposures or body burdens are high and near doses associated with key precursor events in the carcinogenic process
- A nonlinear approach is used when there are sufficient data to ascertain MOA and conclude that it is not linear at low doses and that the agent does not demonstrate mutagenic or other activity consistent with linearity at low doses.
- Both linear and nonlinear approaches may be used when there are multiple MOAs. For example, an agent can act predominantly through cytotoxicity at high doses and through mutagenicity at lower doses where cytotoxicity does not occur.

Source: U.S. EPA Guidelines for Carcinogen Risk Assessment (2005).

United States Environmental Protection Agency

Use of oral Cancer Slope Factors (CSF) in EPA risk assessments

- Risk = dose (mg/kg-day)* CSF $(mg/kg\text{-}day)^{-1}$
- Dose is estimated for a specific exposure scenario (e.g., ingestion of a chemical in drinking water or ingestion of a chemical in soil from a contaminated site).
- CSFs, as developed in IRIS assessments, are derived from human and animal studies for a particular chemical and may be combined with dose estimates for any exposure scenario for that chemical.
- Risk is expressed as a probability, such as 10^{-4} (1/10,000).

United States Environmental Protection Agency

Example: Chlordecone

United States Environmental Protection Agency

Chlordecone (Kepone) Background Information

- Chlordecone is a chlorinated insecticide. It was commercially available under the trade name Kepone.
- First produced in the United States in the early 1950s and introduced commercially in 1958.
- Approximately 3.6 million pounds of chlordecone were produced in the United States between 1951 and 1975.
- Resistant to degradation in the environment.
- Chlordecone production in the United States ended in 1975 after intoxication from severe industrial exposure was observed in employees who worked at the only chlordecone manufacturing plant in the country.
- New IRIS Assessment posted on 09/22/2009 (www.epa.gov/iris).

United States Environmental Protection Agency

Available data to derive a reference dose (RfD) for chlordecone

- Human data:
  - Human health effects studies of a single group of 133 men exposed occupationally to chlordecone in a manufacturing facility.
    - ✓Due to inadequate industrial safety measures substantial inhalation, dermal, and oral exposures likely occurred.
    - ✓Toxicity observed in the exposed workers included effects on the nervous system, liver, and reproductive system.
- Animal studies:
  - Chu et al. (1981): 21 month dietary study using rats.
  - NCI (1976): 20 month dietary study using B6C3F1 mice and Osborne-Mendel rats.
  - Larson et al. (1979): 2 year dietary study using Wistar rats.

Selection of principal study and critical effect for derivation of oral RfD for chlordecone

Species	Sex	Average daily dose (mg/kg-day)	NOAEL (mg/kg-day)	LOAEL (mg/kg-day)	Responses	Reference
Rat	M F	0, 0.6, 1.7 0, 1.4, 2.0	not determined	0.6 1.4	Liver histopathology, neurotoxicity	NCI 1976
Mouse	M F	0, 3.4, 3.9 0, 3.5, 7.0	not determined	3.4 3.5	Liver histopathology, neurotoxicity	NCI 1976
Rat	M	0, 0.07	not determined	not determined	Liver and thyroid histopathology	Chu et al, 1981
Rat	M/F	0, 0.06, 0.3, 0.5, 1.6, 3.9, 7.0	0.06	0.3	Kidney histopathology	Larson et al., 1979
Dog	M/F	0, 0.02, 0.1, 0.5	0.1	0.5	Decreased body weight; organ to body weight changes	Larson et al., 1979

Studies that support selection of principal study and critical effect

- A supporting study by Sobel et al. (2005) found that chlordecone, at doses estimated to be ≥0.2 mg/kg-day, increased the severity and decreased the latency of glomerular disease in mice.
  - Female ovariectomized mice were exposed subcutaneously to sustained-release pellets containing 0.01, 0.1, 0.5, or 1.0 mg chlordecone for up to 30 weeks.
  - Mice treated with 0.5 mg chlordecone pellets (calculated by the authors as an average exposure level of 0.20 mg/kg-day) developed renal impairment significantly earlier than did ovariectomized controls.
  - Renal sections from the chlordecone-treated mice demonstrated severe proliferative glomerulonephritis with the deposition of immune complexes.

- ***Due to the use of subcutaneous dosing, these studies are considered supportive of the kidney effects, but are not appropriate for the derivation of an oral RfD***

United States Environmental Protection Agency

Mode of action studies that support selection of principal study and critical effect (glomerular lesions)

- The mechanism by which chronic dietary chlordecone exposure in rats results in glomerular lesions is unclear.
- Evidence suggests that chlordecone may accelerate glomerular lesions by way of increased deposition of immune complexes in the glomeruli.
- An alternate theory holds that chlordecone damages the glomeruli directly.
  - Chlordecone predominantly binds plasma proteins and lipoproteins (especially albumin and HDL).
  - The glomeruli filter high molecular weight proteins, including albumin, from the blood.
  - This region of the kidney may be subjected to high concentrations of chlordecone that could result in direct chemical insult.

Determination of the point of departure for chlordecone: BMD modeling results

Available models in the U.S. EPA Benchmark Dose Software were fit to quantal incidence data for renal lesions reported in the Larson et al., 1979 study.

Incidence of histopathologic renal lesions (glomerulosclerosis) in female Wistar rats:

Gender	Dose (mg/kg-day)				
	0	**0.06**	**0.3**	**0.5**	**1.6**
Male	12/22	3/11	4/6	6/9	3/4
Female	**4/34**	**2/13**	**8/17***	**8/12***	**3/4***

*Statistically significantly different from controls according to Fisher's exact test ($p < 0.05$)

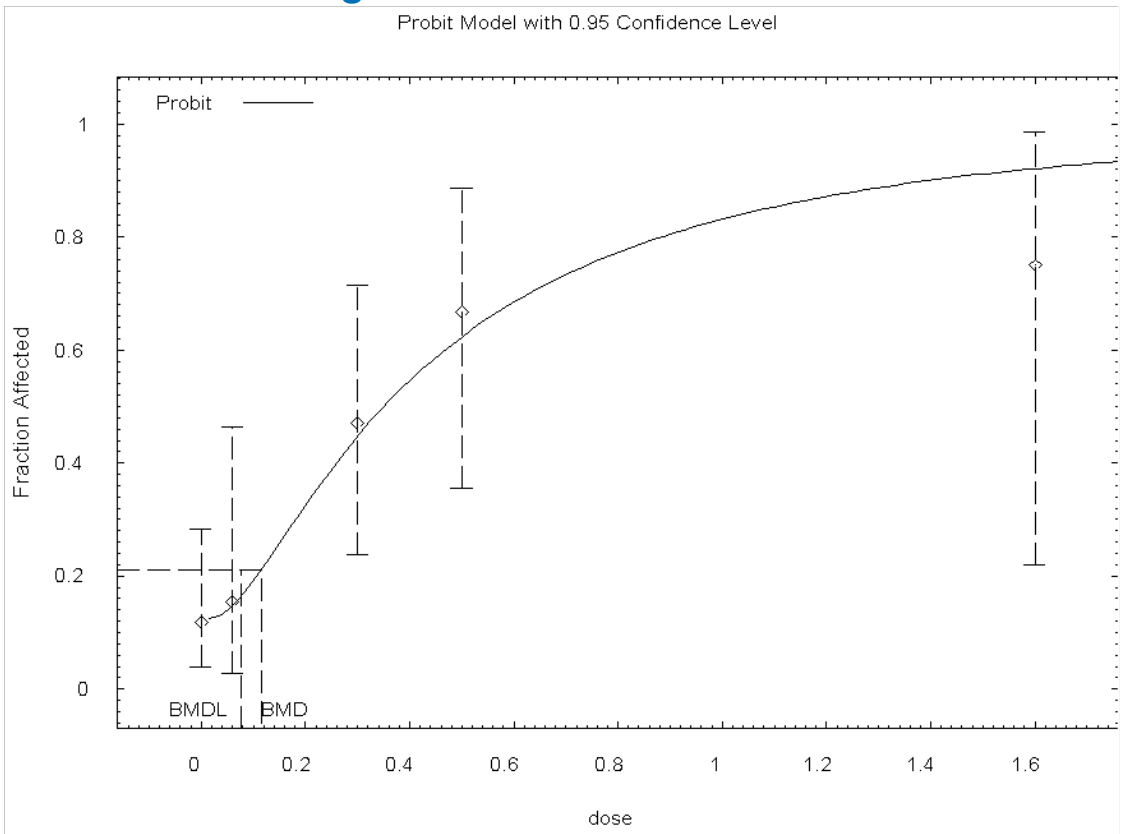
BMD modeling results:

Model	BMD_{10} (mg/kg-day)	$BMDL_{10}$ (mg/kg-day)	χ^2 *p*-value	AIC
Log-probit	0.116	0.076	0.62	84.3
Multistage, Weibull, Gamma	0.071	0.045	0.56	84.7
Log-logistic	0.067	0.026	0.72	85.7

A BMR of a 10% increase in glomerulosclerosis was selected under an assumption that it represents a minimal biologically significant change (U.S. EPA, 2000).

Determination of the point of departure for chlordecone: BMD modeling results

Observed and predicted incidence of renal lesions (glomerulosclerosis) in female Wistar rats following administration of chlordecone in the diet for 1–2 years.



Log-Probit Model of U.S. EPA BMDS (Version 1.3.2).

Uncertainty factors applied to POD for chlordecone

- 10 for interspecies extrapolation from rats to humans (UFA)
  - Aside from a difference in metabolism between rats and humans, the toxicity data from various animal species do not provide evidence that rats or any other species are more sensitive to chlordecone than humans
- 10 for human intraspecies variability (UFH)
  - Insufficient information is available to predict potential variability in human susceptibility
- 3 to account for database deficiencies (UFD)
  - The chlordecone database does not have a standard multigenerational reproductive study, but includes approximately 10 oral repeat-exposure studies assessing reproductive and developmental toxicity studies

A total UF of 300 was applied to the POD of 0.08 mg/kg-day

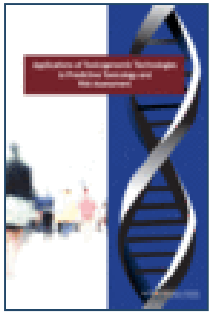
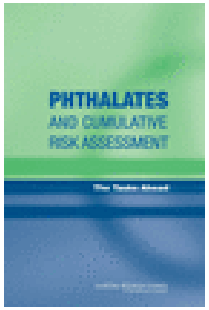
Chlordecone RfD derivation

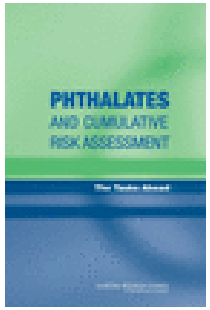
Critical effect	Point of departure	Uncertainty Factors	Chronic RfD
Renal lesions (glomerulosclerosis) in female Wistar rats 2-year feeding study Larson et al., 1979	BMDL10: 0.08 mg/kg-day	300	**0.0003 mg/kg-day**

$BMDL_{10}$ = 95% lower bound on the BMD_{10} (benchmark dose for a 10% response).

Preparing for Change

NAS/NRC Consultations



2007	*Toxicity Testing in the 21st Century: A Vision and a Strategy*
2007	*Applications of Toxicogenomic Technologies to Predictive Toxicology and Risk Assessment*
2008	*Phthalates and Cumulative Risk Assessment*
2008	*Science and Decisions-Advancing Risk Assessment*
2009	*Toxicity Pathway-Based Risk Assessment: Preparing for Paradigm Change, May 11-13, 2009*

NAS/NRC Consultations

Specific challenges identified by the NAS/NRC (integrated across reports):

- Risk assessment data needs cannot be met using the current testing methodologies.
- Broader problem conceptualization can better reflect environmental risks, e.g. cumulative risks, families of similar chemicals, biofuels.
- Current risk assessment practices do not fully utilize 21st century data and systems biology approaches to understanding disease.
- Incorporation of data and insights from scientific advancements for intra- and inter-species extrapolation is a priority.
- Estimates of risk should be refined to include the probability of harm.
- Cumulative risk assessment for mixtures should focus primarily on physiologic consequences, resulting in the same common adverse outcomes, rather than structurally or mechanistically related chemicals.
- The transformation of risk assessment that must occur will be best addressed through the joint efforts of stakeholders.

NexGen Assessments:

Our Strategy for the Future

- Broad questions to be asked include:
  - *What currently available new data and knowledge are not now used in risk assessment but potentially should be?*
  - *How can this new type of information best be incorporated into risk assessments and utilized to inform risk managers?*
  - *What new policies and procedures are needed?*
  - *How can we ensure the redesigned process is scientifically robust, consistent across assessments and matched to the risk context?*
- Difficult technical questions to be considered include:
  - *What is adverse or with what confidence can we predict disease or increased susceptibility based on molecular events?*
  - *How will exposure response be characterized?*
  - *How will variability and uncertainty be evaluated?*

How Does Bench Research Improve Risk Assessment?

- What are the effects of chemical exposure at low doses?
- What are the mechanisms of action and precursor events for chemically-induced adverse effects?
  - Use of highly sensitive new technologies (e.g. “omics”) that can describe biologic pathways and predict effects of exposure on human health at low doses.
- Provide data on cumulative effects of exposure to multiple chemicals at concentrations that represent real world scenarios.
- Address gaps in database and decrease uncertainty in assessments

United States Environmental Protection Agency

Conclusions

EPA will continue to work to:

- Improve the performance and quality of the IRIS program
- Increase production of IRIS assessments
- Accelerate the updating of IRIS assessments that are more than 10 years old and have been identified as having new data that could change a toxicity value or cancer descriptor
- Incorporate new state-of-the-science methods as they become available, and maintain high quality through rigorous peer review

More Information on the IRIS Program

- www.epa.gov/iris - see Recent Additions, Background Documents, and IRIS Track.
- Also, the database could be accessed via OECD's e-chemportal (http://webnet3.oecd.org/echemportal/)
- IRIS Hotline (202) 566-1676: For questions about IRIS database access and content

United States Environmental Protection Agency

Thank you!