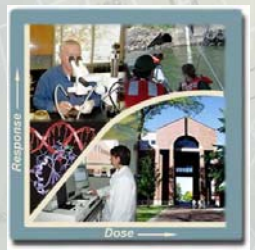
Pesticide Toxicology and Risk Assessment



http://emt.orst.edu

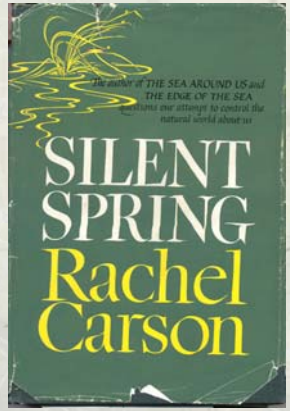
Jeffrey J Jenkins
Department of Environmental & Molecular Toxicology

OSU
Oregon State
UNIVERSITY

Silent Spring

"For the first time in the history of the world, every human being is now subjected to contact with dangerous chemicals, from the moment of conception until death"

Rachel Carson, 1962.



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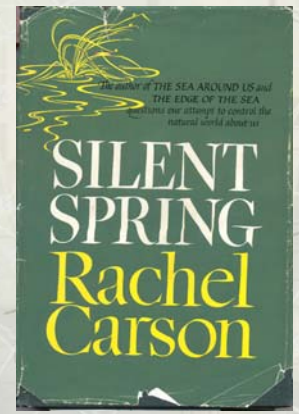
Silent Spring

"In less than two decades of their use, the synthetic pesticides have been so thoroughly distributed throughout the animate and inanimate world that they occur virtually everywhere."

Rachel Carson, 1962.



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DDT mosquito control circa 1955

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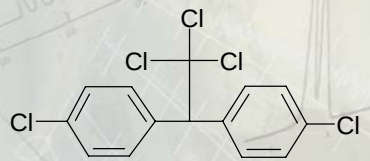
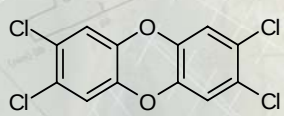
DDT

Dichloro-**D**iphenyl-**T**richloroethane



TCDD

Polychlorinated dibenzo-p-dioxins, including 2,3,7,8-tetrachloro-dibenzo-p-dioxin (TCDD)
Polychlorinated dibenzofurans



TCDD

Oregon Historical Society Catalog Number: OrHi 104979

Persistent Organic Pollutants (POPs)

PCBs
Dioxins
Dibenzofurans
Aldrin
Dieldrin
DDT
Endrin
Chlordane
Hexaclorobenzene
Mirex
Toxaphene
Heptachlor

Persistent Organic Pollutants (POPs)

- 2001 Stockholm Convention: a treaty curtailing the manufacture and use of 12 POPs
- US supports treaty, but cannot join without amendments to FIFRA and TSCA

Chemical Regulation Reporter®

Volume: 32 Number: 16
April 21, 2008

Canadian Health Minister Proposes to Ban Bisphenol A in Polycarbonate Baby Bottles

OTTAWA--Canada will ban the use of bisphenol A in polycarbonate baby bottles but will not take action on use of the chemical in products used by adults, federal Health Minister Tony Clement said April 18.

The action is based on the results of a draft toxicity assessment of bisphenol A to be published April 19 for a 60-day public comment period by Health Canada and Environment Canada, Clement told reporters at a news conference.

"Based on the results of our recently completed assessment, I am proposing precautionary action," he said. "Canada will be the first country in the world to take such action."

The assessment of bisphenol A, conducted under the Canadian Environmental Protection Act, found that most Canadians need not be concerned about their exposure to the chemical, as its negative health effects occur at much higher levels than Canadians' current exposure, Clement said.

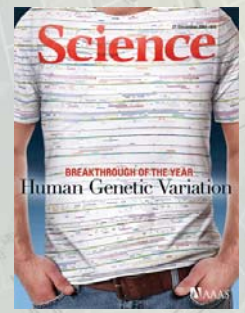
Safety Margin for Children Needs to Be Higher.

However, it is believed that much lower levels can cause harm in newborn children, so action must be taken to protect their health, he said. "We believe that the current safety margin for newborns and young children needs to be higher. It's better to be safe than to be sorry," he said.

A notice accompanying publication of the draft assessment in the April 19 issue of the *Canada Gazette, Part I* will propose banning the import, sale, or advertising of polycarbonate baby bottles, he said. This limited action is "prudent and makes good public health sense," he said.

Bisphenol A is also used in a range of other products, and although the newest and most current scientific information raises issues about the potential migration of the substance into food and beverages from containers lined with the substance, the government is not proposing to take action on those products, Clement said. "Based on our scientific assessment, I can say that this is not of concern to Canadians," he said.

Science Breakthrough of the Year: Human Genetic Variation



2001: Human genome project – DNA sequence (~3 billion bases; ~30,000 genes) for a few individuals

2007: faster, cheaper technologies for sequencing DNA and assessing variation in genomes;

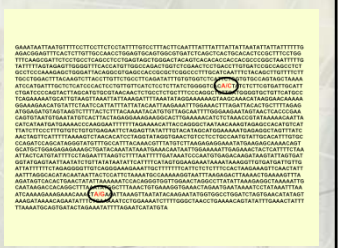
much more is known about how different we are from one another.

23andMe.com – understand your DNA for ~$1000

OSU Oregon State University

In humans two single nucleotide polymorphisms (SNPs) occur in about 2,200 nucleotides (~15 million differences between individuals, ~3 million charted).

Nucleotide (base pair) differences



www.hapmap.org

SNPs – single letter (base pair) differences

Does not account for missing, deleted, repetitive DNA sequences

Used to determine common genetic variants that occur in humans

Link genetic variants to risk (disease, chemical exposure)

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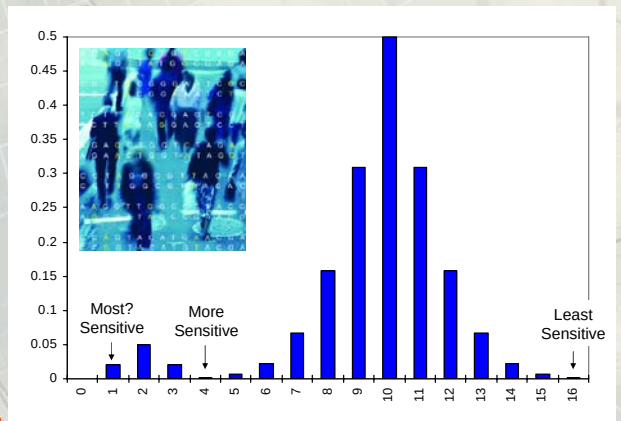
Sensitive populations: Bimodal Frequency Distribution



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Chemicals of Concern and Risk Assessment – US laws

- Federal Insecticide Fungicide and Rotenticide Act – FIFRA (~1000 a.i.)
- Food Drug and Cosmetic Act – FFDCA (~15,000 – humans, ~1,300 – animals)
- Toxic Substances Control Act – TSCA (~80,000)

Risk Assessment – US laws

- Clean Water Act
- Safe Drinking Water Act
- Clean Air Act
- Comprehensive Environmental Response, Compensation, and Liability Act (Superfund)
- Endangered Species Act
- National Environmental Policy Act

EPA Pesticide Risk Assessment

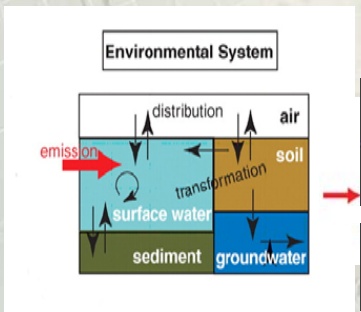
Source: Purdue University Pesticides Program

Risk = f (exposure, toxicity)

Chemical Fate ⟶ Exposure

- Initial distribution into the environment
  - Volume (mass)
  - Point source
  - Non-point source
- Persistence (how long does it last)
- Mobility (where does it go)

Chemical Fate ⟶ Exposure



R. P. Schwarzenbach et al., Science 313, 1072 -1077 (2006)

Toxicity Testing

- Animal models will predict adverse effects in humans.
- High dose, short term, exposure of animals will predict adverse effects of low dose, long term, exposure in humans.

TABLE 4-1 Battery of Tests Required by EPA for New Pesticide Chemicals

Tests	Food Uses	Nonfood Uses
Acute tests		
Acute oral toxicity—rat	R	R
Acute dermal toxicity	R	R
Acute inhalation toxicity—rat	R	R
Primary eye irritation—rabbit	R	R
Primary dermal irritation	R	R
Dermal sensitization	R	R
Delayed neurotoxicity—hen	R	R
Subchronic testing		
90-day feeding studies—rodent and nonrodent	R	C
21-day dermal toxicity	C	C
90-day dermal toxicity	C	C
90-day inhalation—rat	C	C
90-day neurotoxicity—hen or mammal	C	C
Chronic tests		
Chronic feeding of two species—rodent and nonrodent	R	C
Oncogenicity study of two species—rat and mouse preferred	R	C
Teratogenicity in two species	R	C
Reproduction—two-generation	R	C
Mutagenicity tests		
Gene mutation	R	R
Structural chromosomal aberration	R	R
Other genotoxic effects	R	R
Special tests		
General metabolism	R	C
Dermal penetration	C	C
Domestic animal safety	C	C

Note: R = required data; C = conditionally required data on the basis of special pesticide characteristics, potential use and exposure patterns, or results of routinely required studies.
Source: Adapted from 40 CFR 158.340.

NAS Toxicity Testing for Assessment of Environmental Agents: Interim Report (2006)

Chemical Risk Assessment :

Human Health risks

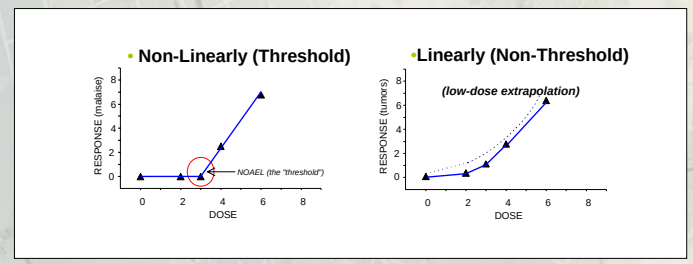
Threshold

There is some dose, below which there will be no effect.

Non-threshold (cancer)

Potency estimated from the probability of developing cancer over a lifetime of exposure.

Toxicological effects are believed to occur either:



NOAEL: No Observable Adverse Effect Level

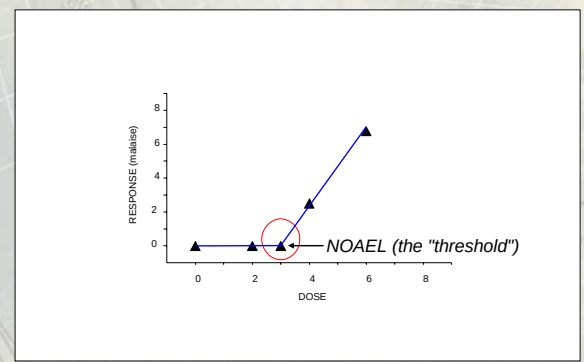
National Academy of Sciences four-step risk assessment paradigm

Hazard Identification	• What are the toxicological effects (endpoints)? For example, cholinesterase inhibition.
Dose-Response Assessment	• At what dose level do the effects occur? For example, what's the NOAEL?
Exposure Assessment	• How much chemical is a person being exposed to?
Risk Characterization	• Combine the hazard, dose-response, and exposure information to describe the overall magnitude of the risk

Pesticide Risk Assessment

- **NOAEL**: EPA scientists examine the results of tests exposing laboratory animals to various doses of a pesticide.
- The highest dose which caused no observable harm or side effects is the *No-Observable Adverse Effect Level* or *NOAEL*.

No Observable Adverse Effect Level (NOAEL)



How Is Dose-Response Assessed?

- How depends on:
  - Duration of exposure (acute, chronic)
  - Type of toxic effect (cancer; non-cancer)
  - Route of exposure (inhalation, dermal, oral)
  - Type of risk assessment (dietary; residential; occupational)

NOAELs from 90-day rat, 24-month rat, 90-day dog, and 12-month dog studies compared with the lowest NOAEL excluding the 12-month dog study (SABRE data)

Active ingredient	Chemical class	90-Day rat NOAEL (mg/kg/day)	90-Day dog NOAEL (mg/kg/day)	1-Year dog NOAEL (mg/kg/day)	2-Year rat NOAEL (mg/kg/day)	Lowest NOAEL all studies	Lowest NOAEL excluding chronic dog
2,4-D	Phenoxyacid	15	1	1	5	1	1
Acetochlor	Acetanilide	80	10	2	10	2	10
Atrazine	Triazine	1	6	5	3.5	1	1
Butylate	Carbamate	32	45	5	100	5	32
Carbaryl	Carbamate	125	1	3.1 (LOAEL)	10	1	1
Cyprodinil	Anilinopyrimidine	3	46	—	2.7	2.7	2.7
Diazinon	Organophosphorothioate	0.3 (LOAEL)	0.02 (LOAEL)	0.004	20	0.004	0.006 (LOAEL/3)
Glufosinate ammonium	Phosphinic analogue of glutamic acid	3.2 (LOAEL)	2	5	2	2	2
Hexaconazole	Triazole	3	5	2	4.7	2	3
Mevinphos	Organophosphate	0.25 (LOAEL)	0.0625 (LOAEL)	0.025	0.025	0.025	0.025
Prallethrin	Pyrethroid	24	3	5	16.3	3	3
Tebuconazole	Triazole	9	73	2.9	5	2.9	5
Triallate	thiocarbamate	3	2	1.275	NA (0.5 = LOAEL)	0.5 (LOAEL)	0.5 (LOAEL)
Vinclozoline	Dicarboximide	4	3	2.4	1	1	1
Dicamba	Dichlorobenzoate	250	6	52	≥125	6	6
Dimethoate	Organophosphate	2	<0.25	<0.18	0.05	0.05	0.05
Chlorfenapyr	Pyrrole	24	4	4	No study	4	4
MCPA	Dithiocarbamate	7	3	1.75	4.38	1.75	3
Metolachlor	Acetanilide	23	10	9.7	15	9.7	10
Benomyl	Benzimidazole	25	13	12.5	>125	12.5	13
Propachlor	Acetanilide	75	38	6.25	2.4	2.4	2.4
2,4-DB	Phenoxyacid	16	8	<2.39	3	2.39	3
Fosetyl-AL	Organophosphate	365	274	250	400	250	274

Critical Reviews in Toxicology, 36:37–68, 2006

No-observable Adverse Effect Levels (NOAELs)

	90 day rat NOAEL (mg/kg/day)	90 day dog NOAEL (mg/kg/day)	1-year dog NOAEL (mg/kg/day)	2-year rat NOAEL (mg/kg/day)	Lowest NOAEL (mg/kg/day)
2,4 D	15	1	1	5	1
Acetochlor	80	10	2	10	2
Atrazine	1	6	5	3.5	1
Carbaryl	125	1	3.1	10	1

Threshold-based Risk Assessment

Threshold: there is some dose, below which there will be no effect.

- **RFD**: *The Reference Dose* is the amount of a pesticide residue a person could consume daily for 70 years with no harmful non-cancer effects.
- **RFD** (EPA) = Allowable daily intake (EU[1])

[1]And other developed countries

Pesticide Risk Assessment

- The RFD is determined by dividing the NOAEL by a uncertainty factor (UF), usually between 100 and 1000
- 10X – uncertainty in extrapolating from animal studies to humans (interspecies).
- 10X – to account for variation in human susceptibility (intraspecies).
- 2-10X – to account for sensitive sub-populations (infants and children)[1].
- 2-10X – optional factor for inconsistent data

[1] FQPA requires EPA to make determination if additional factor necessary.

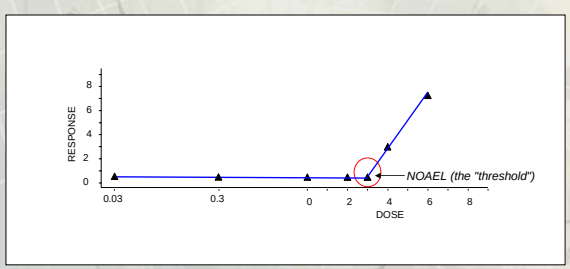
Reference Dose (Non-cancer risk)

- Start with the NOAEL (mg/kg BW/day)
- Calculate a reference dose (RfD):

$$RfD = \frac{NOAEL}{UF}$$

UF: ***10X for Interspecies***
10X for Intraspecies
Other (as needed)
Uncertainty Factors

Reference Dose relative to NOAEL



$$RfD = \frac{NOAEL}{UF} \qquad RfD = \frac{3}{10 \times 10} = 0.03 \text{ mg/kg/day}$$

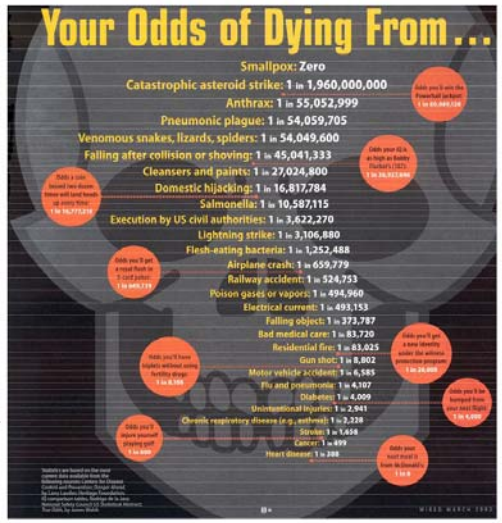
Reference Dose (Non-cancer risk)

Pesticide	Reference dose[1]
Naled	0.002
chlorpyrifos	0.003
malathion	0.02
resmethrin	0.03
permethrin	0.05
glyphosate	0.10

[1] mg/kg/day

Pesticide Risk Assessment: Cancer

- Cancer risk: The amount of a pesticide residue a person could consume daily for 70 years that would result in no more than 1-in-a-million (10^{-6}) increased chance of developing cancer as a direct result of consumption of (exposure to) that chemical.

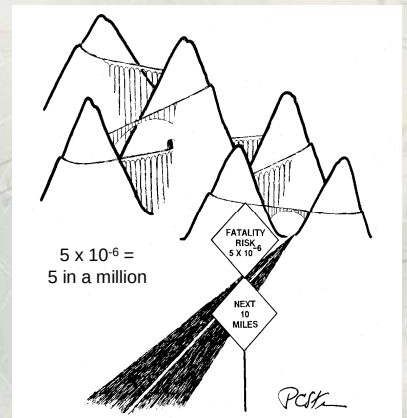


Odds of cancer during lifetime ~ 1 in 4

Actuarial Risk: predict future events based upon past occurrences

Population Risk: probability of injury from well defined random events

Individual Risk: better explained with plausibility rather than probability



5×10^{-6} = 5 in a million

3-08

Cancer "Prevention"

EPA cancer risk assessment goal:

prevent excess cancers due to chemical exposure

- Often assumes a lifetime daily dose (mg/kg/day)
- Excess cancer: >1 in 4 U.S. population

Excess Cancer Risk Terminology

- U.S. cancer rate: 1 in 4 or ¼ or 0.25
- Acceptable excess cancer rate for each chemical exposure = 0.25 + ?
- How about 0.25 + 0.000001=.250001*
- 0.000001 = 1.0 x 10^{-6}, often referred to as 10^{-6} cancer risk, this means that assuming daily exposure over a 70 year lifetime that an individual would have a 1 in 1 million risk of cancer above normal probability.

*Population risk, individual risk will vary with genetic predisposition to cancer, lifestyle, and other factors.

EPA Risk Assessment: FPQA

Reasonable certainty of no harm

"Safety is defined as a reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures and all other exposures for which there is reliable information."

Pesticide aggregate exposure and cumulative risk

- A cumulative risk assessment incorporates aggregate exposure data (from multiple pathways), for example:
  - food
  - drinking water
  - residential/non-occupational exposure
- for those chemicals with a common mechanism of toxicity
  (such as the OP insecticides).

EPA Risk Characterization

Risk = f (toxicity, exposure)

- Threshold Risk Assessment

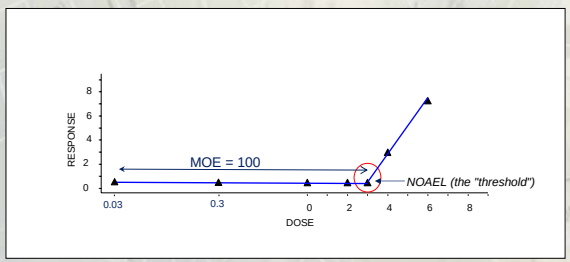
$$MOE = \frac{\text{NOAEL (mg/kg BW day)}}{\text{Exposure (mg/kg BW day)}}$$

- Non-threshold (cancer) Risk Assessment

Risk (probability) = q_1^* X exposure

q_1^*= cancer slope factor, usually expressed in units of proportion (of a population) affected per unit exposure (e.g. mg/kg/day)

Margin of Exposure (MOE)



EPA Risk Characterization: *Level of Concern*

- Threshold risk: values less than the MOE or greater than the RfD are of concern.
- Cancer (non-threshold)
  - expressed as a probability
  - >10^{-6} increased chance of developing cancer

ILSI is a global network of scientists devoted to enhancing the scientific basis for public health decision-making

OP cumulative risk: dietary exposure

Separate assessments were conducted on the various segments of the population as represented in the CSFII 1994-1996/1998. As was done in the 2002 OP CRA, the current updated assessment includes the following standard age groups:

- Infants less than 1 year old
- Children 1-2 years old
- Children 3-5 years old
- Children 6-12 years old
- Youths 13-19 years old
- Adults 20-49 years old
- Adults 50+ years old
- Females 13-49 years old

CSFII: USDA's 1994-1996/1998 Continuing Survey of Food Intake by Individuals

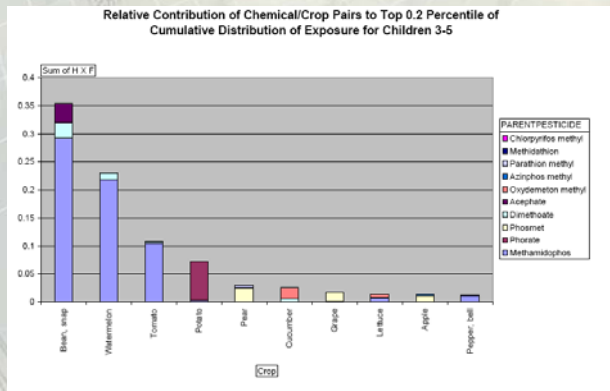


Table I.E-1. OP Pesticides and Toxic Transformation Products Included in the Cumulative Water Exposure Assessment

Pesticide	Transformation Products of Toxicological Concern	Approach for Including Transformation Product
Acephate	Methamidophos	Conversion from parent to product; max rate based on fate studies
Azinphos Methyl	Oxon	Formed by treatment
Bensulide	Oxon	Formed by treatment
Chlorethoxyfos	Oxon	Formed by treatment
Chlorpyrifos	Oxon	Formed by treatment
Diazinon	Diazoxon, Hydroxy-diazinon	Formed by treatment
Dichlorvos (DDVP)	None	na
Dicrotophos	Monocrotophos	Not in field studies
Dimethoate	Oxon	Formed by treatment
Disulfoton	Sulfone, Sulfoxide	Combined residues
Ethoprop	SME, OME, M1	Not modeled; negligible residues; parent relatively stable
Malathion	Malaoxon	Formed by treatment
Methamidophos	None	na
Methidathion	None	na
Methyl Parathion	Methyl Paraoxon	Formed by treatment
Naled	Dichlorvos (DDVP)	Conversion from parent to product; max rate based on fate studies
ODM	Sulfone	Not modeled; negligible residues
Phorate	Sulfone, Sulfoxide	Combined residues
Phosmet	Phosmet Oxon	Formed by treatment
Phostebupirim (also known as Tebupirimphos)	Oxon	Formed by treatment
Profenofos	None	na
Terbufos	Sulfone, Sulfoxide	Combined residues
Tribufos	None	na

OP Transformation in the Environment

azinphos-methyl photo-oxidation to azinphos-methyl oxon

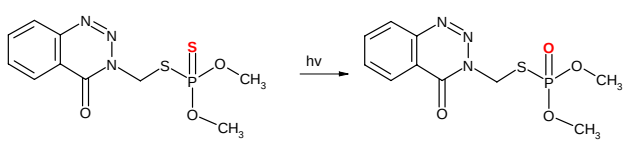
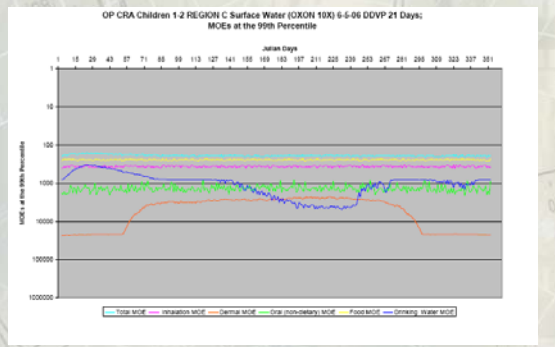


Table I.E-2. New and Old Regions and Representative Vulnerable Sites Used in the Cumulative Water Exposure Assessment

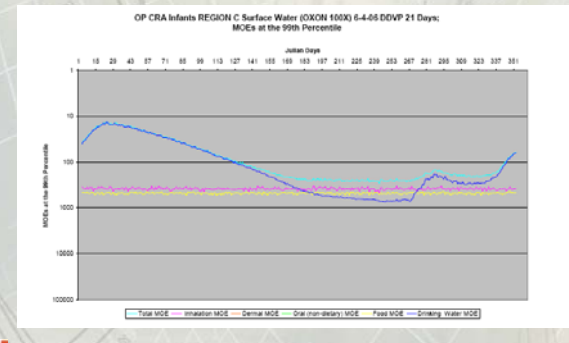
New Region	Old Region	Representative Vulnerable Site
A - Florida	Fruitful Rim, SE (12)	West Palm Beach Co (FL) *
B - Northwest	Fruitful Rim, NW (10)	Willamette Valley (OR) *
C - Arid/Semiarid West	Fruitful Rim, SW (7)	Central Valley (CA) counties of (a) Merced, San Joaquin, Stanislaus * (b) Fresno, Tulare, King, Kern
	Basin & Range (8)	none (Red R. Valley surrogate)
D - Northeast/ Northcentral	Northern Great Plains (3)	Red River Valley (ND/MN) *
	Heartland (1)	Central IL
	Northern Crescent (2)	Southcentral PA
E - Humid Southeast	Southern Seaboard (6), east	Coastal Plain, northern NC *
	Eastern Uplands (5), east section	Western NC
F - Lower Midwest	Prairie Gateway (4)	Central TX Hills *
	Fruitful Rim, TX (11)	Central TX Hills (surrogate)
G - Midsouth	Mississippi Portal (9)	Northeast LA, west-central MS *
	west sections of E. Uplands, S. Seaboard	none

* Scenario used to represent new region in revised OP cumulative risk assessment.

OP Cumulative Risk Example Output: Children 1-2 in Region C (oxon 10X)



OP Cumulative Risk Example Output: Infants in Region C (oxon 100X)



Pesticide Risk Assessment

- How should we assess risks associated with exposure to pesticide mixtures?
- Those concerned about pesticide use often advocate a precautionary approach, requiring stringent measures until there is strong evidence that the problem is not as severe as anticipated.
- Is OP pesticide risk management in the U.S. sufficiently protective of human health?

Focus Questions

- How do chemical risks compare to GMOs?
- How much should we know about chemicals before production and use?
- With regards to chemical exposure, how safe is safe enough?