APPENDIX E

CHAIRPERSON AND EPA PRESENTER OVERHEADS

Peer Consultant Introduction

Harvey Clewell

Workshop:

- Is not a Review
- Has multiple outcomes
  - What can we do today?
  - What can we do tomorrow?
  - What can we do in the future?
- Is not a consensus building exercise
- Has multiple topics
  - water
  - soil
  - toxicity factors
  - uncertainty
  - next steps (and other concerns)
- Has working group and observers

Groups for Breakout Sessions

1	2	3
John Kissel*	Gary Diamond*	Annette Bunge*
Jim Bruckner	Kurt Enslein	Clay Frederick
Rosalind Schoof	Paul Chrostowski	Clint Skinner
Deborah Edwards	Philip Leber	Gerhardt Raabe
Bob Bronaugh	Stephen DiZio	Jim Knack
Lawrence Sirinek	Robert Duff	Val Schaeffer
		Ron Brown

*Chairs

Note: Sharing of Notes from Group Discussions Appreciated

U.S. EPA Risk Assessment Forum's Role

Steve Knott

Risk Assessment Forum

The Forum assembles risk assessment scientists from across the Agency to study and report on issues from an Agency-wide scientific perspective.

Currently 34 EPA Senior Scientists from:

Office of Prevention Pesticides and Toxic Substances
Office of Solid Wastes and Emergency Response
Office of Air Quality Planning and Standards
Office of Water
Office of Research and Development
Regions 1,2,5,6,7, and 10

Risk Assessment Forum

Dermal Uptake Issues

- February 1998 Peer Review of the Superfund Dermal Guidance
- Cross-Agency Interest
  - Aggregate exposure to pesticides
  - Children's risks
  - Dermal uptake of contaminants in drinking water
  - Research Planning

Risk Assessment Forum

Background on the Current Dermal Guidance

Mark Johnson

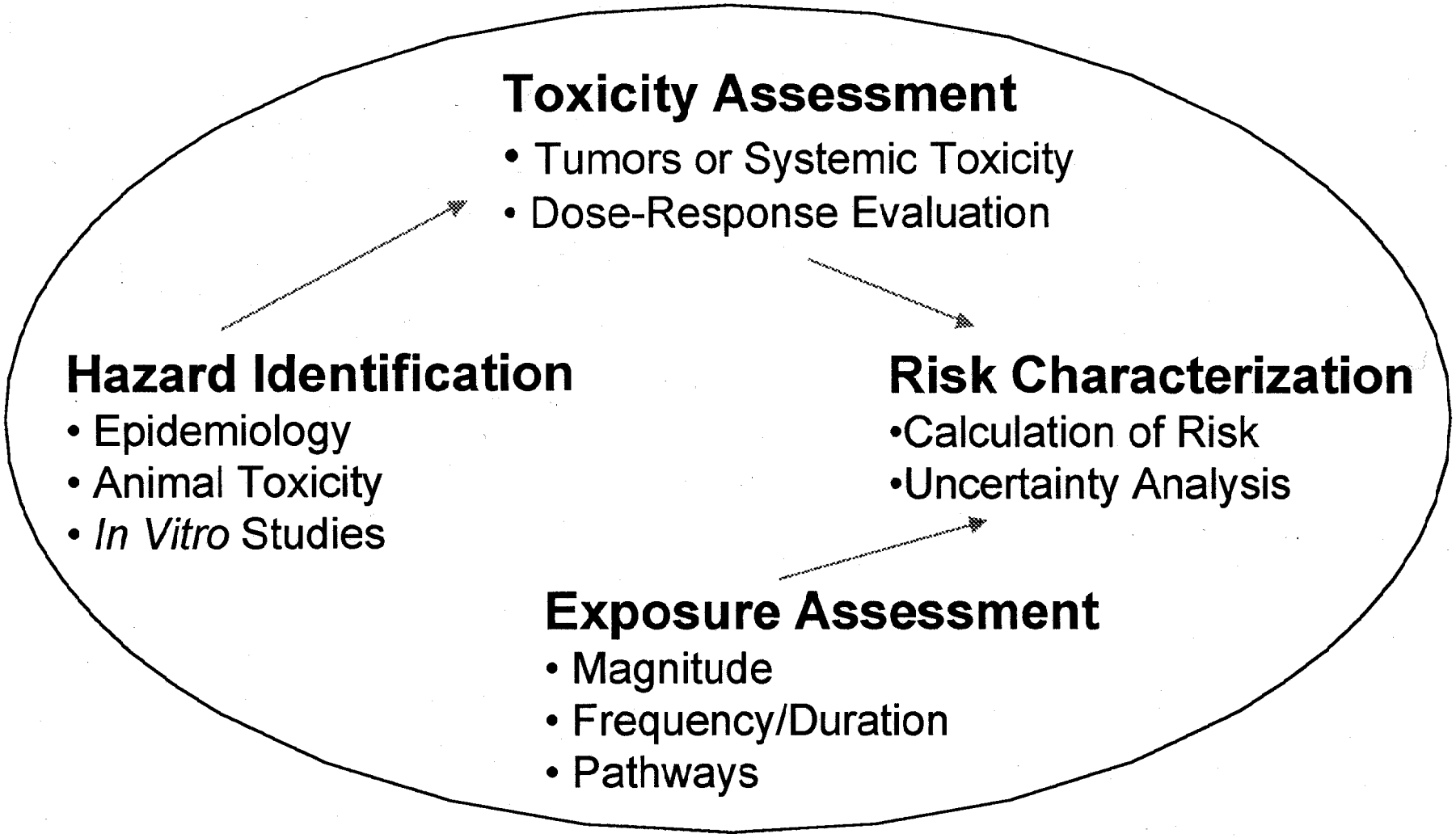
Evolution of EPA Dermal Risk Assessment Guidance

- **1983: NAS recommendations for Risk Assessment methodology**

Risk Assessment Process

- Hazard Identification
- Toxicity Assessment
- Exposure Assessment
- Risk Characterization

Risk Assessment Components



Evolution of EPA Dermal Risk Assessment Guidance

- **1983: NAS recommendations for Risk Assessment methodology**
- **1989: Risk Assessment Guidance for Superfund (RAGS)**

Dermal Contact with Chemicals in Water

$$\text{Absorbed dose} = \frac{CW \times SA \times PC \times ET \times EF \times ED \times CF}{BW \times AT}$$

PC: chemical-specific dermal permeability constant (cm/hr)

EPA Guidance: "consult open literature for values"

Dermal Contact with Chemicals in Soil

$$\text{Absorbed dose} = \frac{CS \times AF \times SA \times ABS \times ET \times EF \times ED}{BW \times AT}$$

AF = soil adherence factor

SA = skin surface area

ABS = absorbed fraction from soil

EPA Guidance: consult the open literature for chemical-specific ABS and AF values; when information is not available, use conservative estimates

Evolution of EPA Dermal Risk Assessment Guidance

- **1983: NAS recommendations for Risk Assessment methodology**
- **1989: Risk Assessment Guidance for Superfund (RAGS)**
- **1992: Dermal Exposure Assessment: Principles and Applications- ORD**

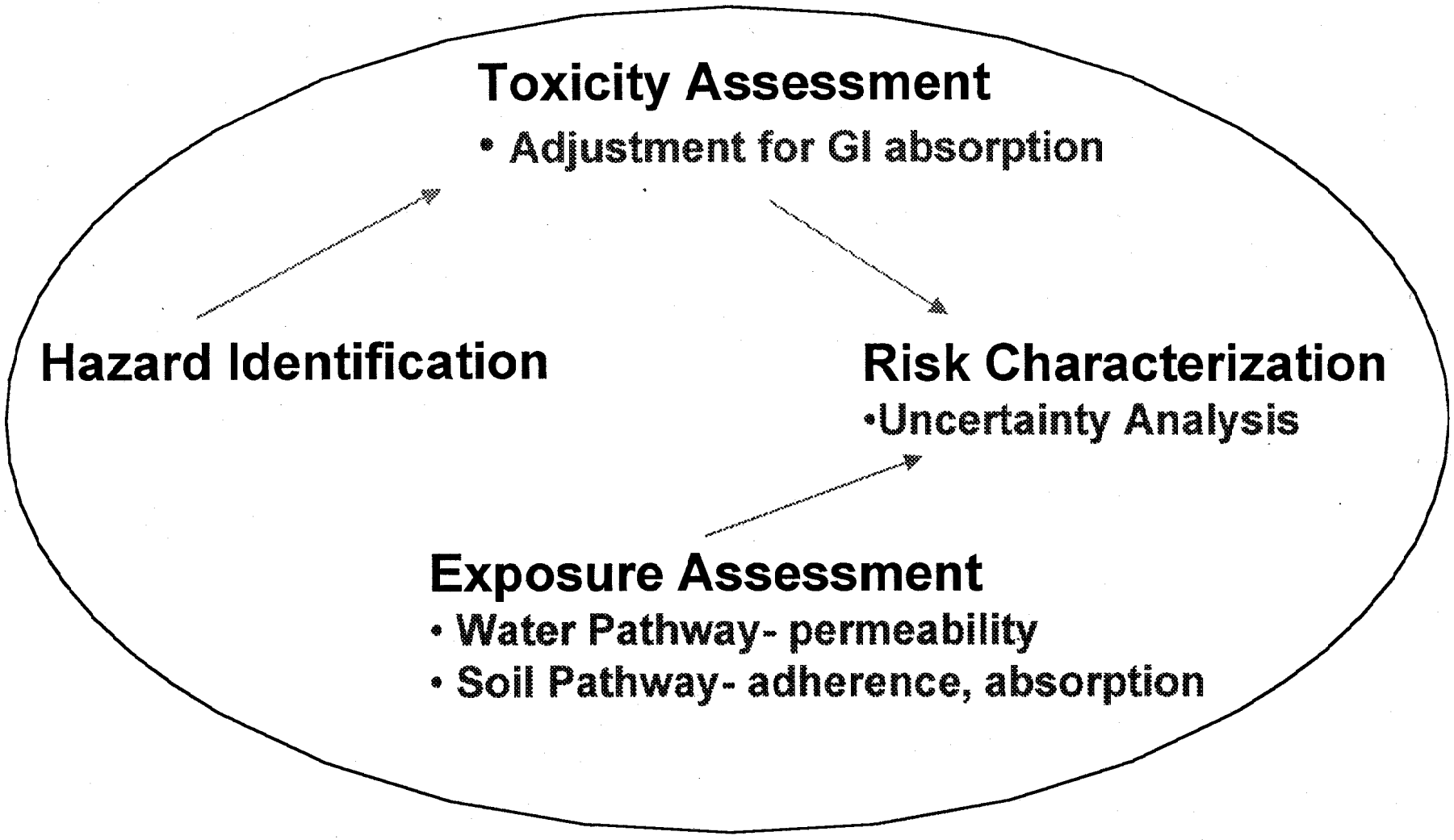
Evolution of EPA Dermal Risk Assessment Guidance

- **1983: NAS recommendations for Risk Assessment methodology**
- **1989: Risk Assessment Guidance for Superfund (RAGS)**
- **1992: Dermal Exposure Assessment: Principles and Applications- ORD**
- **1992: Superfund Interim Dermal Risk Assessment Guidance**

Evolution of EPA Dermal Risk Assessment Guidance

- **1995:** Dermal Workgroup developed to update and finalize Superfund Guidance
- **June, 1997:** Internal Peer Review of Draft Guidance document
- **January, 1998:** External Peer Review of Draft Guidance document
- **August, 1998:** Revised Draft based on Peer Review comments
- **October, 1998:** Identification of issues for further discussion as charge to Peer Consultation Workshop

Dermal Risk Assessment Issues



Presentation on Discussion Issue One:
Dermal Exposure to Contaminants in Water

Kim Hoang

Risk Assessment Guidance for Superfund Supplement Guidance

Dermal Risk Assessment Interim Guidance for Contaminants in Water

Changes from the ORD 1992 Document

- improved K_p correlation for Organics
- 95% CI for predicted K_p of existing chemicals in DEA (EPA 1992)
- Effective Predictive Domain (EPD) for predicted K_p
- $K_{p,max}$ for chemicals outside of EPD
- K_p for inorganics and default values
- Other default exposure assumptions

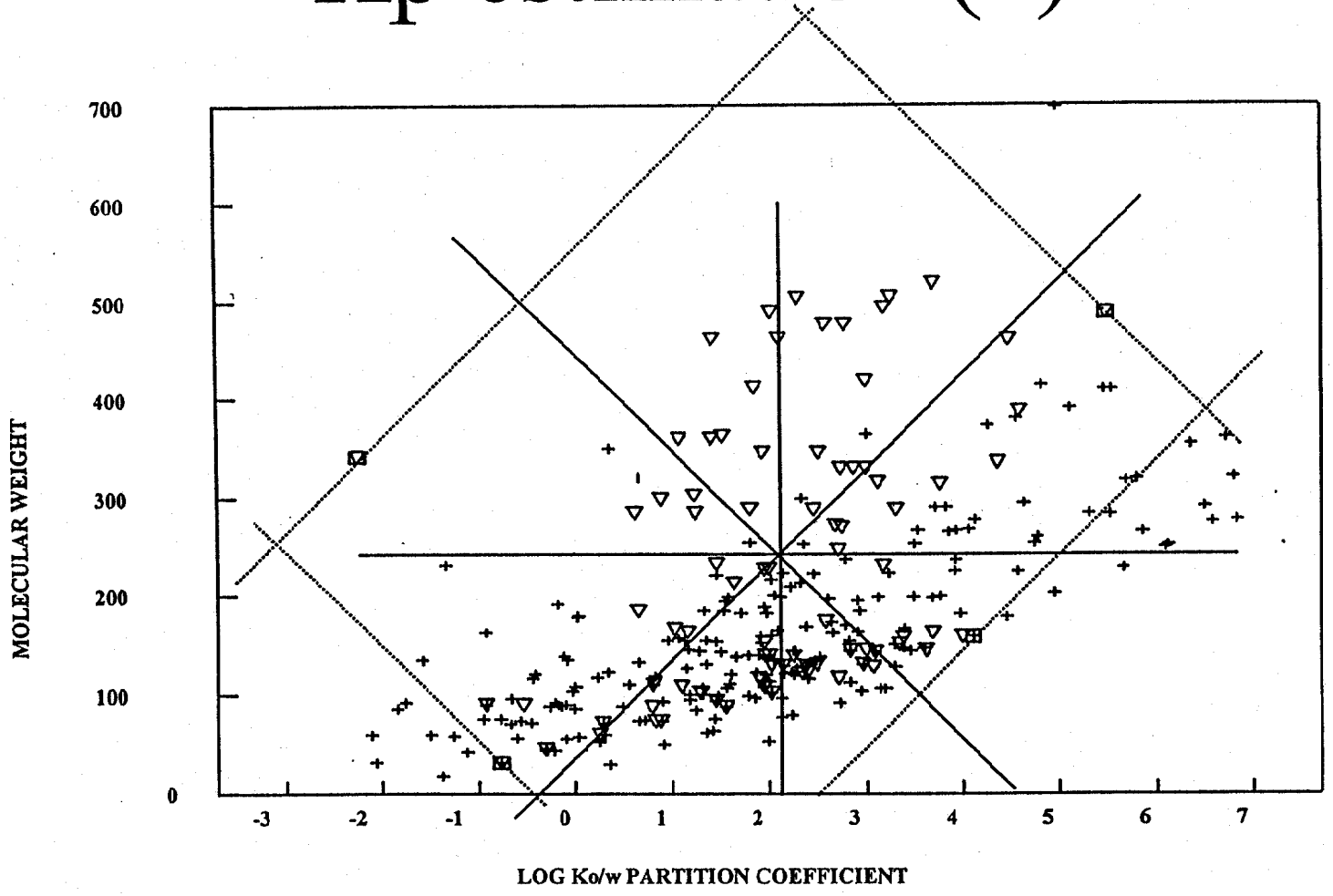
K_p Correlation for Organics

- Flynn's database as in ORD DEA (EPA 1992)
- Take out three in vivo data points (xylene, toluene, styrene)
- Using two predictors: log K_{ow} and MW
- 95% Confidence Intervals calculated for both Flynn's data and two hundred predictions (Appendix B)

Effective Predictive Domain for Kp estimation (1)

- Statistical analysis of collinear data
- From the original experimental data set, allow the determination of an effective predictive domain for extrapolation of unknown K_p

Effective Predictive Domain for Kp estimation (2)



▽ Flynn database - Prediction (Table 5-8 of DEA, EPA 1992) □ EPD

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Effective Predictive Domain for K_p estimation

$$-0.069 \leq 0.508x10^{-4}\, MW + 0.0565 \log K_{o/w} \leq 0.559$$

$$-0.301 \leq -0.508x10^{-4}\, MW + 0.0565 \log K_{o/w} \leq 0.146$$

Chemicals from Table 5-8 of DEA (EPA, 1992) identified to be outside of the Effective Predictive Domain of the Flynn database

Log Kow < -1 and MW < 60			Log Kow > 4 and 150 < MW < 350, and MW > 600		
Chemicals	**Log Kow**	**MW**	**Chemicals**	**Log Kow**	**MW**
Water	-1.38	18	Benzo-a-anthracene	5.66	228
Urea	-2.11	60	Benzo-a-pyrene	6.10	250
Hydrazine H-sulfate	-2.07	32	Benzo-b-fluoranthene	6.12	252
			Chrysene	5.66	228
			DDD	5.80	320
			DDE	5.69	318
			DDT	6.36	355
			Decanol	4.11	158.3
			Dibenzo(a,h)anthracene	6.84	278
			Fluoranthene	4.95	202.3
			Hexachlorobenzene	5.31	284.8
			Indeno()pyrene	6.58	276.3
			Nitrofen	5.53	284.1
			PCB-chlorobiphenyl	6.50	292
			PCB-hexachlorobiphenyl	6.72	361
			Pentachlorophenol	5.86	266
			TCDD	6.80	322
			Tris(2,3-dibromopropyl) phosphate	4.98	697.6

$K_{p,max}$ estimation for outliers

- Kasting and Robinson (1993): $K_{p,max}$ bounded by absorption through epidermis and blood flow rate: deviation from DEA membrane model:

$$\frac{1}{K_{p,\max}} = \frac{1}{K_{p,sc}} + \frac{1}{K_{b/v}\, q_b} + \frac{1}{K_{p,ve}}$$

where:

- $K_{p,max}$: upper limit for $K_{p,w}$ in aqueous layer
- $K_{p,sc}$: steady-state permeability coefficient through the stratum corneum (sc) (obtained from correlation)
- $K_{b/v}$: blood-to-vehicle partition coefficient
- q_b: cutaneous blood flow rate per unit area of skin
- $K_{p,ve}$: steady-state permeability coefficient through the viable epidermis (ve)

- $K_{p,max}$ used only when $t_{event} > t^*$, for steady-state absorpion through all layers of skin

K_p for Inorganics

Table 3.1 Permeability Coefficients for Inorganics

Compound	Permeability Coefficient K_p (cm/hr)
Cadmium	1×10^{-3}
Chromium (+6)	2×10^{-3}
Chromium (+3)	1×10^{-3}
Cobalt	4×10^{-4}
Lead	1×10^{-4}
Mercury (+2)	1×10^{-3}
Methyl mercury	1×10^{-3}
Mercury vapor	0.24
Nickel	2×10^{-4}
Potassium	2×10^{-3}
Silver	6×10^{-4}
Zinc chloride	6×10^{-4}
All other inorganics	**1×10^{-3}**

Other Default Exposure Factors

Table 3.2 Recommended Dermal Exposure Values for Central Tendency and RME Residential Scenarios - Water Contact

Exposure Parameters		Central Tendency Scenario		RME Scenario	
		Bathing	Swimming	Bathing	Swimming
Concentration- C_w (mg/cm^3)		Site-specific	Site-specific	Site-specific	Site-specific
Event duration (hr/event)		0.17	Site-specific	0.25	Site-specific
Event frequency (events/day)		1	Site-specific	1	Site-specific
Exposure frequency (days/yr)		350	Site-specific	350	Site-specific
Exposure Duration (yr)	Adult	9	9	30	30
	Child	6	6	6	6
Skin surface area (cm^2)	Adult	18,000	18,000	18,000	18,000
	Child	6,600	6,600	6,600	6,600
Permeability coefficient-K_p (cm/hr)		Chemical-specific	Chemical-specific	Chemical-specific	Chemical-specific

Charges (1)

- For Organics
  - Comment on the database used to derive the correlation equation
  - Comment on the correlation equation (predictors K_{ow} and MW) used to estimate the skin permeability coefficient (K_p) and the 95% CI
  - Comment on the statistical analysis used to establish the Effective Predictive Domain for the K_p correlation equation
  - Comment on the use of $K_{p,max}$
  - Discuss the use of estimated K_p vs. experimental data

Charges (2)

- For Inorganics: comment on the approach recommended for metals and inorganic chemicals.
- Comment on the other exposure default values
- Discuss the Issue of Using Model Instead of Chemical Specific Study?

Presentation on Discussion Issue Two:
Dermal Exposure to Contaminants in Soil

Mark Johnson

Absorbed systemic dose for dermal contact with soil

$$DAD = \frac{DA_{event}\ EF\ ED\ EV\ SA}{BW\ AT} \qquad (3.11)$$

where:

DAD = Dermally Absorbed Dose (mg/kg-day)
DA_{event} = Absorbed dose per event (mg/cm^2-event)
SA = Skin surface area available for contact (cm^2)
EF = Exposure frequency (events/year)
ED = Exposure duration (years)
EV = Event/day (default assumption= 1 event/day)
BW = Body weight (kg)
AT = Averaging time (days), for noncarcinogenic effects AT = ED * 365 days/yr, and for carcinogenic effects AT = 70 years * 365 days/yr or 25,550 days

Absorbed dose per exposure event

$$DA_{event} = C_{soil}\ CF\ AF\ ABS_d \qquad (3.12)$$

where:

DA_{event}	=	Absorbed dose per event (mg/cm^2-event)
C_{soil}	=	Contaminant concentration in soil (mg/kg)
CF	=	Conversion factor (10^{-6} kg/mg)
AF	=	Adherence factor of soil to skin (mg/cm^2-event) (also referred to as Contact Rate in RAGS Part A)
ABS_d	=	Dermal absorption fraction

Soil Adherence Factors

- Soil properties influence skin adherence (i.e. hydration, particle size, soil type)
- Soil adherence to skin varies across different body parts
- Soil adherence varies with exposure activity

Association of Activities with Specific Exposure Scenarios

Activities	Exposure Scenarios
Children Playing	Residential child
Daycare Kids	
Kids-in-Mud	Residential adult
Groundskeepers	
Landscapers	Commercial/Industrial Worker
Gardeners	
Irrigation Installers	Recreational
Construction Workers	
Equipment Operators	
Utility Workers	
Farmers	
Soccer players	
Rugby players	
Archeologists	
Reed gatherers	

Body Part-Weighted Average

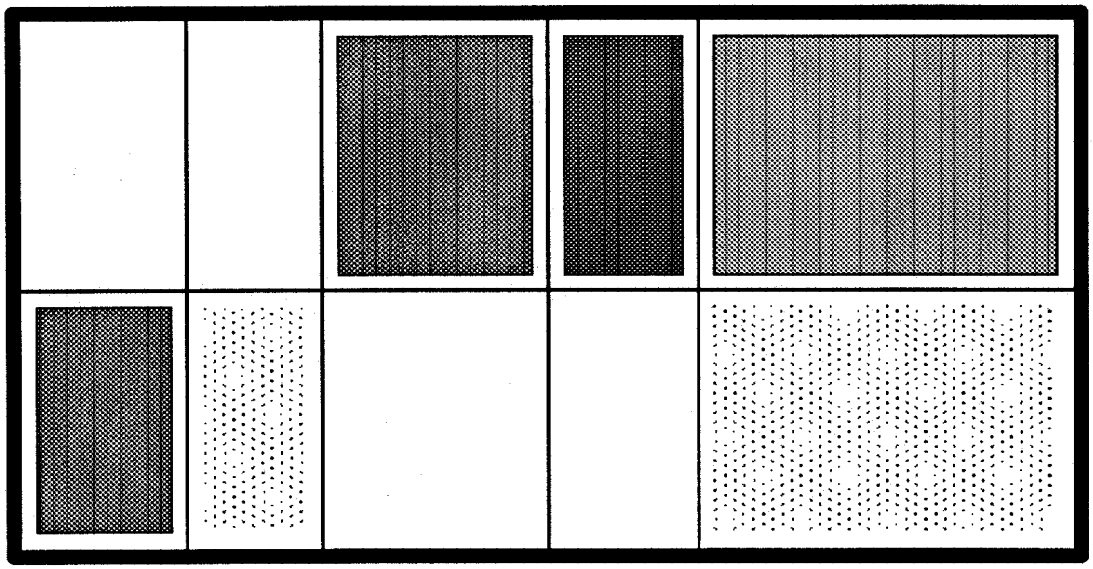


Table 3.3 Activity Specific-Surface Area Weighted Soil Adherence Factors

		Weighted AF (mg/cm^2)	
	Age (yr)	50th %	95th %
CHILDREN[1]			
Children Playing (dry soil)	8-12	0.04	0.2
Daycare Kids	1-6.5	0.06	0.2
Children Playing (wet soil)	8-12	0.2	2.7
Kids-in-mud	9-14	22	123
RESIDENTIAL ADULTS[2]			
Groundskeepers	>18	0.01	0.5
Landscape/Rockery	>18	0.04	0.1
Gardeners	>16	0.07	0.3
COMMER/INDUSTR ADULTS[3]			
Groundskeepers	>18	0.02	0.7
Landscape/Rockery	>18	0.04	0.1
Irrigation Installers	>18	0.08	0.2
Gardeners	>16	0.1	0.4
Construction Workers	>18	0.1	0.3
Equip. Operators	>18	0.2	0.6
Utility Workers	>18	0.2	0.8
OTHER RECEPTORS[4]			
SoccerNo. 1 (teens:moist conditions)	13-15	0.04	0.2
Soccer Nos. 2&3 (adults)	>18	0.01	0.07
Archeologists	>16	0.09	0.3
Farmers	>18	0.1	0.4
Rugby	>18	0.1	0.6
Reed Gatherers	>18	0.3	6.3

[1] Weighted AF based on exposure to face, forearms, hands, lowerlegs, & feet.

[2] Weighted AF based on exposure to face, forearms, hands, & lowerlegs.

[3] Weighted AF based on exposure to face, forearms, & hands.

Note: this results in different weighted AFs for similar activities between residential and commercial/industrial exposure scenarios.

[4]Weighted AF based on all body parts for which data were available.

Presentation on Discussion Issue Three:
Adjustment of Toxicity Factors To Reflect Absorbed Dose

Mark Maddaloni

Toxicity Adjustment

1) Process issue ⇨ Basis (RAGS,1989)

2) Impacts dermal risk

Risk = Dose x Toxicity

Notes:

1) Units need to be harmonious

2) Typically, dose and toxicity represented in administered dose

3) PROBLEM: dermal exposure pathway ⇨ absorbed dose

4) SOLUTION: adjust toxicity factor to reflect absorbed dose

$$\text{Dose}_{\text{abs}} = \text{Dose}_{\text{adm}} \times \text{Fraction}_{\text{abs}}$$

Examples:

1) complete ($\approx$100%) $\Rightarrow$ abs dose = adm dose $\Rightarrow$ no toxicity adjust

2) poor ($\approx$10%) $\Rightarrow$ abs dose << adm dose $\Rightarrow$ Δ in toxicity factor

Issues Related to Toxicity Adjustment

1) Absorption estimation in critical study

2) Application in risk assessment

Absorption Fraction in Critical Study

Critical Study - forms basis of toxicity factor

a) toxicity assessment - dose/response

b) rarely include bioavailability determination

⇨ Performed literature review of chemical-specific bioavailability studies. Emphasis on similarities to critical study:

a) host characteristics (species, age, sex)

b) dosing regimen (route, vehicle, dosage)

Applying Bioavailability Data

Theoretically, toxicity adjustment would be indicated anytime absorption in critical study was less than 100%

Practical considerations:

a) limited precision and variability in studies

b) surrogate approach

⇨ Policy decision for managing uncertainty (i.e, 50% cutoff proposed)

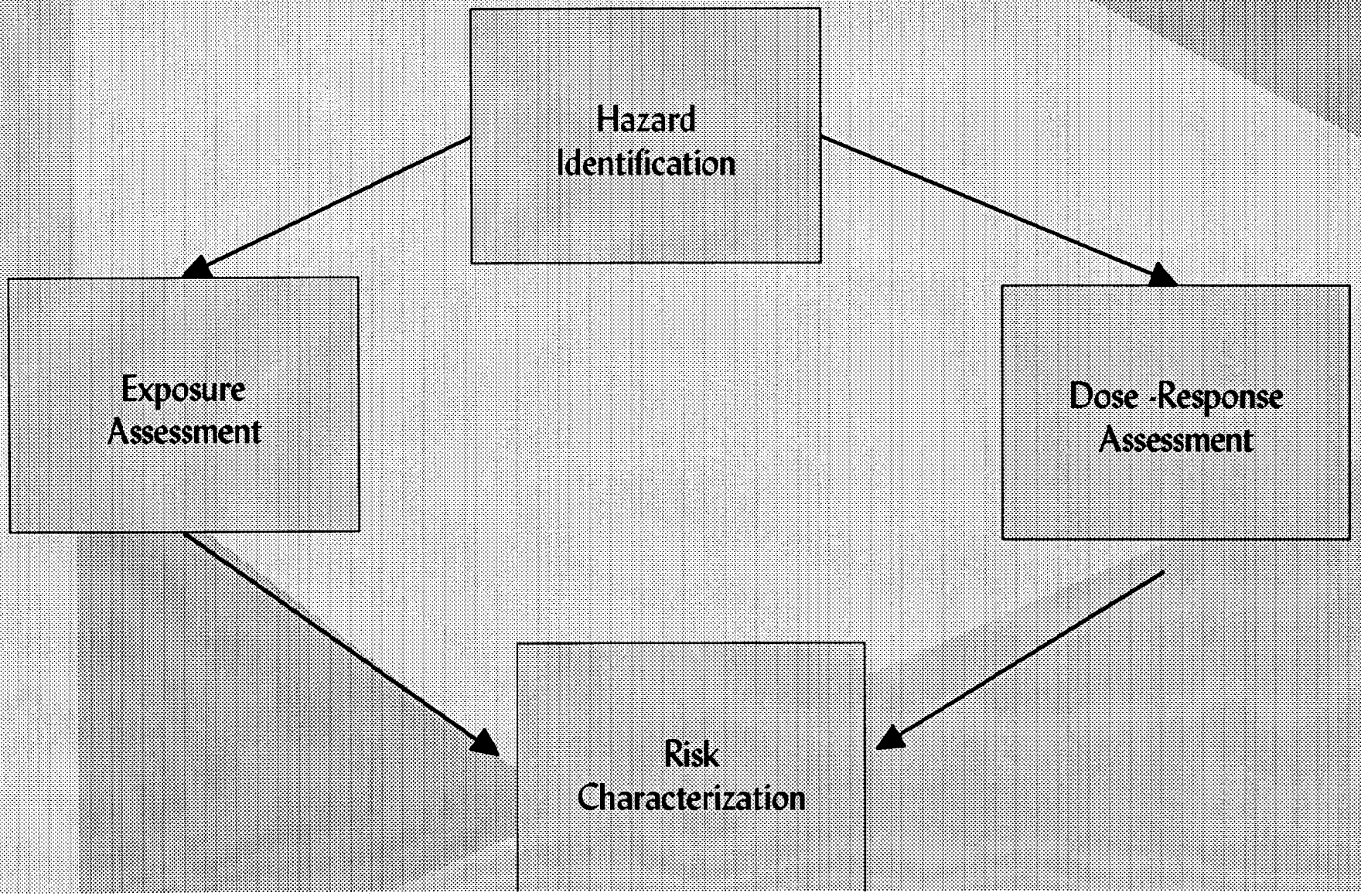
Presentation on Discussion Issue Four:
Risk Characterization and Uncertainty

Ann-Marie Burke

RISK CHARACTERIZATION AND UNCERTAINTY IN DERMAL RISK ASSESSMENT

EPA Workshop on Issues Associated with Dermal Exposure and Uptake
December 10-11, 1998

4 STEPS OF THE RISK ASSESSMENT PROCESS



EPA'S POLICY FOR RISK CHARACTERIZATION (1995)

"Greater clarity, transparency, reasonableness and consistency in Agency risk assessments"

To achieve:

- ►discuss the confidence and major uncertainties and their influence on the outcome of the risk assessment
- ►present several types of risk info
  - range of exposures (hi end, central tendency risk)
  - sensitive subgroups
- ►act as interface between risk assessors and risk managers

ISSUES FOR DISCUSSION

- Have the factors which make the most significant contribution to uncertainty been id in this guidance? Is the discussion of uncertainties complete?

- How should these uncertainties be characterized in the dermal risk assessment in order to effectively communicate the results to risk managers and the public?

- Using the default assumptions in this guidance, the estimated risks associated with dermal exposures are often greater than the risks for the ingestion or inhalation routes, particularly for contaminants in soil. How does the magnitude of the uncertainty for estimating dermal risks compare to the uncertainty for these other routes of exposure? How should this info be used to characterize the uncertainty for the dermal route?

- How can the magnitude of thes uncertainties be reduced in order to improve the overall quality of dermal risk assessments?

HAZARD IDENTIFICATION

- Identifies subset of chemicals detected which are most likely to result in adverse health effects.
- Considers;
  - info about occurrence and distribution in env.
  - fate, mobility and persistence in env.
  - concentration of chemical
  - toxicity based on animal and/or human studies

<u>For dermal-water pathway</u>
chemical retained in risk assessment if dose from dermal route contributes at least 10% of dose from oral route

<u>For dermal-water pathway</u>
chemical retained in risk assessment if has dermal abs. value

UNCERTAINTIES ASSOCIATED WITH THE EXPOSURE ASSESSMENT STEP OF DERMAL RISK ASSESSMENT

Dermal-Water Pathway

- model for DA_{event}
  - K_p ⟶ K_{ow}
- concentration term for water
- exposure time

UNCERTAINTIES ASSOCIATED WITH THE EXPOSURE ASSESSMENT STEP OF DERMAL RISK ASSESSMENT

Dermal-Soil Pathway

- model for DA_{event}
- concentration term for soil
- event time
- surface area
- frequency
- adherence factor
- dermal-soil absorption values
- default absorption values for classes of chemicals

DOSE-RESPONSE ASSESSMENT

- Evaluate toxicity info and characterize the relationship between the dose of the contaminant received with the incidence of adverse health effects in the exposed population

  - develop reference dose and slope factors

  - same approach for dermal-water and dermal-soil pathways

UNCERTAINTIES ASSOCIATED WITH THE DOSE RESPONSE STEP OF DERMAL RISK ASSESSMENT

- lack of reference doses and cancer slope factors specific for the dermal pathway

- lack of dermal slope factor for cPAHs

RISK CHARACTERIZATION

- Cancer Endpoints: Excess cancer risk = DAD x SF_{abs}
- Noncancer Endpoints: Hazard Quotient = $\frac{DAD}{RfD_{abs}}$

- confidences and uncertainties highlighted

Uncertainties

- lack of info on GI absorption
- toxicity at the skin surface

Next Steps: Plenary Discussion on Dermal Exposure Issues

(typed from Harvey Clewell's handwritten notes)

TODAY

(SGD)

- 95% CI for K_p & EPD
- "Underpredicts halogenated chemicals"—can use C to assist
- Monolayer correction
- Acknowledge preferred RTR (G & H)
- Sensitivity/uncertainty analysis (qualitative/quantitative) H, M, L
- Define/illustrate/bound
  τ_1
- Define recreational exposure assumptions
- Establish standing SDWG
  — w/ funding
- Acknowledgement of loss to air of VOCs in shower
- Add vehicle to RfD table

TOMORROW

A.M.

- Regression analysis for K_p
  - — Vecchia database
  - — MV, T

P.M. SUBSTRUCTURE

P.M.

- Sensitivity/uncertainty analysis of parameters
- Depository (website) for reviewed K_p values etc. (not another IRIS)
- Standard criteria for exposure K_p protocols (& soil)
  - — retrospective & prospective

  (OECD—K_{ow})
- REFINED SOIL ADHERENCE (KISSEL)
- CONCRETE & OTHER SURFACES
  (TRANSFER FACTORS)
- DEPOSITION (pesticides)
  - — pesticide absorption vs. water
- STANDING AGENCY DERMAL W.G.
- TRANSFER/INTEGRATION OF DATA ACROSS PROGRAMS

THE NEXT MILLENNIUM

MORE DATA

- INORG. FROM SOIL
  - CHEM. FORM
  - SOIL TYPE
- DERMAL TOX. (P.O.E.)—in situ
  - DERMAL RfDS
    - SYSTEMIC & P.O.E.
  - human in vivo studies
  - soil vs. existing data
  - internal biomarkers
  - PK/kinetic models
    - human validation
      - butoxyethanol
      - isopropanol
  - in vitro soil studies
    - variability of soil
    - chemical form
    - contamination/preparation
    - classes of chemical
      - inorg.
      - SVOCs
      - pesticides
      - persistent
    - develop screening tests
    - mixtures
  - move beyond absorbed dose to target tissue
    - skin metab.
    - reservoir