Development of Tissue Residue Threshold Values

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Background

A chemical residue-based approach for evaluating dose, also called critical body residue (CBR) or lethal body burden (LBB), has been advocated as an improvement for prediction of toxicity to organisms in the environment (Friant and Henry, 1985; McCarty, 1986; Cook et al., 1987; Van Hoogen and Opperhuizen, 1988; Cook et al., 1991; McCarty, 1991; McCarty et al., 1991; Tas et al., 1991; Landrum et al., 1992; and McCarty and MacKay, 1993). The correlation of body residues to toxic effects (residue-based dose) has a number of advantages over using an exposure-based approach (i.e., water or food concentrations that cause toxic effects). As outlined by McCarty and MacKay (1993), these advantages include the following: (1) bioavailability is explicitly considered; (2) accumulation kinetics are considered, which reduces the confounding effect of exposure duration when interpreting results; (3) uptake from food (as distinct from water) is explicitly considered; (4) toxic potencies are expressed in a less ambiguous manner, facilitating identification and investigation of different modes of toxic action; (5) effects of metabolism on accumulation are considered; (6) mixture toxicity can be more readily assessed; and (7) experimental verification can be more readily determined between laboratory and field.

Bioaccumulation testing is being used increasingly in various environmental monitoring and regulatory programs involving sediments. In these tests, sediment organisms are exposed to sediment samples for a prescribed time period (e.g., 28 days). Following this uptake period, exposed organisms are analyzed for chemicals of interest. While these tests are one mechanism for assessing the bioavailability and accumulation of sediment contaminants, they do not intrinsically predict the toxicological effects of bioaccumulative toxicants. For this prediction, some association between tissue residues and toxicological effects must be developed. Thus, bioaccumulation tests are a natural application for residue-based effects assessment.

To help evaluate the basis for, and applicability of, residue-based effects assessment, we have undertaken the development of a comprehensive database containing literature data on tissue concentrations of toxicants and associated biological effects for aquatic animals. The purpose of this presentation is to describe the database and provide some examples of analyses that can be conducted from these data.

Database Content and Development

Pertinent literature was identified through several search mechanisms, including electronic databases (e.g., POLTOX I®; Cambridge Scientific Abstracts), in-house literature files, Current Contents®, and other assorted sources. For all literature, hard copies of the primary literature were obtained and are maintained in the project files.

From this literature, residue/effect information was manually extracted. General inclusion criteria were:

- Organism was a marine or freshwater fish, invertebrate, or aquatic lifestage of amphibian (terrestrial animals, birds, and plants were not included);
- There was a *measured* chemical concentration in the whole body or in a specific tissue; and
- There was some observation of biological effect in the form of survival, growth, or reproduction (physiological and biochemical endpoints were not considered).

In general, only data from exposures using a single chemical were used; information from mixture studies was not used unless the mixture contained only related chemicals (same mode of action). Control treatments were required as a basis for comparison of biological effect, except in studies where survival was $\geq$90 percent (thus survival was not reduced). All chemical types (e.g., organic and inorganic, ionic and nonionic) were included.

For references meeting these criteria, specific information was extracted for inclusion in the database. Database fields are as follows:

- **Study Type**: acute or chronic
- **Chemical Name**: exact chemical form (e.g., metal salt) is included parenthetically
- **CAS Number**

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- **Log K_{ow}**
- **Molecular Weight**
- **Species**
- **Life Stage**: life stage exposed, or range if multiple life stages were exposed
- **Lab/Field**: whether exposures were conducted in the laboratory or in the field
- **Test Conditions**: static, static-renewal, flow-through, microcosm, mesocosm, etc.
- **Exposure Route**: water, sediment, diet, injection, maternal
- **Exposure Concentration**: measured if given, otherwise nominal
- **Test Duration**: in days
- **Tissue Analyzed**: whole body, soft parts, blood, carcass, organ(s)
- **Tissue Residue**: in µg/g wwt and µmol/wwt
- **Biological Response**: survival, growth, or reproduction; no effect observations included
- **Reference**: literature source
- **Comments**: flags on unusual conditions (e.g., control performance problems, discrepancies in the data, etc.)

As of September 1996, the database contained residue data from more than 480 literature sources, spanning 237 chemicals, and resulting in approximately 3,000 individual residue/effect pairs. Chemicals with the greatest number of residue/effect pairs at this time are:

- **More than 400 residue/effect pairs**
  cadmium
- **100 to 250 residue/effect pairs**
  DDT, TCDD, hexachlorobenzene, mercury, PCB(s), selenium
- **40 to 100 residue/effect pairs**
  aminocarb, arsenic, copper, 2,4 dinitrophenol, endosulfan, endrin, fenvalerate, kepone, lead, lindane, nickel, 4-nitrophenol, pentachlorophenol, terbufos, toxaphene, tributyltin, zinc

Example Data Sets

Compilation and analysis of the data are ongoing at this time. However, as an example of data analyses than can be performed using the database, we extracted data for chlorpyrifos (Jarvinen et al., 1983; Macek et al., 1972; Serrano et al., 1995; Hansen et al., 1986; Montanes et al., 1995) and kepone (Buckler et al., 1981; Hansen et al., 1977a, 1977b; Fisher and Clark, 1990; Sanders et al., 1981; Stehlik and Merriner, 1983; Fisher et al., 1983; Fisher et al., 1986; Goodman et al., 1982).

Figures 1 and 2 display the residue/effect pairs for chlorpyrifos and kepone, segregated by biological endpoint (survival, growth, or reproduction). Although all residues reported for these chemicals were for whole-body analyses, the exposure regimes varied widely with regard to species, lab versus field, and route of exposure, among other variables. Regardless of these differences, these values do suggest a range of chemical residues associated with biological effects, with the threshold for reported effects in the vicinity of 1 µg/g wwt for both chemicals.

Once data entry, accuracy checking, and initial analysis are complete, it is our intention to make this database available to the scientific community for further analysis.

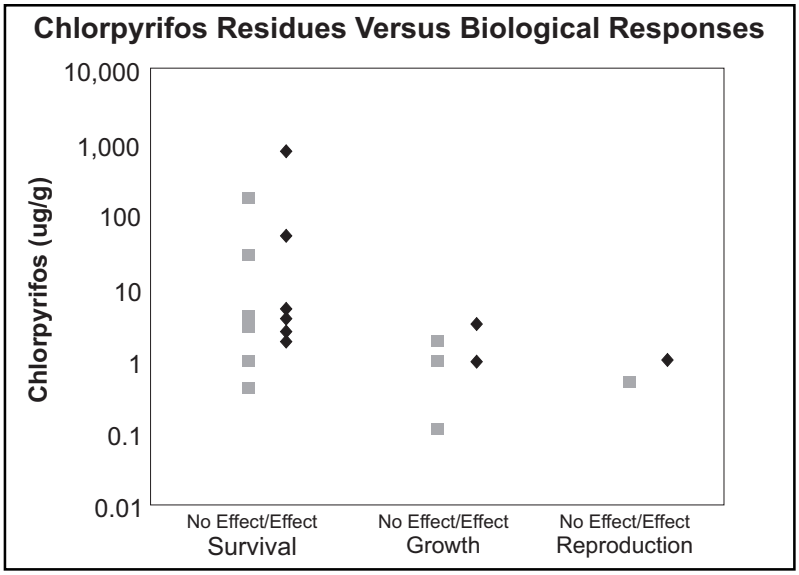

Figure 1. No effect (squares) and effect (diamonds) concentrations for chlorpyrifos in tissues.

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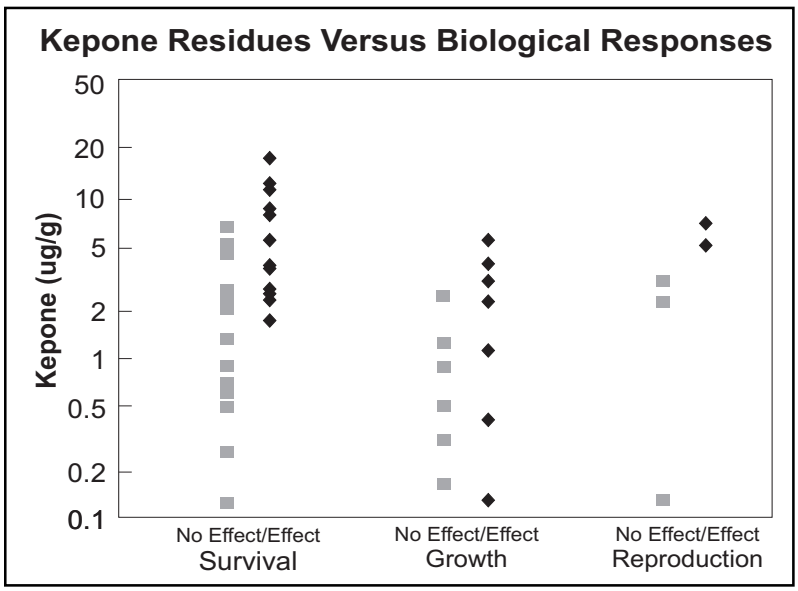

Figure 2. No effect (squares) and effect (diamonds) concentrations for kepone in tissues.

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Impetus for Research

- Need for interpretive guidance for bioaccumulation testing
- Desire for decision criteria that are based on biological effects

Impetus for Research

- Proposal that risk assessment be based on tissue residues rather than concentrations in environmental matrices
- Assemble data necessary to evaluate a tissue residue approach
- Evaluate tissue residue approach relative to mode of action or other characteristics

Tissue Residue/Toxicity Database

- Exhaustive search of literature for residue data linked to biological effect observations
- Selection criteria designed to maximize quality, comparability, and interpretability of resulting data

Scope of Data Collection

- marine and freshwater, fish and invertebrates
  - does not include amphibians, terrestrial vertebrates or birds
- endpoints focused on survival, growth, and reproduction
  - histological/biochemical/physiological endpoints not included
- virtually all chemicals included, regardless of mode of action

Database Fields

- Acute/chronic
- Chemical name
- CAS number
- Log Kow
- Molecular weight
- Species
- Life stage
- Lab/field
- Test conditions
- Exposure route
- Exposure concentration
- Test duration
- Tissue analyzed
- Residue
- Effect
- Reference
- Comments

Criteria for Data Inclusion

- Measured tissue residue (whole body or specific tissue)
- Effect data or statement concerning the health of the test organisms
- Mixture papers used only if no effect was observed
- Control not necessary if no mortality was observed

Database Content

- Currently, the database contains approximately:
  - 485 references
  - 200 chemicals
  - 2,552 residue/effect pairs

Largest Datasets

- More than 400
  - cadmium
- 100-250
  - DDT
  - TCDD
  - hexachlorobenzene
  - mercury
  - PCB(s)
  - selenium
- 40 to 100
  - aminocarb
  - arsenic
  - copper
  - 2,4 dinitrophenol
  - endosulfan
  - endrin
  - fenvalerate
  - kepone
  - lead
  - lindane
  - nickel
  - 4-nitrophenol
  - pentachlorophenol
  - terbofos
  - toxaphene
  - tributyltin
  - zinc

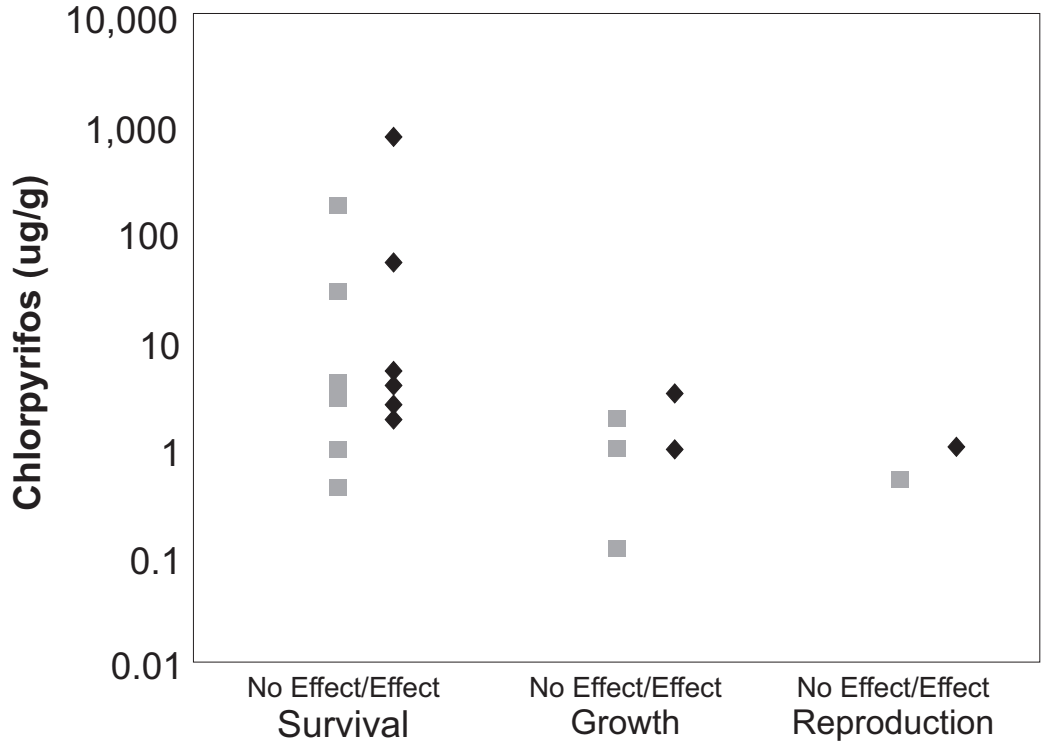
Kepone Data

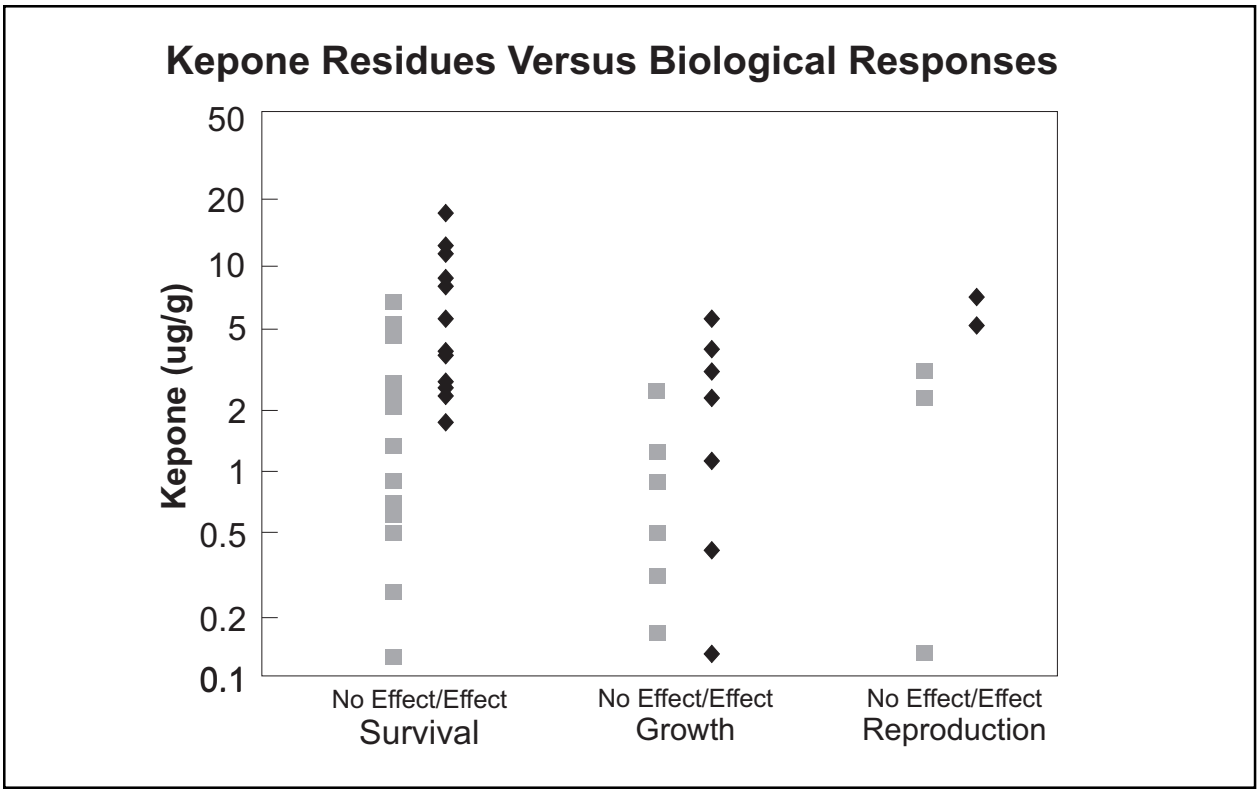
- 32 residue/effect pairs
  - 8 references
  - 6 species (3 fish, 3 invertebrate)
  - lab exposures only
  - water, diet, parental exposures
  - exposures 4 to 141 days

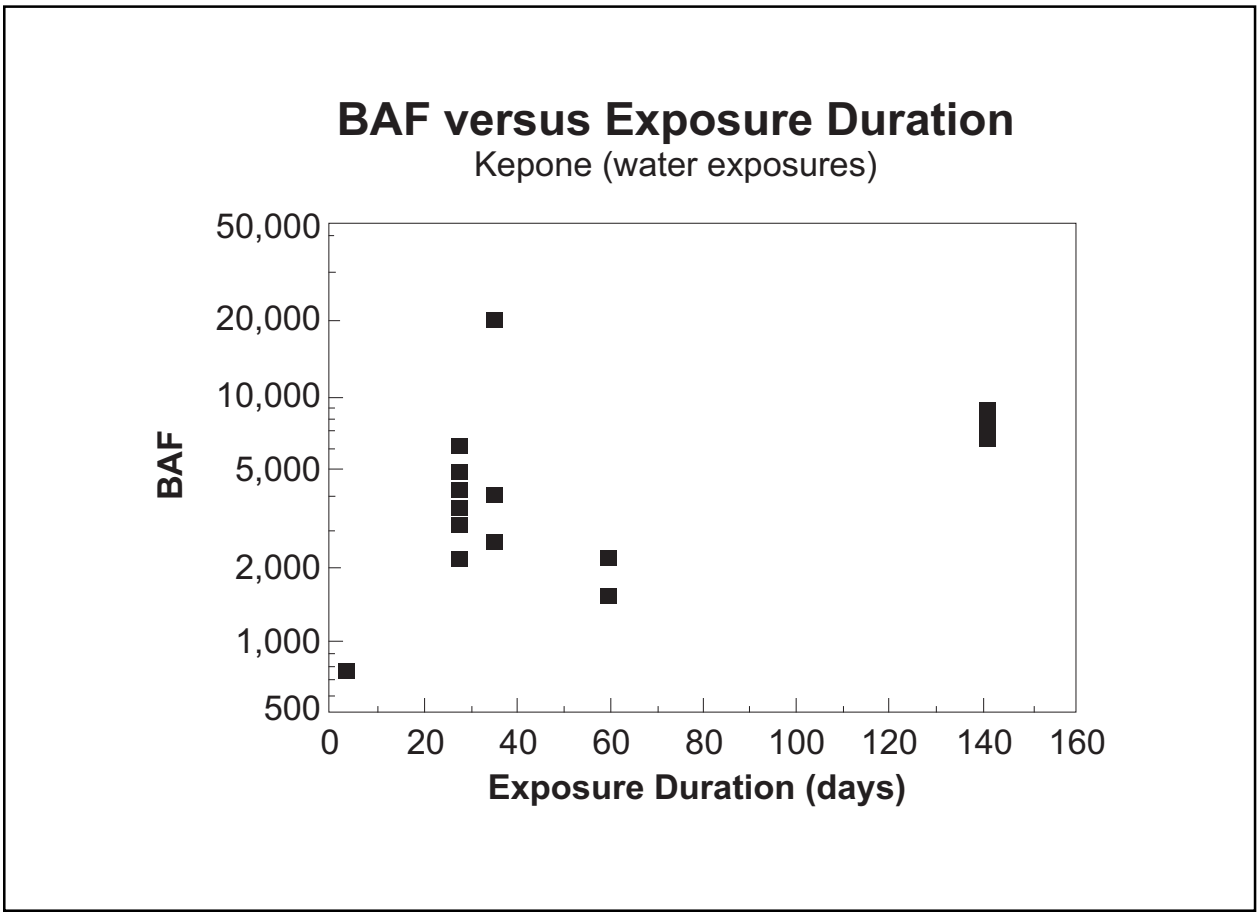
Chlorpyrifos Data

Species (n)	Age	Days	S/G/R	Source
Fathead minnow (6)	Larva	Lab 200	S,G,R	Jarvinen et al. 1983
Bluegill (2)	Juvenile	Field 63	S	Macek et al. 1972
Largemouth Bass (2)	Juvenile	Field 63	S	Macek et al. 1972
Mussel (*Mytilus*) (2)	Adult	Lab 4	S	Serrano et al. 1995
Mussel (*Venus*) (1)	Adult	Lab 4	S	Serrano et al. 1995
Gulf toadfish (4)	ELS	Lab 49	S,G	Hansen et al. 1986
Isopod (*Asellus*) (3)	Adult	Field 23	S,G	Montanes & Hattum 1995

Chlorpyrifos Residues Versus Biological Responses

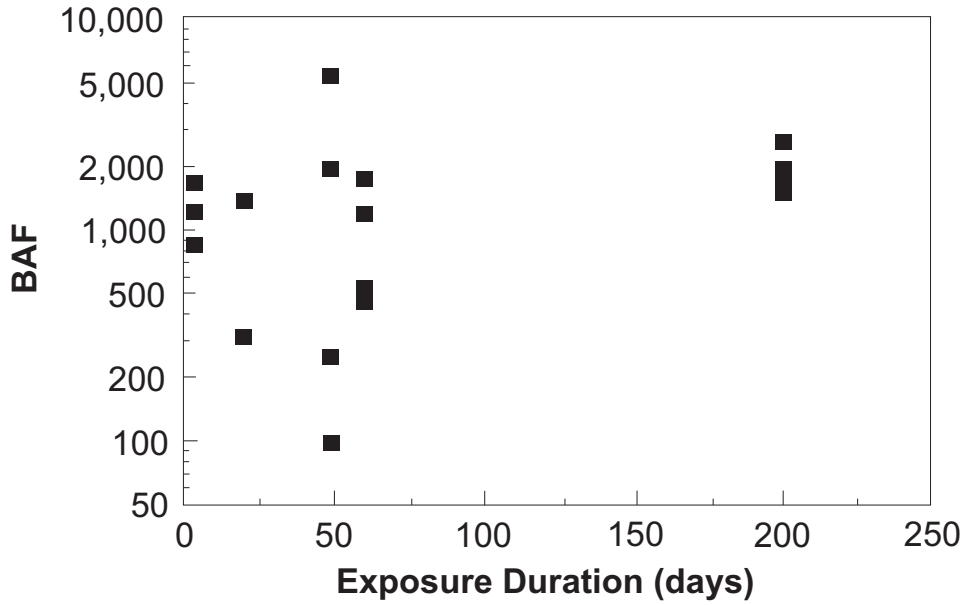






BAF versus Exposure Duration

Chlorpyrifos (water exposures)



Paired Effect/No Effect Data

Chlorpyrifos

	Effect	No Effect	Geo. Mean
Survival			
Gulf toadfish	770	175	367
Mussel (*Mytilus*)	53	4	14.6
Fathead minnow	5.11	3.03	3.93
Isopod (*Asellus*)	1.79	0.97	1.32
Bluegill	3.82	0.42	1.27
Largemouth Bass	2.55	0.47	1.09
Growth			
Fathead minnow	3.03	0.95	1.70
Gulf toadfish	0.95	0.14	0.36
Reproduction			
Fathead minnow	0.95	0.47	0.67

Paired Effect/No Effect Data

Kepone

	Effect	No Effect	Geo. Mean
Survival			
Sheepshead minnow	11	4.7	7.19
Fathead minnow	3.8	2.6	3.14
Sheepshead minnow	2.3	1.3	1.73
Sheepshead minnow	2.5	0.9	1.50
Spot	2.7	0.7	1.37
Fathead minnow	1.7	0.26	0.66
Growth			
Fathead minnow	3.8	2.6	3.14
Sheepshead minnow	2.2	1.2	1.62
Sheepshead minnow	0.41	0.30	0.35

Interpretation Issues

- Quantity and type of data varies greatly between chemicals
- Target tissue data not available consistently
- Relatively few data for individual PAH
- PCB mixtures vs. single congeners

Next