ESTIMATION OF POTENTIAL POPULATION LEVEL EFFECTS OF CONTAMINANTS ON WILDLIFE

Bradley E. Sample[1], Kenneth A. Rose[2], and Glenn W. Suter, II[3]

[1] Oak Ridge National Laboratory*
[2] Louisiana State University
[3] U.S. Environmental Protection Agency, National Center for Environmental Assessment

*managed by Lockheed Energy Research Corp. for the U.S. Dept. of Energy under contract number DE-AC05-96OR22464

Introduction

Actions taken at CERCLA sites must prevent unacceptable risks to wildlife. Although risk managers are concerned with risks to wildlife populations, risk assessments for wildlife are typically based on effects on individuals. This discrepancy occurs because:

- toxicity data available for wildlife are, like those for humans, based on effects on individuals,
- toxicity data are in a form that describes statistical significance rather than biological effects, and
- the relationship of toxic effects on individuals to effects on populations is poorly modeled by existing methods.

The disjunction between policy and practice in wildlife risk assessment may lead to inappropriate remedial decisions:

- Toxicity values may be too conservative, risks may be overstated and remediation recommended when it is not needed. As a consequence, limited remediation funds may be spent for insignificant or non-existent risks, possibly causing a net increase in environmental damage due to unnecessary habitat destruction.
- Toxicity values may not be adequately protective, risks may be understated and remedial actions are not recommended when they are needed. The consequences of this uncertainty is environmental damage and potential NRDA liability. Either of these alternatives results in inefficient use of limited EM funds.

Objective of Project

- To provide DOE with the means to appropriately assess risks to wildlife populations. The objective is being met through four tasks:

  1: Development of a wildlife toxicity database for contaminants of concern to EM.

  2: Development of improved approaches for inter-species extrapolation of toxicity data.

  3: Development of dose-response models.

  4: Development of matrix-based population models for wildlife species.

- Goal is to integrate contaminant exposure-response data with species-specific population models to estimate the magnitude of population effects for a given level of exposure to a particular contaminant.

- Preliminary results on tasks 1-3 are reported below. Task 4 is to be addressed in years 2 and 3 of the project.

Task 1: Toxicity Database Development

- Database in development includes chemicals of interest to DOE EM and chemicals being considered as part of EPA Ecological soil screening levels (ECO SSL) effort.

- To facilitate use of information, a Microsoft Access database is being developed with following fields:

  - Chemical information (CAS No., class, acute and chronic mode of action, chemical characteristics, etc.)
  - Study information (citation, test species, type of test, duration, dose route, test endpoint considered, etc.)
  - Test species information (common and scientific names, body weights, etc.)

- To date, data accumulation has focused on acute toxicity data for scaling analyses (see Task 2).

Task 2: Allometric Scaling of Toxicity Data

- Allometric scaling is one of several approaches for interspecies extrapolation of toxicity data.
- It is based on the observation that many biological properties vary directly with body weight or a power of body weight.
- These functions are best described using the allometric or power function:

$$A = a(BW)^b$$

where A = biological attribute,
a = intercept,
BW = body weight,
b = allometric scaling factor.

Allometric Scaling of Toxicity Data

- Allometric scaling factors applied in toxicology include:
  - $BW^{0.66}$ = equivalent to body surface area
  - $BW^{0.75}$ = equivalent to metabolic rate
  - BW^{1} = simple body weight scaling.
- Carcinogenicity assessment for human health uses 0.75 factor (EPA 1992).
- Basis for use of specific scaling factors is weak.
  - Mammalian data based primarily on one study of anti-cancer drugs (Frierich et al.1966). These data have been re-analyzed by multiple authors. Resulting scaling factors generally 0.66 to 0.75.
  - Single avian study (Mineau et al. 1996) used organophosphate and carbamate insecticides. Observed scaling factors to be variable but most not significantly different from 1.

Allometric Scaling of Toxicity Data: Methods

- Avian and mammalian acute toxicity values were obtained from:
  - Unpublished studies at the Denver Wildlife Research Center,
  - NIOSH Registry of Toxic Effects of Chemical Substances (RTECS) database.

- Data criteria generally followed Mineau et al. (1996):
  - Original sources cited in RTECS were obtained to verify values;
  - data restricted to oral exposure;
  - used body weights from studies if reported, else used weights from Silva and Downing (1995), Dunning (1993), or EPA (1988);
  - if male and female values were reported, used median value;
  - if range of LD_{50}s was reported, used median value; and
  - LD_{50} values reported as open-ended ranges were rejected.

Allometric Scaling of Toxicity Data: Methods

- Analyses

  - Simple linear regression analyses performed on natural-log transformed data:

$$\ln(LD_{50}) = \ln(a) + b(\ln[BW \text{ in kg}]).$$

Where:

LD_{50} is in mg/animal and
BW is in kg.

- t-tests were performed to determine if scaling factor (b) differed significantly from 0, 0.66, 0.75, and 1.

Allometric Scaling of Toxicity Data: Results

- Database included a total of 2850 observations for both birds and mammals with diverse taxonomic and chemical representation. (Tables 1 and 2.)
- Median number of animal species tested per chemical was 6 and 5 for birds and mammals, respectively (Fig. 1).
- Example scatterplots dose vs body weight for four selected chemicals are presented in Figs. 2 and 3.
- The distributions of chemical-specific avian and mammalian scaling factors, while highly variable, were centered near 1 (Fig. 4).

Table 1. Summary of data from which allometric scaling factors were developed.

Number of:	Birds	Mammals
total no. chemicals	195	166
no. chemicals with $\geq$3 animal species	138	95
species in database	69	42
families in database	20	23
orders in database	9	8

Table 2. Representative chemical classes included in allometric scaling database	
Chemical Class	**Representative Chemicals**
Organochlorines	dieldrin, endrin, DDT, chlordane
Organophosphates	ethyl parathion, chlorpyrifos, diazinon
Carbamates	aldicarb, carbaryl, mexacarbate
Herbicides	2,4-D
Fungicides	captan, zineb
Pharmaceutical drugs	librium, secanol, pentabarbital
Vertebrate pesticides	1080, gophacide, zinc phosphide
Chlorinated solvents	1,1,2,2 tetrachloroethylene, choroform
Mercurial compounds	ceresan, MeHgCl, $HgCl_2$
Inorganic compounds	arsenic trioxide, sodium selenite

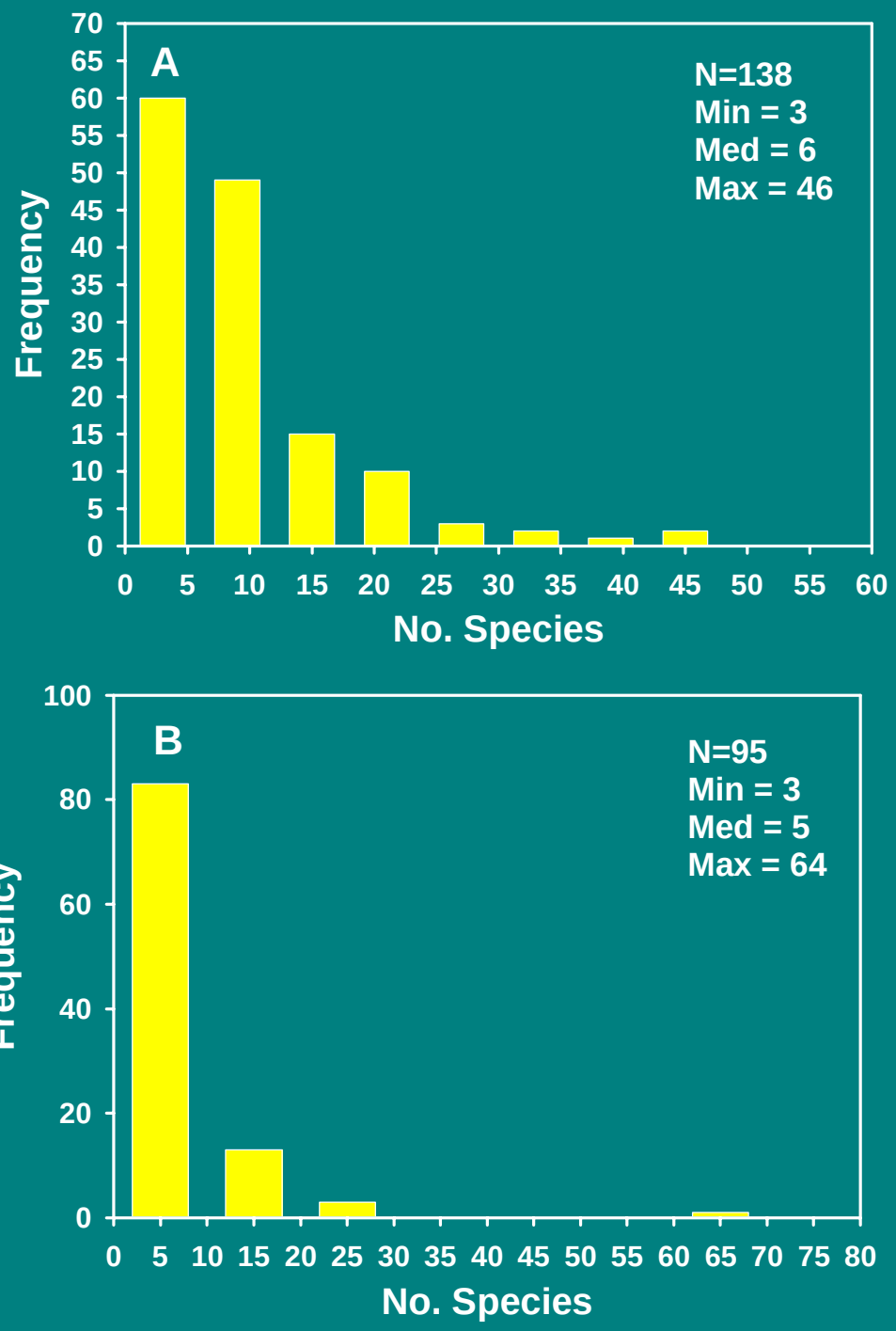

Figure 1. Distribution of number of species/chemical for birds (A) and mammals (B).

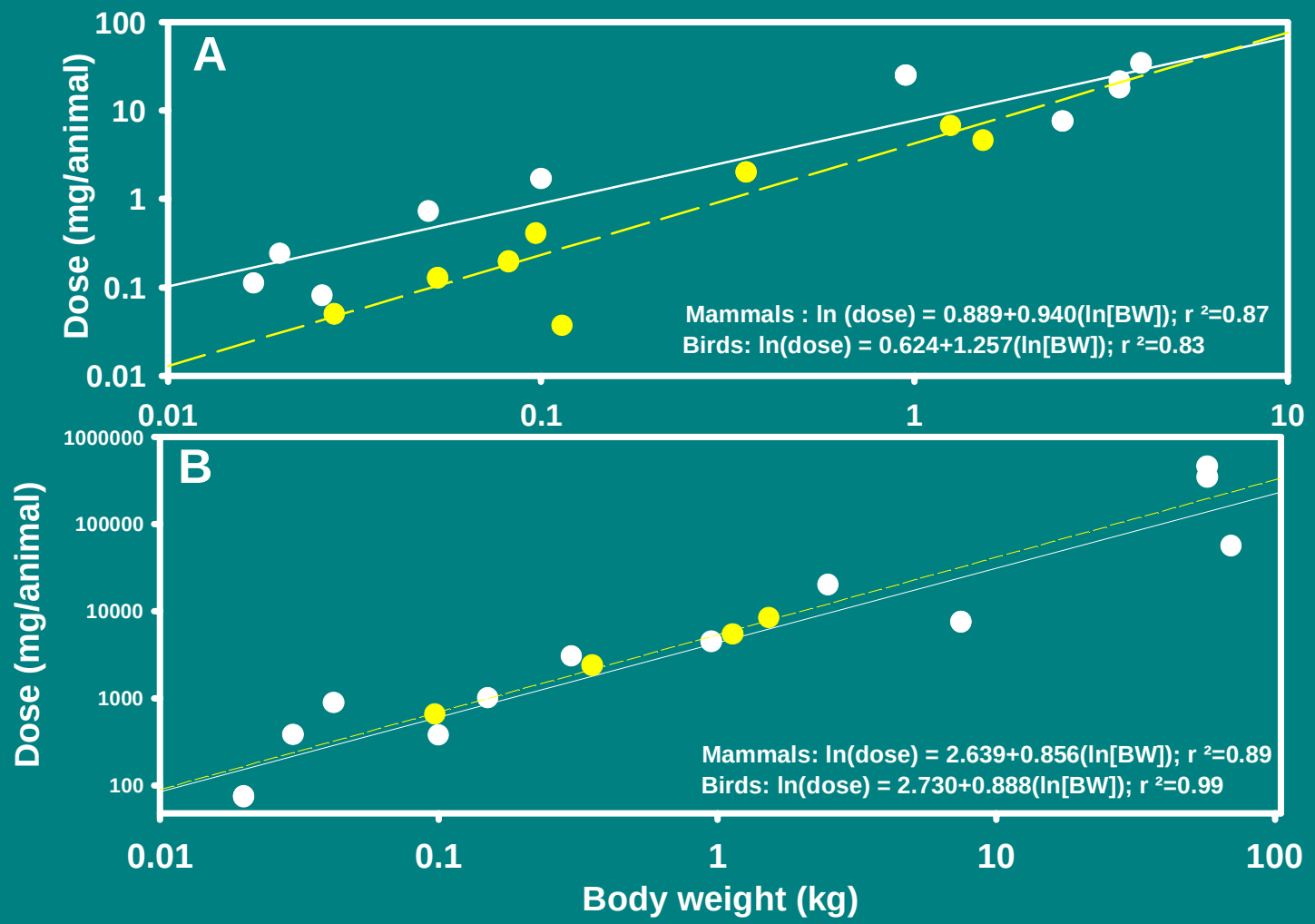

Figure 2. Scatterplot of avian and mammalian acute toxicity data for the organochlorine insecticide endrin (A) and the herbicide 2,4-D (B).

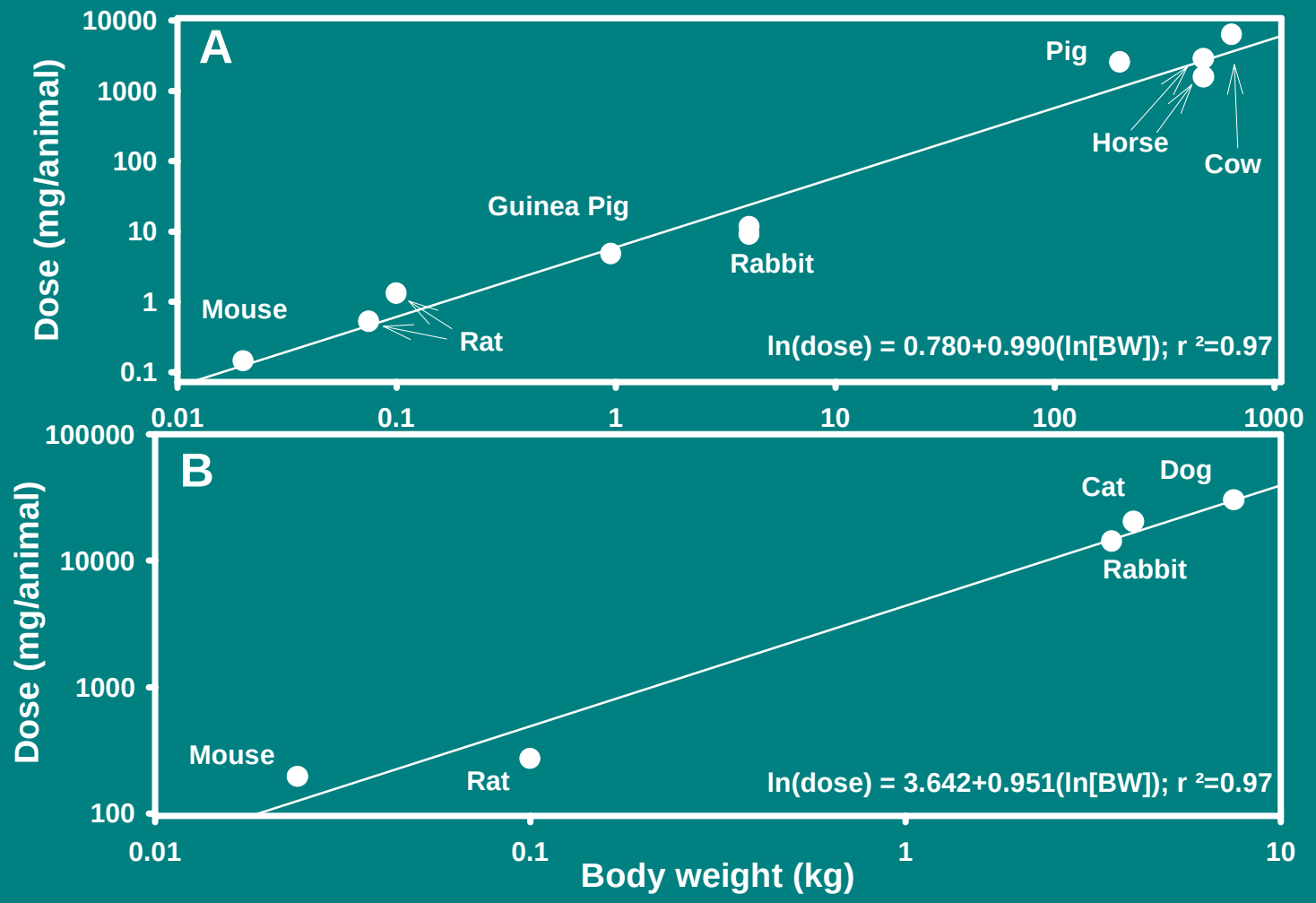

Figure 3. Scatterplot of mammalian acute toxicity data for the inorganic chemical sodium selenite (A) and the chlorinated solvent 1,1,2,2 tetrachloroethylene (B).

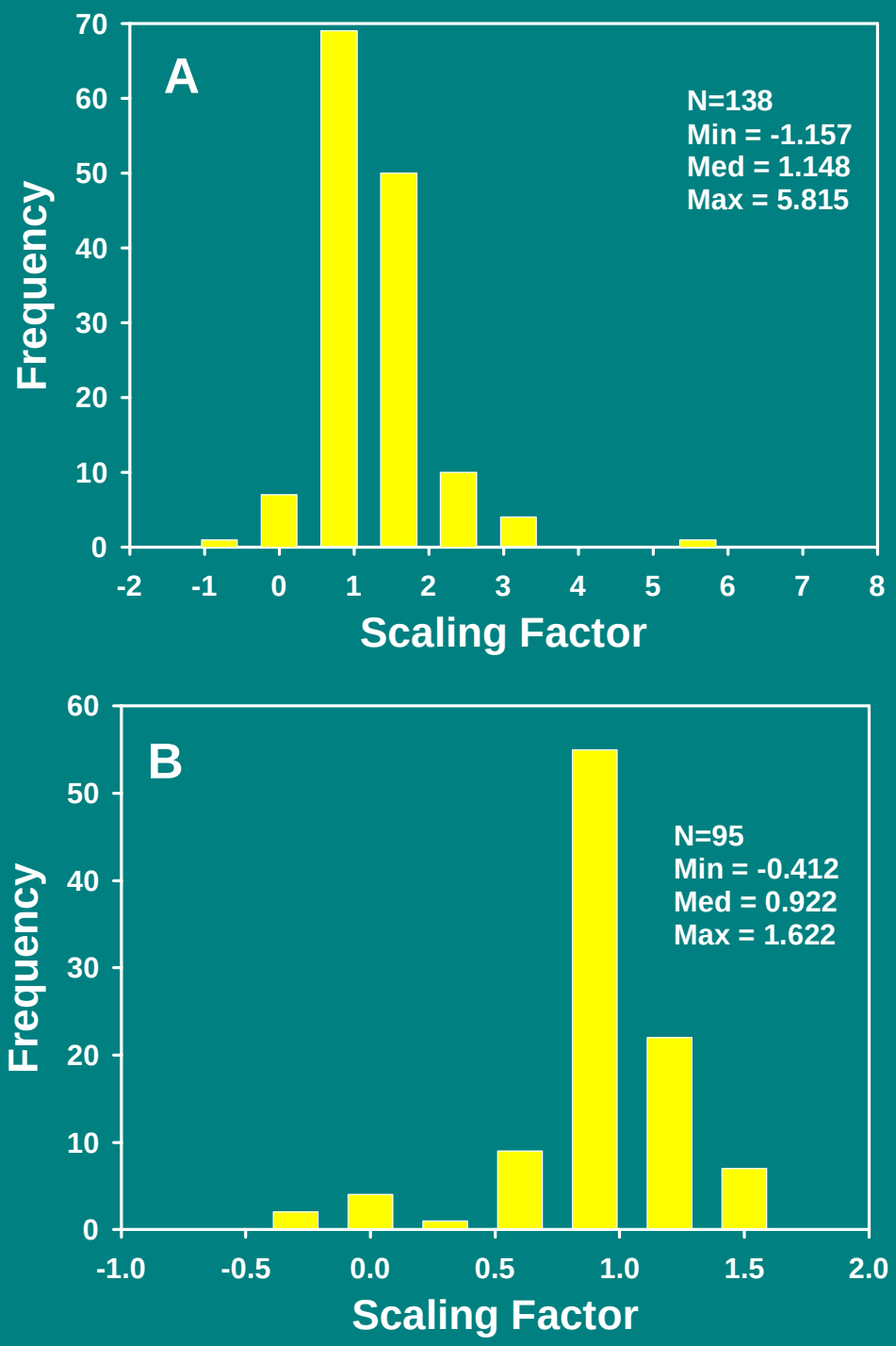

Figure 4. Distribution of allometric scaling factors for birds (A) and mammals (B).

Allometric Scaling of Toxicity Data: Results

Based on t-test results (Table 3) the following conclusions can be made:

- A scaling factor of 1 (simple body weight scaling) is suitable for 62% of chemicals for birds and 70% for mammals.
- A scaling factor of 0.75 (metabolic rate scaling) is suitable for 37.7% of chemicals for birds and 56.8% for mammals.
- A scaling factor of 0.66 (body surface area scaling) is suitable for 31.2% of chemicals for birds and 40% for mammals.

Table 3. Summary of t-test results to determine if scaling factors (b) differed significantly ($p<0.05$) from 0, 0.66, 0.75, and 1.

Result (H_0: b=0, 0.66, 0.75, or 1)	Percent of Chemicals	
	Birds	Mammals
b not different from 0.66, 0.75, or 1 and b≠0	28.3%	31.6%
b not different from 1 and b≠0, 0.66, or 0.75	27.5%	23.2%
b not different from any value	21%	6.3%
b significantly>1	13%	10.5%
b not different from 0.75 or 1 and b≠0 or 0.66	6.5%	15.8%
b not different from 0.66 or 0.75 and b≠0 or 1	2.9%	8.4%
b significantly<0	0.7%	1%
b not different from 0 and b≠0.66, 0.75, or 1		1%
b not different from 0.75 and b≠0, 0.66, or 1		1%
b different from all values but >0 and <1		1%

Allometric Scaling of Toxicity Data: Conclusions

- Results of these preliminary analyses indicate that scaling factors vary widely but that the 0.66 and 0.75 factors may be suitable for many chemicals.
- If a single value is to be chosen however, simple body weight scaling (b=1) is most broadly applicable.
- Due to the wide variation in scaling factors and to achieve the maximal reduction in uncertainty associated with inter-species extrapolation of toxicity data, use of a chemical-specific scaling factor is recommended.

Task 3: Development of Dose- response models:

- Toxicity data used in wildlife risk assessments generally consist of statistically derived point-estimates of effects.

  - NOAELs (No Observed Adverse Effects Levels), highest exposure levels at which no effects are observed to differ statistically significantly from controls, or

  -LOAELs (Lowest Observed Adverse Effects Levels), lowest exposure levels at which effects are observed to differ statistically significantly from controls.

- These endpoints do not indicate whether the statistically significant effect is, for example, a large increase in mortality or a small decrease in growth.

Development of Dose-response models:

- The level of effect at a NOAEL or LOAEL is an artifact of the replication and dosing regime employed.
- Use of the NOAEL or LOAEL does not indicate how effects increase with increasing exposure, so the effects of slightly exceeding a NOAEL or LOAEL are not qualitatively or quantitatively distinguishable from those of greatly exceeding it.
- In order to estimate risks, it is necessary to estimate the nature and magnitude of effects that are occurring or could occur at the estimated exposure levels.
- To do this, exposure-response distributions must be developed for chemicals evaluated in wildlife risk assessments

Dose-response model:

- The objective was to develop a modeling approach that could be applied to dose response data in published literature.

- A modeling approach derived from the Benchmark dose methodology (Crump 1984) being evaluated by the USEPA for human health risk assessment (e.g., Kimmel et al. 1995) was adopted.

  The model is of the form:

$$y = a_0 + \frac{(a_1 - a_0)}{1 + e^{b_0 + b_1 x}}$$

where;

y	= response
x	= dose or transformed dose (e.g., log)
a_0	= minimum expected value for response (y)
a_1	= maximum expected value for response (y)
b_0, b_1	= slope and inflection parameters.

Attributes of Dose-response model:

- Model is a 2, 3, or 4 parameter logistic-type model that may be applied to either binary (e.g. survival) or continuous (e.g., growth, reproduction, etc.) data. Number of parameters is determined by the attributes of the dose-response data.

- Initial estimates of a_0 and a_1 are based on the min and max response data.

- Initial estimates of b_0 and b_1 are obtained by regressing:

$$z = \ln\left[\frac{(\hat{a}_1 - y)}{(y - \hat{a}_0)}\right]$$

on x. The slope and intercept are the initial estimates of b_1 and b_0, respectively.

- Using the above initial estimates, the NLIN procedure (SAS 1989) is used to obtain the weighted least-squares estimates of the parameters and their associated standard errors. Weights are based on response standard errors.

- The resulting model is then used to define the dose level (and 95% confidence limits) that corresponds with selected standardized effect levels (e.g., ED_5 to ED_{50}).

Application of Dose-response model:

- A SAS macro program has been developed to facilitate the utility and application of the model.
- The program runs on PC SAS and reads dose-response data from a separate ASCII file.
- The program fits models to transformed and untransformed dose data, generates graphs of results, and calculates ED_5 to ED_{50} values with corresponding upper and lower confidence limits.
- Examples of models fit to binary and continuous avian toxicity data are presented in Figs 5 and 6.

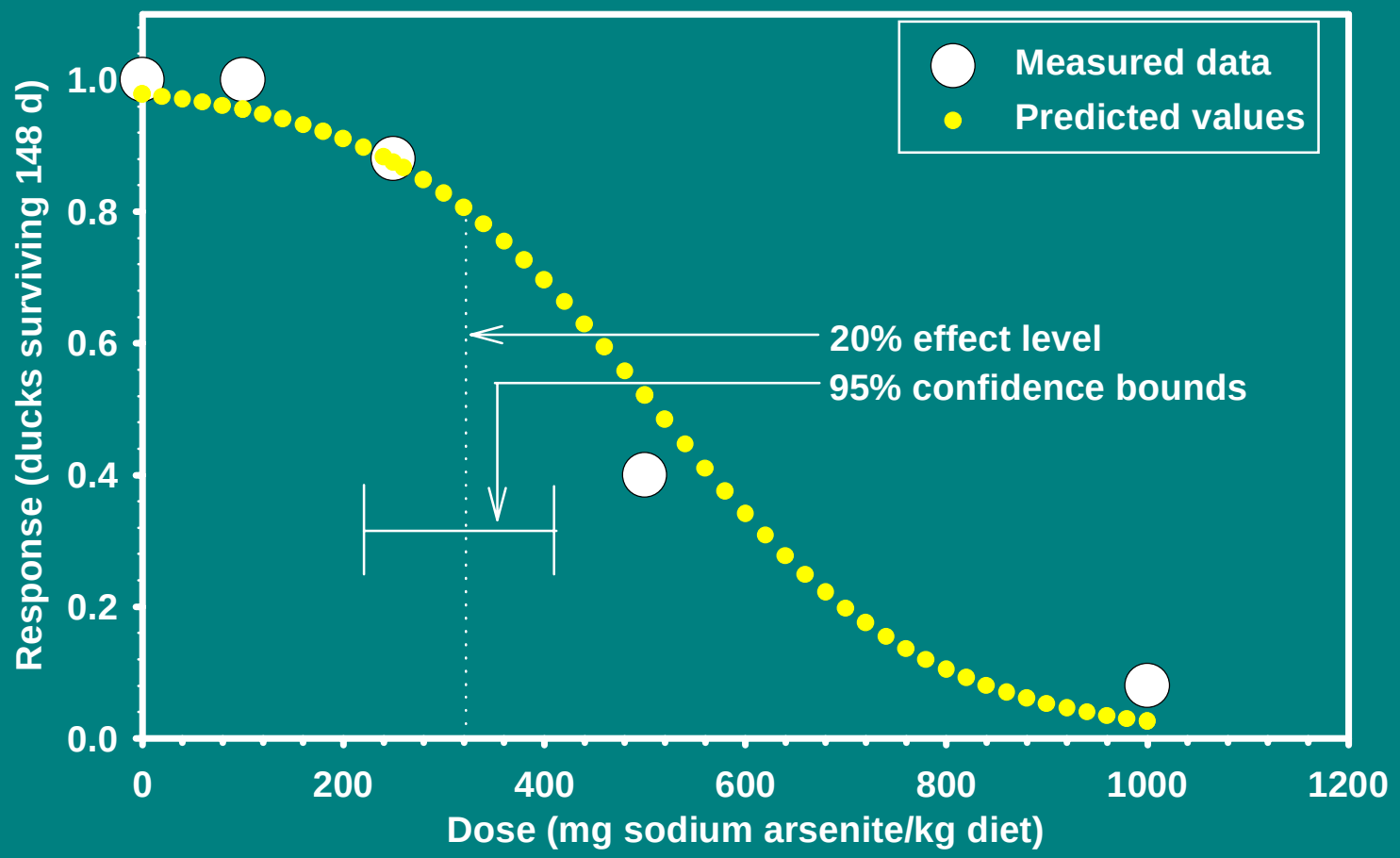

Figure 5. Dose-response relationship for mallard ducks exposed to sodium arsenite in their diet. Data from USFWS (1964). Two-parameter logistic model fit to untransformed mortality data. Minimum and maximum responses set to 0 and 1, respectively.

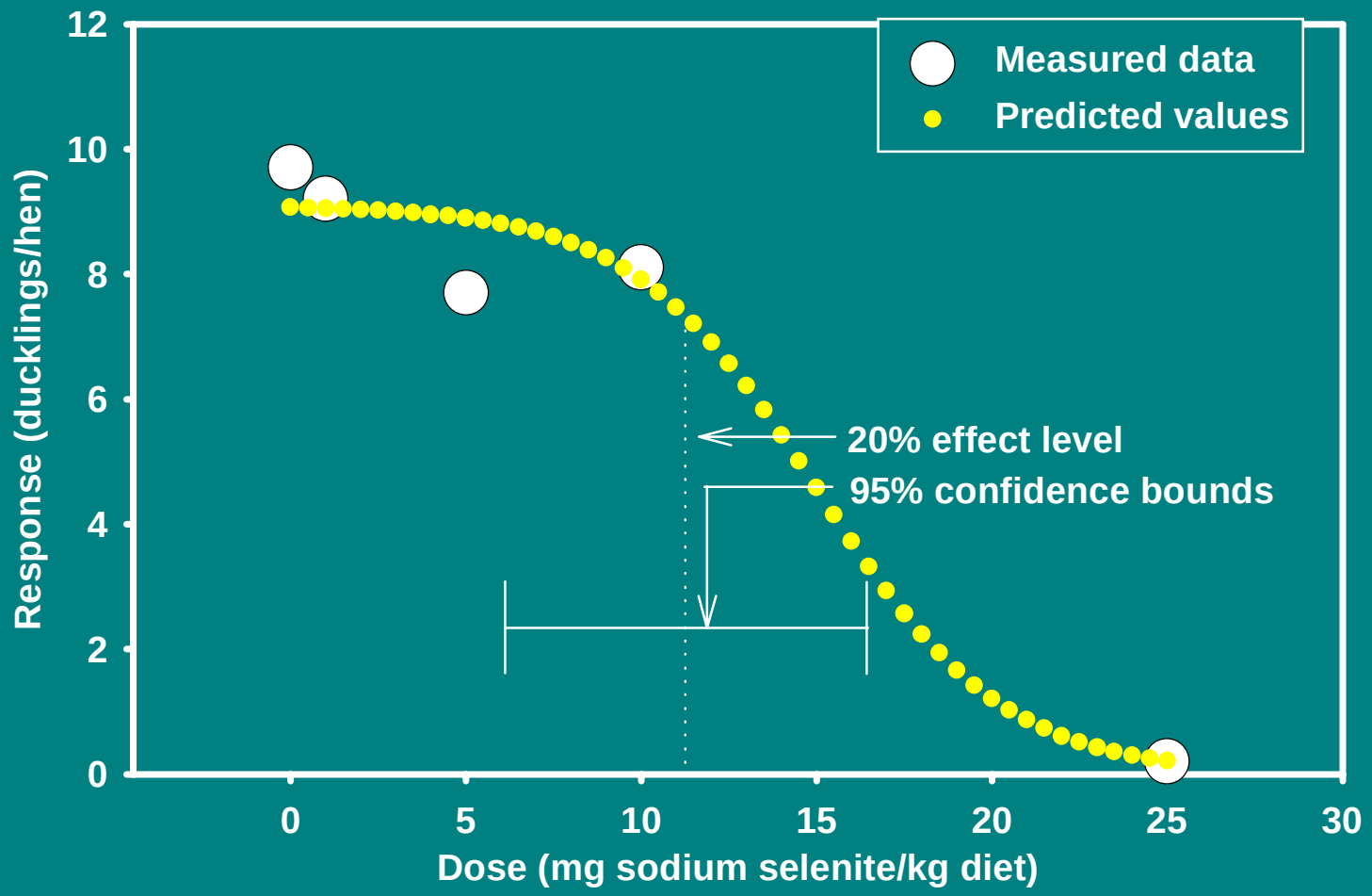

Figure 6. Dose-response relationship for mallard ducks exposed to sodium selenite in their diet. Data from Heinz (1987). Three-parameter logistic model fit to untransformed reproductive success data. Minimum response set to 0.

Future Work for Entire Project:

- Determine if allometric scaling factors differ for birds and mammals or by class of chemical or mode of action.

- Apply dose-response model to sub-chronic and chronic toxicity data to develop standardized response parameters (e.g., ED_{50} for reproductive effects). Compare allometric models based on these chronic data to those developed from acute data to determine if scaling differs by exposure duration and effect endpoint.

- Develop matrix-based population models (Task 4) and integrate toxicity data to determine population effects associated with individual-level exposure. Initial modeling has begun in preparation for a paper to be presented at a US Fish and Wildlife Service/Society for Environmental Toxicology and Chemistry symposium on the population effects of contaminants on wildlife in October 1998.

Literature Cited

Crump, K.S. 1984. A new method for determining allowable daily intakes. Fund. Appl. Toxicol. 4: 854-871.

Dunning, J.B. 1993. CRC handbook of avian body masses. CRC Press, Boca Raton, FL. 371 pp.

EPA (U.S. Environmental Protection Agency). 1988. Recommendations for and documentation of biological values for use in risk assessment. U.S. EPA Office of Research and Development. EPA/600/6-87/008.

EPA (U.S. Environmental Protection Agency). 1992. Draft Report: A cross-species scaling factor for carcinogen risk assessment based on equivalence of $mg/kg^{3/4}$/day; Notice. Federal Register. 57(109)24152-24173.

Freireich, E.J., E.A. Gehan, D.P. Ral, L.H. Schmidt, and H.E. Skipper. 1966. Quantitative comparison of toxicity of anticancer agents in mouse, rat, hamster, dog, monkey, and man. Cancer Chemotherapy Repts. 50: 219-244.

Kimmel, C.A., R.J. Kavlock, B.C. Allen, and E.M. Faustman. 1995. The application of the benchmark dose methodology to data from prenatal developmental toxicity studies. Toxicol. Lett. 82/83: 549-554.

Mineau, P., B.T. Collins, and A. Baril. 1996. On the use of scaling factors to improve interspecies extrapolation of acute toxicity in birds. Reg. Toxicol. and Pharmacol. 24: 24-29.

SAS. 1988. SAS/STAT User's Guide. Release 6.03. SAS Inst. Inc. Cary, NC.

Silva, M., and J.A. Downing. 1995. CRC handbook of mammalian body masses. CRC Press, Boca Raton, FL. 359 pp.

Acknowledgements

Support of this research was provided by the U.S. Department of Energy, Environmental Management Science Program to Oak Ridge National Laboratory. Christine Arenal was responsible for data acquisition and toxicity database development. The dose-response model was developed by John Beauchamp. The SAS macro program for the implementation of the dose-response model was developed by Barbara Jackson. Heather Brooks assisted with data acquisition.