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Performing Ecological Risk Assessments

Edward J. Calabrese
Linda A. Baldwin

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Uncertainty Factors for Ecological Risk Assessment

A. INTRODUCTION

The use of uncertainty factors (UF) in human risk assessment is well known, widely recommended, and implemented at the federal and state level. The types of UFs employed in human risk assessment have traditionally included those dealing with uncertainty to: interspecies differences, interindividual (intraspecies) variation, less- than-lifetime (LL) exposures, and extrapolation from a dose that defined a lowest observable adverse effect level (LOAEL) to a no observable adverse effect level (NOAEL). In addition, for uncertainty not covered by this series of UFs, the Environmental Protection Agency (EPA) uses an additional UF factor called a modifying factor to address the residual uncertainty area(s). In Table 4.1, the EPA provides a description of each UF and its proposed magnitude.

No comparable articulation of the use of UFs in ecological risk assessment has been recommended by expert committees or advisory organizations such as the National Academy of Sciences or by federal regulatory agencies such as the EPA. Nonetheless, the use of UFs in ecological risk assessment has a long history, has been widely discussed, is not viewed as inherently controversial (ASTM 1978; Slooff et al. 1986), and is recommended for use under certain circumstances at hazardous waste sites such as the Rocky Mountain Arsenal (RMA) (HLA 1991). The use of the UF concept in ecological risk assessment has also been employed under a variety of descriptive terms such as application factor (AF) (Kenaga 1982) and assessment factors (EPA 1984).

Table 4.1. Types of Uncertainty Factors (UFs) Used in Human Risk Assessment**Standard Uncertainty Factors (UFs)**

Use a 10-fold factor when extrapolating from valid experimental results from studies using prolonged exposure to average healthy humans. This factor is intended to account for the variation in sensitivity among the members of the human population. (10H)

Use an additional 10-fold factor when extrapolating from valid results of long-term studies on experimental animals when results of studies of human exposure are not available or are inadequate. This factor is intended to account for the uncertainty in extrapolating animal data to the case of humans. (10A)

Use an additional 10-fold factor when extrapolating from less than chronic results on experimental animals when there are no useful long-term data. This factor is intended to account for the uncertainty in extrapolating from less than chronic NOAELs to chronic NOAELs. (10S)

Use an additional 10-fold factor when deriving a RfD from a LOAEL, instead of a NOAEL. This factor is intended to account for the uncertainty in extrapolating from LOAELs to NOAELs. (10L)

Modifying Factor (MF)

Use professional judgment to determine another uncertainty factor (MF) which is greater than zero and less than or equal to 10. The magnitude of the MF depends upon the professional assessment of scientific uncertainties of the study and database not explicitly treated above; e.g., the completeness of the overall database and the number of species tested. The default value for the MF is 1.

Source: Adapted from Dourson, M. L., and J. F. Stara, *Regulatory Toxicology and Pharmacology* 3:224-238 (1983).

This chapter will provide a direct comparison of how ecological and human risk assessments have incorporated the concept of UFs in their respective analyses. In addition, the chapter will provide the biological basis and toxicological rationale for deriving UFs for use in ecological risk assessment.

B. ACUTE-TO-CHRONIC EXTRAPOLATION UNCERTAINTY FACTOR

1. Introduction

Perhaps the most commonly employed and most readily accepted

UF in ecological risk assessment deals with acute to chronic extrapolation [i.e., the application factor (AF)]. This is based on the large experimentally derived acute toxicity database (i.e., 96 hour LC_{50}) for aquatic organisms and the need to derive chronic Maximum Allowable Toxicant Concentration (MATC) values.

The concept of the AF in the process of ecological risk assessment is employed in the prediction of chronic toxicity to organisms from known acute toxicity data within the same species. The AF was first proposed in 1967 by Mount and Stephan, environmental scientists specializing in aquatic toxicology for the U.S. EPA in Duluth, Minnesota. By definition, the AF is a ratio derived by dividing the 96 hour LC_{50} in an acute flow-through test into the no observed adverse effects exposure level (MATC) obtained in a chronic test for the same species. The experimentally derived ratio is then employed to estimate an MATC for other species or test conditions for which only acute LC_{50} data are available.

Mammalian risk assessment has generally not emphasized extrapolation from LD_{50}/LC_{50} values to chronic NOAELs (see McNamara, 1976 for an extensive review), although Layton et al. (1987) have proposed numerical schemes to estimate how extrapolation from acutely toxic doses to chronic NOAELs could be undertaken. Thus, the term AF as widely used in the field of aquatic toxicology has no history of use in the field of human risk assessment and is not mentioned in texts and articles in this area. Despite the general absence of discussion of how to extrapolate from acute to chronic values in human risk assessment, the range of recommended AFs (Kenaga 1978, 1982) are comparable to the observations of Layton et al. (1987) for human risk assessment when starting with LD_{50} data and estimating a chronic NOAEL (i.e., factor of 50-75-fold). The principal concern over the use of an UF for LD_{50} -type data has related to the probability that the acute response may be mechanistically unrelated to a chronic effect. It was thus believed that UFs for acute to chronic extrapolation are principally numerical values without adequate biological underpinnings. While this remains the prevailing view, it should be noted that Zeise et al. (1986) found a strong association between the LD_{50} and cancer potency in rodents. Such findings clearly support the need to reexamine the toxicological basis for acute to chronic relationships, and may provide a vehicle to derive a more biologically plausible rationale for the use of acute to chronic UFs as well as AFs.

2. Deriving Generic Application Factors Based on Acute to Chronic Ratios (ACR)

One approach to determine the ACR size has been to assess ratios of acute and chronic toxicity in aquatic organisms. Kenaga (1979) derived a large number of ACRs for pesticides and heavy metals based on bioassays with fish and daphnids. Acute to chronic ratios ranged over four orders of magnitude with such ACRs ranging from 1.1 to 11,100. A follow-up study by Kenaga (1982) assessed the chemical basis for why some agents have very large ACRs while others have ratios several orders of magnitude lower. In this subsequent analysis, data compiled from numerous sources utilized LC_{50} values from both static renewal and flow-through water systems and MATC values almost exclusively from flow-through water systems. Studies designed to derive MATC values employed both *partial* and *complete life-cycle* experiments. This assessment, based on data from 9 species of fish and 2 species of aquatic invertebrates, generated 135 AFs for 84 chemicals including chlorinated hydrocarbon insecticides (e.g., chlordane, heptachlor, endrin, DDT), fused ring aromatics (e.g., naphthalene), benzene and substituted benzenes (e.g., toluene), phenol and substituted phenols, halogenated aliphatics (e.g., trichloroethylene), herbicides (e.g., 2,4-D), cholinesterase-inhibiting insecticides (e.g., malathion), and miscellaneous organic and inorganic chemicals (e.g., cadmium, nickel, beryllium).

This analysis revealed a range of ACR values from 1 to 18,100. Approximately 86% of the chemicals displayed ACR values ≤ 100 regardless of which species was used to derive the ratio, and approximately 99% of all agents exhibited an ACR within a factor of 1,000 (Table 4.2). When Kenaga (1982) arranged the chemicals according to class, cholinesterase-inhibiting pesticides and heavy metals displayed the greatest percentage of ACR values above 125. Further analyses revealed no association between the magnitude of the ACR value and the degree of acute toxicity. For example, those agents with very low LC_{50} values did not display different ACRs than agents with moderate or low acute toxicity values. Likewise, this analysis did not reveal any predictive association between the magnitude of ACR values with parameters such as bioconcentration factor, persistence in the environment, or octanol-water partition coefficients.

Table 4.2. Relationship of Vertebrate and Invertebrate Species to Acute-Chronic Toxicity Ratio (ACR) Ranges for All Chemicals

ACR	All Species (%)	Fathead Minnow (%)	<i>Daphnia Magna</i> (%)
1-9	43.0	36	52.8
1-99	86.7	86	86.1
1-999	98.6	96	100.0
1-9,999	99.3	98	—
1-99,999	100.0	100	—
No. of examples	135.0	50	36

Source: Kenaga, 1982.

The AF as derived by Kenaga (1982) could be markedly affected, depending on the statistical approach employed to estimate the MATC as well as on the nature of the most sensitive endpoint. Refer to the discussion of Suter et al. (1987) in this chapter on "sensitive life-stage models" concerning statistical methods and endpoint selection and their impact on MATC derivation.

A practical application of acute-to-chronic UFs has been proposed by ESE (1989) with respect to their work at the Rocky Mountain Arsenal. Consistent with the above discussion that approximately 99% of all agents would be expected to be adequately handled by an UF of 1,000, the ESE report recommended the use of an acute LOAEL (i.e., LD₅₀) to a chronic NOEL UF of 1,000. This value reflected within species acute to chronic extrapolation and did not address interspecies variability.

3. Modeling Approaches

Slooff et al. (1986) attempted to predict chronic toxicity from acute lethality using correlation and regression analysis with fish and daphnia for 164 chemicals including pesticides, nonpesticides, organic and inorganic agents. A high correlation was shown between acute and chronic toxicity within a species ($r = .89$). The mathematical relationship between acute and chronic toxicity was determined to be $\log \text{NOEC} = -128 + 0.95 \log L(E)C_{50}$. Their findings are in strong quantitative agreement with the ACR methodology noted above for Kenaga (1979, 1982).

In contrast to the ACR approach for acute to chronic extrapolation, Suter et al. (1983a) used a least-squares regression model

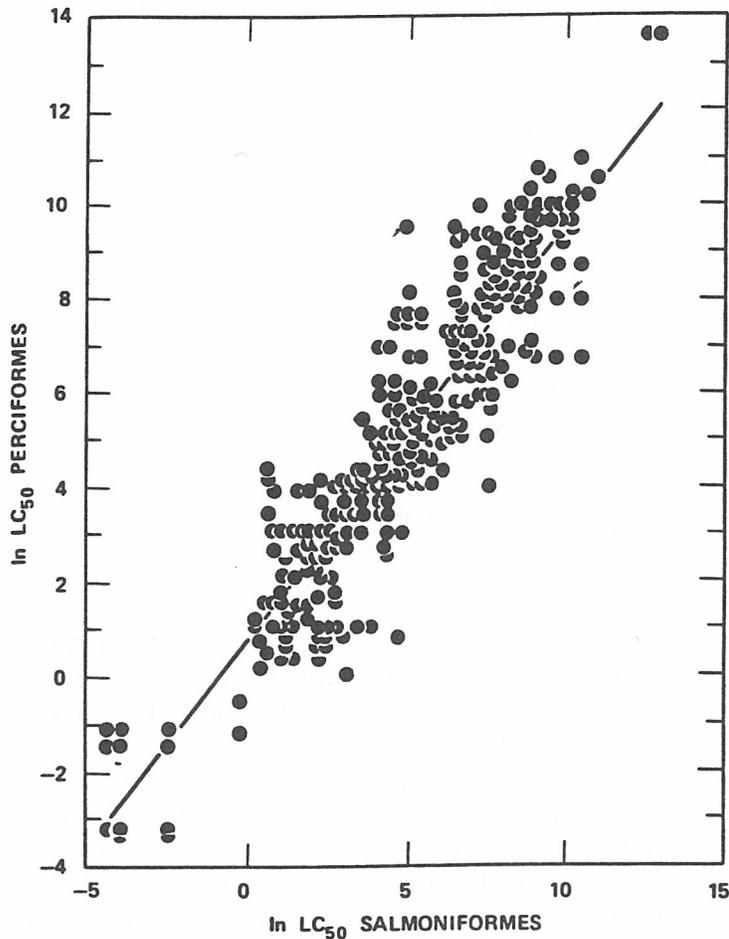


Figure 4.1. Natural logarithms of LC_{50} values for Perciformes plotted against Salmoniformes (orders of the same class, Osteichthyes). The solid line represents the least-squares linear regression of the natural logarithm of LC_{50} values for Perciformes species on the natural logarithm of LC_{50} values for Salmoniformes species. Data from Johnson and Finley (1980). Source: Suter et al., 1983a.

200-fold (i.e., weighted mean 264.9), with the most sensitive parameter (i.e., egg weight) having a 99% UF of 2,247 (Table 4.3).

The data from Table 4.3 indicate, therefore, that the size of the UF for acute to chronic extrapolation depends both on the endpoint measured and the degree of protection desired. Based on

Table 4.3. Acute-Chronic Extrapolation: Means and Weighted Means Calculated for the 95% and 99% Prediction Intervals for Uncertainty Factors Calculated from Regression Models

X Variable	Y Variable	n	Uncertainty Factor		
			Prediction Interval		
			90%	95%	99%
Acute-Chronic Extrapolation					
LC ₅₀	Hatch EC25	31	42	50	67
LC ₅₀	Parent Mort EC25	28	27	32	43
LC ₅₀	Larval Mort EC25	89	26	31	41
LC ₅₀	Eggs EC25	42	53	63	84
LC ₅₀ ^a	Fecundity EC25	26	41	50	68
LC ₅₀ ^a	Weight ^b EC25	37	43	52	70
LC ₅₀ ^a	Weight/Egg EC25	14	200	245	344
Mean				74.7	102.4
Weighted Mean				54.3	73.5

^aRegression analysis from Suter et al. 1987.

^bDecrease in weight of fish at end of larval stage.

these data the 95% UF and the 99% UF would be reasonably approximated by 50 and 200, respectively, using weighted mean values for the following endpoints (e.g., hatch EC25, fecundity EC25).

It is important to consider the implications of whether the ACR UF was based on incomplete or complete life-stage data. In the case of Kenaga (1982), data on both incomplete/complete life-stages were employed. The data of Barnthouse et al. (1990) can be related to this life-stage dichotomy (i.e., incomplete vs complete) by consideration of specific endpoints (e.g., larval mortality, hatchability, etc.).

If the ACR UF were based on incomplete life cycle data it would appear that an additional UF addressing the incomplete life-stage is necessary. If the ACR UF were based on complete life cycle endpoints, then the sensitive life-stage UF should not be used. Of concern is how to select the endpoint upon which to base the regression. The large differential sensitivity and variability in endpoint response (e.g., hatch EC25 versus egg weight EC25) is problematic, and represents an area in need of further consideration.

If a frankly toxic effect other than lethality (e.g., LC₅₀) occurs, it is recommended that the UF be reduced to an intermediate position between the LOAEL to NOAEL UF (i.e., 10-fold, see below) and the acute toxicity value to NOAEL UF (i.e., 50-fold). This is

consistent with dose response functions in toxicology and would hold for nonendangered and endangered species.

4. Comparison of Acute to Chronic Ratio Approach with Modeling

The question then arises as to whether there is a best or most appropriate way to estimate the MATC from acute data. Suter et al. (1983a) compared three approaches, including their regression analysis and two AF (i.e., ACR) methods. The AF methods were: (1) a GMATC derived directly with the fathead minnow (FM) for the chemical in question (i.e., FM-GMATC) and (2) a GMATC derived from the ratio of LC₅₀ values for the species in question, based on the LC₅₀ and GMATC values for the fathead minnow for the same chemical (i.e., AF-GMATC approach). Table 4.4 compares the three approaches to the true GMATC based on tested MATCs for each species and chemical. No approach distinguished itself, with each estimation procedure being closest to the GMATC in six cases and with the FM-GMATC and AF-GMATC estimates tying once. Both the FM-GMATC and AF-GMATC approaches had two instances where the error exceeded 10, while the extrapolation (i.e., regression) method had three such instances. The largest errors were found for the FM-GMATC derivation for malathion with bluegill and flagfish where it underestimated toxicity by some 68- and 34-fold, respectively. The third highest error was reported for the regression technique where it overestimated toxicity by 25-fold for zinc in the brook trout. Of the 11 instances where the FM-GMATC method was in error by a factor of two or greater, eight underestimated the risk. Of the 11 instances where the AF-GMATC method was in error by a factor of two or greater, seven underestimated the risk. Of the 13 instances where the regression technique was in error by a factor of two or more, seven underestimated the risk.

This comparison revealed that all three methods provided estimates of the GMATC for another species that were generally within one order of magnitude of the true (i.e., experimentally derived) GMATC. In seven of the 54 (12.9%) comparisons, the estimates were in error by more than one order of magnitude but not greater than two orders of magnitude. In addition, in the true GMATC derivation experiments, the AFs ranged from .0002 to .8530 (4265-fold range) which is generally comparable to that reported earlier for Kenaga (1982). Within this context it is important to note that 11 of the 18 examples had ACR values within 99-fold, while 15 of

ns Calculated
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ty Factor	Interval
	99%
	67
	43
	41
	84
	68
	70
	344
.7	102.4
.3	73.5

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Table 4.4. Comparison of Methods for Estimating the Geometric Mean of the Maximum Acceptable Contaminant Concentration (GMATC)

Chemical	Species	True GMATC ^a	FM GMATC ^b	AF GMATC ^c	Extrapolation GMATC ^d
Atrazine	Bluegill	0.218	0.330	0.149	0.098 *
	Brook trout	0.088	0.330 *	0.109	0.075 *
Cadmium	Bluegill	0.050	0.046	0.135 *	0.253 *
	Flagfish	0.006	0.046 *	0.016 *	0.042 *
Chromium	Brook trout	0.265	1.987 *	3.257 **	0.584 *
	Rainbow trout	0.265	1.987 *	3.809 **	0.662 *
Copper	Bluegill	0.029	0.025 *	0.204 *	0.021
	Bluntnose minnow	0.009	0.025 *	0.017	0.005
Lindane	Brook trout	0.013	0.025	0.019	0.003 *
	Bluegill	0.011	0.015	0.006	0.001 **
Malathion	Brook trout	0.012	0.015	0.006	0.001 **
	Bluegill	0.005	0.341 **	0.004	0.003
Methyl mercury	Flagfish	0.010	0.341 **	0.001 *	0.008
	Brook trout	0.0005	0.0001 *	0.0001*	0.0019*
Toxaphene	Flagfish	0.0002	0.0001 *	0.0004*	0.0055*
	Channel catfish	0.0002	0.00004*	0.0001*	0.0005*
Zinc	Brook trout	0.853	0.088	0.355 *	0.035 **
	Flagfish	0.102	0.088	0.266	0.027 *

Source: Suter et al., 1983a.

^aTrue GMATC based on geometric mean of tested MATCs.

^bFM GMATC based on GMATC for fathead minnow tested with same contaminant.

^cAF GMATC based on application factor or ratio of LC₅₀ values for listed species to LC₅₀ values for fathead minnow for same contaminant.

^dExtrapolation GMATC calculated by Equation 4.3. The best estimate of the true value is in italics; estimates which differ from the true GMATC by a factor of 2 or greater and by 10 or greater are indicated by single and double asterisks, respectively.

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18 were within 999-fold. Three had ACR values of greater than 1,000.

While this direct comparison did not reveal a preferred approach, it must be emphasized that the comparison was limited to only nine agents in widely differing chemical classes and generalizations cannot be reliably made. However, a toxicologically-based evaluation can be used to differentiate the approaches as to their inherent capacity to yield biologically defensible predictions.

The FM-GMATC approach assumes that the fathead minnow would have identical LC_{50} and GMATC values as the species of interest. Since no data exist on the species of interest, the prediction relies entirely upon the capacity of the fathead minnow to simulate the response of the species of interest. This approach involves a direct interspecies extrapolation. It does not involve an acute to chronic extrapolation, since experimental data are collected for both types of endpoints.

In contrast to the FM-GMATC, the AF-GMATC utilizes experimental data from the fathead minnow on acute and chronic endpoints to derive an acute to chronic ratio. This ratio (not the absolute values) is believed to be identical with that of the species of interest. The key difference between the FM- and AF-GMATC methods is that the AF-GMATC method has acute data on the species of interest. This represents a substantial improvement over the FM-GMATC, since it should eliminate much of the uncertainty inherently present in the FM-GMATC approach. The uncertainty (i.e., interspecies) of the AF-GMATC approach is that the acute to chronic ratio of the fathead minnow is assumed to be identical to that of the species of concern. The AF-GMATC would be expected to be a better predictor than the FM-GMATC approach based on the extensive analyses of Slooff et al. (1986), which indicated that interspecies extrapolation was much more uncertain than estimates of acute to chronic ratios.

The strongest of the three approaches is expected to be the extrapolation E-GMATC method because it makes use of a robust database of acute to chronic ratios to derive its regression equation and then employs the acute toxicity value for the species of interest to estimate the E-GMATC.

The critical issue is how reliable the regression equation estimate of a GMATC would be, compared to the ratio offered by the fathead minnow. If the fathead minnow were an excellent predictor for the species of interest, then clearly it would be a potentially

the GMATC based on GMATC for fathead minnow tested with same contaminant.

b) FM GMATC based on application factor or ratio of LC_{50} values for listed species to LC_{50} values for fathead minnow for same contaminant.

c) AF GMATC based on application factor or ratio of LC_{50} values for listed species to LC_{50} values for fathead minnow for same contaminant.

d) Extrapolation GMATC calculated by Equation 4.3. The best estimate of the true value is in italics; estimates which differ from the true GMATC by a factor of 2 or greater and by 10 or greater are indicated by single and double asterisks, respectively.

attractive option. However, since this is not likely to be inherently known, it is usually more attractive to use a broader database. This would likely lead to predictions that are not especially excellent, but not far off the mark.

In the cases of the AF- and E-GMATC, the type of extrapolation should be viewed as that involving acute to chronic (i.e., high to low dose extrapolation). In contrast to the FM-GMATC method, these methods do not include interspecies uncertainty.

The work of Slooff et al. (1986) indicates that considerably greater uncertainty exists with interspecies rather than acute to chronic extrapolation. This perspective also supports the conclusion noted above that the FM-GMATC is the least attractive methodology of the three reviewed.

5. Recommendation

This analysis revealed that a substantial database exists upon which to derive an acute to chronic UF for use in ecological risk assessment. Various approaches including the ACR method and statistical modeling provide comparable estimates of the acute to chronic UFs with respect to the proportion of the population protected. The ACR also appears to be quantitatively similar for aquatic as well as terrestrial animals. These collective findings support the recommendation that an acute to chronic UF of 50 be employed if the intent is to provide protection at the 95% level. Other-sized UFs could be estimated, depending on the level of protection desired and endpoint selected.

C. LOAEL TO NOAEL UF

1. Comparison Between Human and Ecological Approaches

The most common high to low dose extrapolation seen in mammalian risk assessment covers a much more modest dosage range than typically seen in aquatic risk assessment involving extrapolation from a known LOAEL dosage to an unknown dosage approximating the highest NOAEL. While considerable ecologically-based acute to chronic (i.e., application factor) extrapolation examples exist, there is little evidence (see HLA, 1991) that LOAEL (LOEC) to NOAEL (NOEC) extrapolation procedures have been

implemented in ecological risk assessment. In the 1991 HLA report, which was directed toward both aquatic and terrestrial animals, the concept of LOAEL to NOAEL extrapolation was used in a manner qualitatively comparable to that seen in human risk assessment.

While it is unknown precisely why the concept of LOAEL to NOAEL extrapolation has not been used widely in ecological risk assessment, it is most likely related to the long history in aquatic toxicology of emphasizing the determination of principally acute effects. Thus, the chronic effects database has only more recently begun to become robust with respect to a wide range of chronic endpoints. As the field of aquatic toxicology continues to evolve in such a manner as to incorporate the types of endpoints measured in mammalian toxicology (e.g., reversible toxic responses), there will become greater pressure to adopt the use of the LOAEL to NOAEL UF. The usual aquatic study design involves a concurrent control and five treatment groups. This wide range of treatment groups provides an enhanced opportunity to estimate both the NOAEL and LOAEL. In such instances extrapolation uncertainties will be markedly reduced. Secondly, Suter et al. (1983a) have advocated the adoption of a geometric MATC (GMATC) which was defined by calculating the geometric mean of the NOEC and LOEC. In theory this may more closely estimate the actual highest NOEC than simple acceptance of the highest experimentally derived NOEC.

There is no reason for the dichotomy between ecological and human risk assessment goals to preclude the LOAEL to NOAEL UF. In fact, it is likely that the NOAEL could be estimated via regression analysis at an a priori response level, assuming the presence of an adequate database.

2. Recommendation

The derivation of the LOAEL to NOAEL UF in ecological risk assessment may be on the basis of a generic UF, as seen in the case of human risk assessment (see Table 4.1), regardless of whether the species of concern was nonendangered or protected. Another legitimate approach for deriving a NOAEL from a LOAEL may be via the use of regression modeling. The biological and statistical rationale for the use of modeling is presented in Section E1 of this chapter. The decision to use a generic UF or modeling approach should be made on a weight of evidence basis including

consideration of study design, statistical analysis, endpoints measured, and biological relevance.

D. INTERSPECIES (TAXONOMIC) VARIATION UF

1. Introduction

The use of an interspecies extrapolation factor in ecological risk assessment has been discussed by a variety of authors (Suter et al., 1983a; Barnthouse et al., 1987, 1990; Slooff et al., 1986), and EPA (EPA, 1984, Stephan and Rogers, 1985). While all acknowledge that interspecies variation exists, no uniform approach has been presented to derive an UF to account for such variability. This lack of consensus of how to deal explicitly with interspecies variation for the purposes of ecological risk assessment stands in marked contrast to the generally accepted use of an interspecies UF of 10 in human risk assessment.

It may be argued that human risk assessment has had an inherently easier time since its goal (i.e., protecting humans) is more clearly defined and limited, while ecological risk assessors must consider interspecies differences for extrapolation purposes over a broad range of taxa with the goal of protecting not just one species but the ecosystem itself. Thus, the ecological risk assessor is confronted with a more formidable challenge so that a simple factor of 10 may be inadequate to deal with this apparently broader range of uncertainty. While extrapolation across numerous taxa may seem to be in the domain of the ecological risk assessors, how they "solve" the problem is likely to be of considerable theoretical and practical interest to the field of human risk assessment, since this could evolve procedures by which nonmammalian models could be used for extrapolation to humans.

2. Magnitude of Interspecies Variation

Numerous attempts have been made to assess the occurrence and magnitude of interspecies variation in response to ecological toxicants. Such studies have typically focused on interspecies variation with respect to acute toxicity in the aquatic environment (Pearson et al. 1979, Kenaga and Moolenaar 1979; Kenaga 1978, 1979; Suter et al. 1983a; Kimerle et al. 1983; Maki 1979; Doherty

1983; LeBlanc 1984; Slooff et al. 1986; Niederlehner et al. 1986). While these studies generally involved a wide range of agents with only a limited number of species, the comparative susceptibilities of aquatic species in general were shown to be contingent on their taxonomic relationship as well as the chemical tested. Table 4.5 shows the extreme range of EC_{50} values for cadmium as a function of taxonomic grouping (Niederlehner et al. 1986). In addition, while invertebrates and fresh and saltwater fish responded in a comparable manner to nonpesticide organics (r ranging from 0.79 to 0.95), no association was seen for pesticide susceptibilities between fish and invertebrates ($r = .02$) (LeBlanc 1984). Likewise, an assessment of acute toxicity by Suter et al. (1983) on 28 fish species from 17 genera, 10 families, and 6 orders for 271 chemicals (75% of which were pesticides) revealed a declining correlation (r) with increasing taxonomic distance (i.e., cogenetic species 0.90, genera 0.89, families 0.8, and orders 0.74) (Table 4.6).

Expansion of the database to include acute exposure values for 35 different species from 11 taxonomical groups to 15 agents was undertaken by Slooff et al. (1986). In their study, correlation and regression analyses were performed on log-transformed acute toxicity values for the 15 chemicals (Table 4.7) for each possible binary combination of species. The 95% uncertainty factors (UFs) provide an estimate of the variation in interspecies response (Figure 4.2).

Slooff et al. (1986) found a positive correlation in interspecies relationships in response to toxic agents with somewhat higher correlations being observed for species within the same phylogenetic grouping as compared to taxonomically more distant species. With respect to the 95% UF, despite the highly correlated relationship between species sensitivities to chemical, the UF values were quite variable and on occasion exceeded 1,000-fold. This extensive analysis resulted in an estimated 95% UF of nearly 1,200 for the various binary interspecies comparisons. Figure 4.3 displays the distribution of the interspecies UFs (Slooff et al. 1986). These results show that only a small proportion of the UFs were within a factor of 10, while the majority (60%) were between a factor of 10 and 100. A substantial percentage, approximately 30%, exceeded the 100-fold value, while about 11% exceeded 320-fold.

These findings led the authors to conclude that interspecies acute toxicity predictions possess greater uncertainty than predictions of chronic from acute effect levels in the same species (see previous

Table 4.5. Summary of Single-Species Toxicity Test Data for Cadmium in $\mu\text{g/L}$

Taxonomic Family	Mean EC ₅₀ ^a	Mean EC ₉₅ ^a	Hardness Adjusted Mean EC ₅₀ ^a (at 65 mg/L)	Mean MATC ^a
Rotifers				
Philodinidae	311	458	597	—
Oligochaetes				
Naididae	1,700	—	2,304	—
Aeolosomatidae	2,445	6,115	1,448	43.28
Tubificidae	5,829	—	114,184	—
Lubriculidae	745	—	5,162	—
Turbellarians				
Planariidae	4,900	—	19,221	—
Mollusks				
Hydridae	1,600	—	970	—
Bithyniidae	8,400	—	11,383	—
Physidae	410	—	111	—
Planorbidae	201	665	201	—
Lymnaeidae	1,600	—	970	—
Cladocerans				
Daphnidae	39	93	52	1.39
Copepods				
Cyclopidae	340	—	1,334	—
Cyclopidae	—	15,650	—	—
Calanoididae	—	3,700	—	—
Ostracods				
Cypridopsidae	190	—	745	—
Isopods				
Talitridae	85	—	333	—
Amphipods				
Gammaridae	218	—	241	—
Insects				
Ephemereidae	7,483	48,000	3,143	—
Heptageniidae	270	—	270	—
Pteronarcyidae	18,435	52,000	18,872	—
Odonate	8,100	—	10,977	—
Chironomidae	3,079	—	3,754	6.60
Culicidae	4,806	—	2,915	—
Trichopteran	3,400	—	4,207	—
Glossosomatidae	308,750	—	308,611	—
Hydropsychidae	5,750	—	5,747	—
Psephenidae	372,120	—	371,953	—
Bryozoans				
Pectinatellidae	700	1,364	190	—
Lophopodidae	150	3,550	41	—
Plumatellidae	1,090	3,508	296	—

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Table 4.5

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Taxonomic Family	Mean EC ₅₀ ^a	Mean EC ₉₅ ^a	Hardness Adjusted Mean EC ₅₀ ^a (at 65 mg/L)	Mean MATC ^a
Fish				
Anguillidae	820	—	995	—
Salmonidae	3	—	7	3.60
Salmonidae	—	16,841	—	—
Cyprinidae	429	—	809	45.92
Cyprinodontidae	524	—	724	5.76
Poecillidae	2,445	17,488	6,569	—
Oryziatidae	213	—	87	—
Gasterosteidae	12,227	82,990	6,574	—
Percichthyidae	8,400	—	10,192	—
Centrarchidae	5,961	—	5,337	19.18
Esocidae	—	—	—	7.36
Catostomidae	—	—	—	7.10
Amphibians				
Ambystomidae	1,300	—	788	—
Pipidae	3,200	—	1,941	—

Source: Niederlehner et al., 1986.

^aSee text for definitions of terms.

section on application factors). The magnitude of the interspecies UF was reduced to some extent when comparisons were made within their same taxonomic group (e.g., bacteria, algae, protozoa, crustacea, insecta, pisces, amphibia, etc.). For instance, although no examples of regression derived UFs greater than 1,000 were seen for within taxa, comparison values greater than 100 were common.

The study of Slooff et al. (1986) is striking in its magnitude of interspecies comparisons. However, it is uncertain how the selection of species within taxonomic groups, as well as the number and range of chemical agents, affected the predictions. For example, one species was used to represent Coelenterata, Turbellaria, and Mollusca, seven species were employed to represent Insecta and Pisces, and the remaining taxonomic groups were intermediate in their species representation.

Slooff et al. (1986) provided no recommendations for how this information could or should be employed in the ecological risk assessment process. However, although not conclusive, the data of Slooff et al. (1986) provide a basis for assessing the association of

continued

Table 4.6. Listing of Acute Toxicity Comparisons at Four Taxonomic Levels (genus, family, order, class) for Data from Columbia National Fisheries Research Laboratory

Taxon 1	Taxon 2	n	R ²
Species			
<i>Salmo clarki</i>	<i>Salmo gairdneri</i>	31	0.88
<i>Salmo clarki</i>	<i>Salmo salar</i>	7	0.67
<i>Salmo clarki</i>	<i>Salmo trutta</i>	7	0.93
<i>Salmo gairdneri</i>	<i>Salmo salar</i>	11	0.91
<i>Salmo gairdneri</i>	<i>Salmo trutta</i>	14	0.91
<i>Salmo salar</i>	<i>Salmo trutta</i>	5	0.99
<i>Salvelinus fontinalis</i>	<i>Salvelinus namaycush</i>	5	0.93
<i>Ictalurus melas</i>	<i>Ictalurus punctatus</i>	11	0.95
<i>Lepomis cyanellus</i>	<i>Lepomis macrochirus</i>	14	0.95
Genera			
<i>Oncorhynchus</i>	<i>Salmo</i>	54	0.93
<i>Oncorhynchus</i>	<i>Salvelinus</i>	18	0.81
<i>Salmo</i>	<i>Salvelinus</i>	85	0.83
<i>Carassius</i>	<i>Cyprinus</i>	6	0.96
<i>Carassius</i>	<i>Pimephales</i>	18	0.95
<i>Cyprinus</i>	<i>Pimephales</i>	8	0.92
<i>Lepomis</i>	<i>Micropterus</i>	48	0.92
<i>Lepomis</i>	<i>Pomoxis</i>	6	0.90
Families			
<i>Salmonidae</i>	<i>Esocidae</i>	9	0.18
<i>Centrarchidae</i>	<i>Percidae</i>	65	0.91
Orders			
<i>Salmoniformes</i>	<i>Cypriniformes</i>	246	0.76
<i>Salmoniformes</i>	<i>Siluriformes</i>	218	0.59
<i>Salmoniformes</i>	<i>Atheriniformes</i>	9	0.82
<i>Salmoniformes</i>	<i>Perciformes</i>	503	0.85
<i>Cypriniformes</i>	<i>Siluriformes</i>	98	0.80
<i>Cypriniformes</i>	<i>Atheriniformes</i>	5	0.99
<i>Cypriniformes</i>	<i>Perciformes</i>	218	0.73
<i>Siluriformes</i>	<i>Atheriniformes</i>	6	0.54
<i>Siluriformes</i>	<i>Perciformes</i>	204	0.59
<i>Atheriniformes</i>	<i>Perciformes</i>	11	0.94

Source: Suter et al., 1983a.

phylogenetic relatedness and the magnitude of uncertainty in interspecies extrapolation.

3. Interspecies Variation and Phylogenetic Relatedness

In a similar manner to the approach put forth by Slooff et al. (1986), we have estimated the 90% UF, 95% UF, and 99% UF of

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Table 4.7. Agents Used in Toxicity Assays Reported by Slooff et al. 1986

	Mercury(III)chloride
	Cadmium nitrate
	N-Propanol
	n-Heptanol
	Ethyl acetate
	Ethyl propionate
	Acetone
	Trichloroethylene
	Benzene
	Aniline
	Allylamine
	Pyridine
	o-Cresol
	Salicylaldehyde
	Pentachlorophenol

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	R ²
1	0.88
7	0.67
7	0.93
1	0.91
4	0.91
5	0.99
5	0.93
11	0.95
14	0.95
54	0.93
18	0.81
85	0.83
6	0.96
18	0.95
8	0.92
48	0.92
6	0.90
9	0.18
65	0.91
246	0.76
218	0.59
9	0.82
503	0.85
98	0.80
5	0.99
218	0.73
6	0.54
204	0.59
11	0.94

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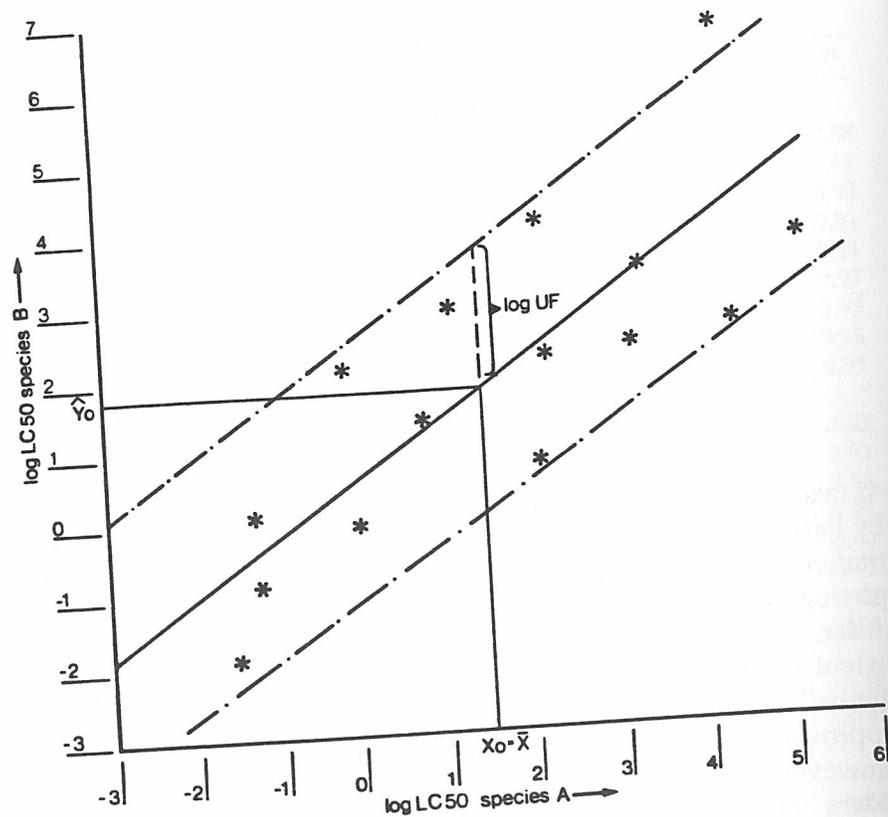
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42 taxonomic binary toxicity comparisons of fish species published by Barnthouse et al. (1990). These assessments represent a quantitative estimate of interspecies toxicological predictions based on phylogenetic relatedness as seen at the species, genus, family, order, and class levels of organization. The data indicate that the extent of taxonomic variation is similar for the "species within genus" and the "genera within family" categories with values of approximately 6-fold at the 95% level, and 10-fold at the 99% level. However, the phylogenetic relatedness diminishes when one considers "families within order" and "orders within class," with the size of the UFs increasing appreciably. For example, excluding #46, the mean UF for "orders within class" was 23.5-fold for 95% and 31.7-fold for 99% levels, respectively.

The magnitude of the interspecies variation seen in this further evaluation of the Barnthouse et al. (1990) data support the premise that interspecies variation is generally inversely associated with phylogenetic relatedness. The magnitude of the 99% UF for "species within genera" was about 10-fold, while up to 32-fold for "orders within class." These findings are generally consistent with the above data of Slooff et al. (1986), although the absolute magnitude of interspecies variation is somewhat less in the Barnthouse et al. (1990) data. This is probably due to the fact that some of the Slooff et al. (1986) comparisons were across major taxa ranging from bacteria to amphibia.

The present analysis of the Barnthouse et al. (1990) data is restricted to the use of aquatic models. Whether similar relationships



$$\hat{y}_0 \pm t \cdot s \left(1 + \frac{1}{n} + \frac{(x_0 - \bar{x})^2}{\sum_1^n (x_i - \bar{x})^2} \right)^{1/2}$$

where $t = 1/2$ percentile of a Student distribution with $n - 2$ degrees of freedom; $s =$ estimated residual variance; $n =$ number of observations; $x =$ known log LC_{50} species A; and $y =$ estimated log LC_{50} species B. When $x_0 = \bar{x}$, the prediction interval becomes $\hat{y}_0 \pm t \cdot s [1 + (1/n)]^{1/2}$. The uncertainty factor is defined as the minimum ratio of the estimated toxicity value and its 95% upper or lower prediction limit after back transformation: $UF = 10^{t \cdot s} [1 + (1/n)]^{1/2}$. In applied terms: If the toxicity of a given compound for A is known, the value for B is in the range of $A/UF < B < A \cdot UF$ with a probability of 95%.

Figure 4.2. Determination of uncertainty factors (UF). Toxicity values were logarithmically transformed and the line of best fit was constructed through least-squares estimation. Source: Slooff et al., 1986.

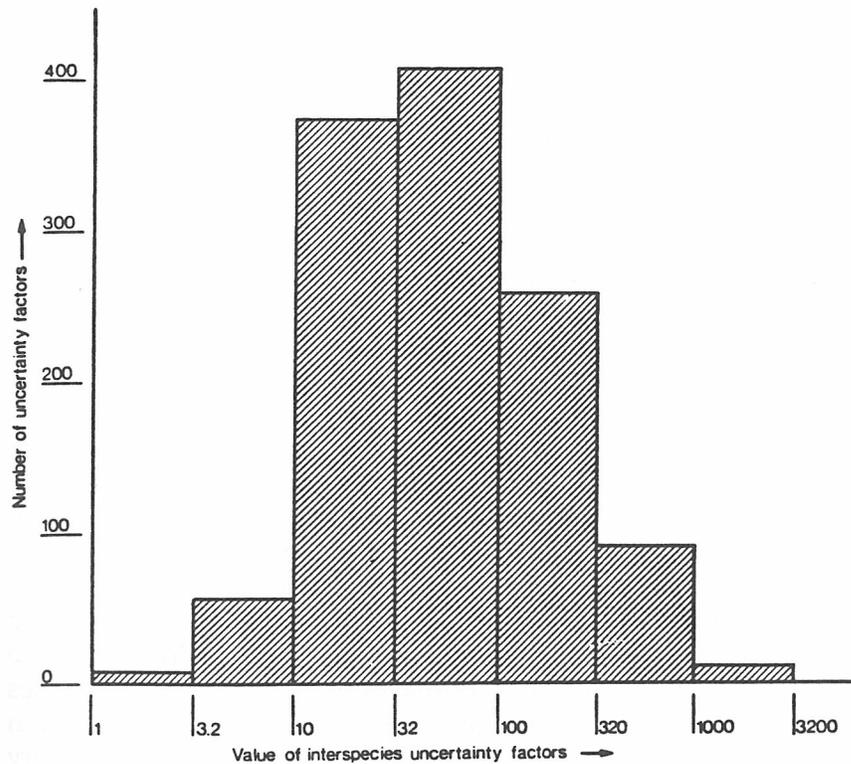


Figure 4.3. Distribution of interspecies uncertainty factors based on acute toxicity data for 15 chemical compounds and 35 freshwater species. Source: Slooff et al. 1986.

hold for terrestrial species is unknown. Nonetheless, the data analysis has the theoretical potential to offer a toxicologically based process for deriving UFs for ecological risk assessments based on phylogenetic relatedness. However, one must recognize that extreme outliers exist, such as #34 and especially #46, that must temper enthusiasm for the derivation of generic UFs for ecological risk assessment procedures. Despite these exceptions, the above approach offers an encouraging foundation upon which UFs could be derived and for which underlying biological regularities could be discerned for predicting the basis of interspecies variation.

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4. Deriving an Interspecies UF for Ecological Risk Assessment: Recommendations

When deriving a generic interspecies UF for use in ecological risk assessment, it will be necessary to consider (1) the magnitude of protection built into the UF (e.g., 95%, 99%, or other), (2) the relevance of the chemicals comprising the model, (3) whether interspecies comparisons based on phylogenetic relatedness can be legitimately made to the chemicals of concern for a site-specific analysis, and (4) whether and how to develop a "weighted" UF (within each UF category) based on the available data (Table 4.8).

This exercise in UF estimation must be placed within the context of its limitations. For example, the approach used for UF derivation assumes that the species have been randomly selected from the broader population and are representative of that population. This fundamental assumption is not satisfied for the data of Table 4.8. This is not a minor consideration, but one that can drastically alter estimated values. However, the amount of data available for each category is also highly variable, with 102 comparisons offered for the species within genera, 212 comparisons offered for the genera within families, 125 comparisons offered for the families within orders, and 1803 comparisons offered for the orders within classes. The "orders within classes" comprises the vast majority of the database (80.4%). On this basis, it would appear that the most reliable database would be the orders within classes.

What should the interspecies UF be for ecological risk assessment? The data from Barnthouse et al. (1990) support the premise that the size should be a function of the degree of phylogenetic relatedness. However, to make a fair assessment, the categorical comparisons (i.e., species within genera, genera within families, etc.) need to be made on the same compounds under similar testing protocol. As it currently stands, the possibility exists that the reason for the phylogenetic relationship may be simply a matter of chemical selection and not interspecies variation. Until the proper comparison is made, the data from Barnthouse et al. (1990) present the best argument for interspecies UFs being based on phylogenetic relatedness.

Assuming that the individual binary comparisons are appropriate, we contend that the average of the upper percentiles (95%,

Table 4.8. Taxonomic Extrapolation: Means and Weighted Means Calculated for the 95% and 99% Confidence Intervals for Uncertainty Factors Calculated from Regression Models

X Variable	Y Variable	n	Uncertainty Factor		
			Prediction Interval		
			90%	95%	99%
Taxonomic Extrapolation: Species within Genera					
<i>Salmo clarkii</i>	<i>S. gairdneri</i>	18	8	9	13
<i>Salmo clarkii</i>	<i>S. salar</i>	6	5	6	10
<i>Salmo clarkii</i>	<i>S. trutta</i>	8	4	6	8
<i>Salmo gairdneri</i>	<i>S. salar</i>	10	6	7	11
<i>Salmo gairdneri</i>	<i>S. trutta</i>	15	3	4	5
<i>Salmo salar</i>	<i>S. trutta</i>	7	4	5	8
<i>Ictalurus melas</i>	<i>I. punctatus</i>	12	4	5	7
<i>Lepomis cyanellus</i>	<i>L. macrochirus</i>	14	5	6	9
<i>F. heteroclitus</i>	<i>Fundulus majalis</i>	12	5	6	8
Mean				6.1	10.1
Weighted Mean				6.0	7.7
Taxonomic Extrapolation: Genera within Families					
<i>Oncorhynchus</i>	<i>Salmo</i>	56	4	5	6
<i>Oncorhynchus</i>	<i>Salvelinus</i>	13	3	4	5
<i>Salmo</i>	<i>Salvelinus</i>	56	5	5	7
<i>Carassius</i>	<i>Cyprinus</i>	8	3	4	6
<i>Carassius</i>	<i>Pimephales</i>	19	5	7	9
<i>Cyprinus</i>	<i>Pimephales</i>	10	5	7	10
<i>Lepomis</i>	<i>Micropterus</i>	30	7	8	11
<i>Lepomis</i>	<i>Pomoxis</i>	8	7	9	13
<i>Cyprinodon</i>	<i>Fundulus</i>	12	5	6	8
Mean				6.1	8.3
Weighted Mean				5.8	7.7
Taxonomic Extrapolation: Families within Orders					
<i>Centrarchidae</i>	<i>Percidae</i>	47	9	10	14
<i>Centrarchidae</i>	<i>Cichlidae</i>	6	3	4	6
<i>Percidae</i>	<i>Cichlidae</i>	5	10	13	24
<i>Salmonidae</i>	<i>Esocidae</i>	11	7	9	13
<i>Atherinidae</i>	<i>Cyprinodontidae</i>	32	6	7	9
<i>Mugilidae</i>	<i>Labridae</i>	12	45	55	78
<i>Cyprinodontidae</i>	<i>Poecillidae</i>	12	3	3	5
Mean				14.4	21.3
Weighted Mean				12.6	17.9

continued

Table 4.8. *Continued*

X Variable	Y Variable	n	Uncertainty Factor		
			Prediction Interval		
			90%	95%	99%
Taxonomic Extrapolation: Orders within Classes					
<i>Salmoniformes</i>	<i>Cypriniformes</i>	225	17	20	27
<i>Salmoniformes</i>	<i>Siluriformes</i>	203	33	39	51
<i>Salmoniformes</i>	<i>Perciformes</i>	443	10	12	16
<i>Cypriniformes</i>	<i>Siluriformes</i>	111	9	11	15
<i>Cypriniformes</i>	<i>Perciformes</i>	219	27	32	43
<i>Siluriformes</i>	<i>Perciformes</i>	190	53	63	83
<i>Anguiliformes</i>	<i>Tetraodontiformes</i>	12	10	13	18
<i>Anguiliformes</i>	<i>Perciformes</i>	34	21	25	34
<i>Anguiliformes</i>	<i>Gasterosteiformes</i>	8	13	16	24
<i>Anguiliformes</i>	<i>Atheriniformes</i>	46	7	9	12
<i>Atheriniformes</i>	<i>Cypriniformes</i>	7	393	501 ^a	786 ^a
<i>Atheriniformes</i>	<i>Tetraodontiformes</i>	46	11	13	17
<i>Atheriniformes</i>	<i>Perciformes</i>	148	21	25	33
<i>Atheriniformes</i>	<i>Gasterosteiformes</i>	36	17	20	27
<i>Gasterosteiformes</i>	<i>Tetraodontiformes</i>	8	16	20	30
<i>Gasterosteiformes</i>	<i>Perciformes</i>	33	26	32	43
<i>Perciformes</i>	<i>Tetraodontiformes</i>	34	21	25	34
Mean				23.5	31.7
Weighted Mean				26.0	34.5

Source: Barnthouse et al., 1990.

^aNot included in calculations.

99%) of experimentally derived values (i.e., Tables 4.6 to 4.8) not be used to derive directly the categorical interspecies UFs. However, those values should be considered as representative of the larger and as yet untested population of potential binary comparisons within their respective categories. With these values as input data, we propose to follow the scheme of Van Straalen and Denneman (1989) to estimate the upper 95% UF of the listing of 95% or 99% UF factors, assuming a logistic distribution of UFs within the category (Table 4.9). For the sake of argument, this would yield a UF of 10 for the species within genera category and up to 65-fold for the orders within class for the given individual 95% UF values. If the given individual upper 99% UFs were used, this would yield a 99% UF of 16 for the species within genera category and up to 88 for the orders within classes category. These data suggest that interspecies UFs for ecological risk assessment could range from a low of 10-fold for the species within genera to a high of roughly 100-fold for the orders within class category (i.e., 95% P.I.).

Table 4.9. Upper 95% UFs Calculated for the 95% and 99% Prediction Intervals Based on the Scheme of Van Straalen and Denneman (1989)

Regression Model	Prediction Interval	
	95%	99%
Species within genus extrapolation	10.0	16.3
Genera within family extrapolation	11.7	16.9
Families within order extrapolation	99.5	145.0
Orders within class extrapolation	64.8	87.5

The intermediate category UFs (i.e., genera within families, families within orders) could be assigned separate values intermediately spaced, such as 30 and 60, respectively. Table 4.10 summarizes the recommended UFs and how these UFs based on phylogenetic relatedness could be applied.

In the case of interspecies comparisons at the classes within phylum category, the most relevant data are from Slooff et al. (1986). Their findings, as discussed previously, support an approximate 95% generic UF of 1000-fold (Table 4.10).

E. INTRASPECIES UF

1. Sensitive Life-Stage UFs in Species Not Specially Protected by Legislation (e.g., Endangered Species)

a. Introduction

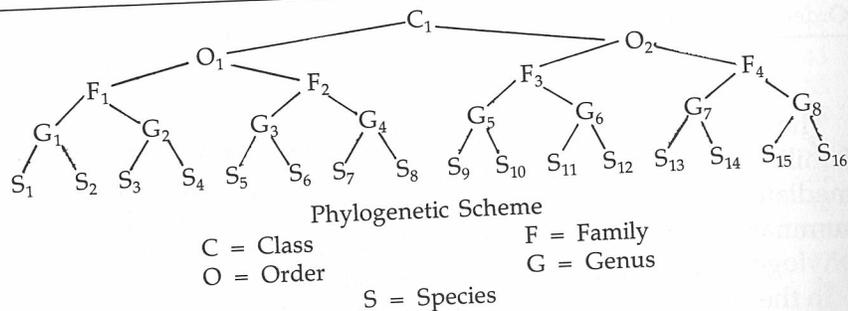
Ecological risk assessments frequently address the issue of life stage extrapolation. This situation exists when investigators have opted to perform experimentation on a presumed sensitive early life stage (e.g., hatching, larval survival, etc.) and then estimate a MATC for the adult. This type of extrapolation is seen to bridge a gap between both the traditional UF in human risk assessment for less-than-lifetime (LL) exposure and interindividual variation. The life stage extrapolation feature of ecological risk assessment occupies a legitimate place in both of these human risk assessment UFs. This is because the studies with young animals constitute a less-than-lifetime study duration. The experiments also point out that differential susceptibility in the population may exist as a function of age. The presence of the life stage extrapolation information

Uncertainty Factor	
Prediction Interval	
95%	99%
20	27
39	51
12	16
11	15
32	43
63	83
13	18
25	34
16	24
9	12
501 ^a	786 ^a
13	17
25	33
20	27
20	30
32	43
25	34
23.5	31.7
26.0	34.5

es 4.6 to 4.8) not
ies UFs. However,
f the larger and as
within their respec-
ve propose to fol-
(1989) to estimate
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of 10 for the spe-
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99% UF of 16 for
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Table 4.10. Interspecies UFs for Ecological Risk Assessment: Listing and Application

Interspecies (Species within Genus)	UF	10
Interspecies (Genus within Family)	UF	30
Interspecies (Families within Order)	UF	60
Interspecies (Orders within Class)	UF	100
Interspecies (Classes within Phylum)	UF	1000



Application of Interspecies UF Based on Phylogenetic Relatedness

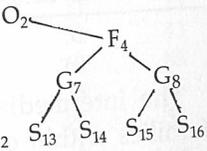
	UF Size	Explanation for UF Selection
S_1 (data available) and S_2 (species of concern)	10	Species within Genus
S_1 (data available) and S_3 (species of concern)	30	Genera within Family
S_1 (data available) and S_5 (species of concern)	60	Families within Order
S_1 (data available) and S_9 (species of concern)	100	Orders within Class

in both of these human UFs indicates that these two UFs are not fully independent as generally assumed, but are to some extent interdependent.

The life stage UF does not address the remaining aspects of interindividual variation (e.g., sex differences, genetic variation, nutritional status, preexisting disease contributions). This is most likely because the age factor, being a developmental process, is more fundamental to species success, while the other factors are more limited in their range of influence on species survival. This also appears to be the case for the less-than-lifetime UF. The life stage factor is not concerned with differential susceptibility of the old, nor with the issue of cumulative damage as long as the reproductive success is assumed. This limited use of aspects of the interindividual UF and less-than-lifetime UF as seen in the life stage extrapolation scheme is clearly a function of the historical role of ecological risk assessment being concerned with the survival of the population and not the individual.

ment: Listing and

- 10
- 30
- 60
- 100
- 1000



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etic Relatedness

Explanation for UF Selection
Species within Genus
Genera within Family
Families within Order
Orders within Class

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Long-term chronic experiments are life cycle studies that are designed to determine a lowest observed effect concentration (LOEC) and a no observed effect concentration (NOEC) on survival, growth and reproduction. Based on the results of such chronic studies an estimate of the MATC can be made (ASTM 1978). Fish chronic toxicity tests have traditionally been long-term exposures of up to 12 months in duration. However, due to the need for more rapidly required information and cost containment, much alteration has been directed to (1) aquatic species such as Daphnia where chronic toxicity tests can be conducted in 28 days, as well as to (2) fish species where the focus is on only a partial life-cycle test that includes the most sensitive life-stages (i.e., usually early development periods).

b. Sensitive Life-Stage Models

It has been argued that the estimation of MATC values from early life stage tests using criteria such as hatchability, survival, growth, and deformities was within a factor of 2 in most instances of the MATCs derived from chronic studies (McKim 1977; Macek and Sleight 1977). These findings were supported by Woltering (1984) who, based on data from 173 long-term fish toxicity tests, concluded that fry survival data would have estimated MATC values within a factor of 2 to 7.

Despite the above supportive argument in favor of the "short-term chronic" studies to estimate MATC values, Suter et al. (1987) have challenged its use. Based on an analysis of 176 tests on 93 chemicals with 18 species, the authors concluded that the measured endpoints (i.e., hatching success, larval survival, etc.) were consistently less sensitive than reduction in fecundity. According to the authors, the principal reason why fecundity has been overlooked as the most sensitive response is that prior statistical analyses were based on hypothesis testing and not on the levels of effect as estimated via regression analyses. More specifically, Suter et al. (1987) indicate that since fecundity is quite variable and only small numbers of fish are employed in this aspect of life-cycle tests, large reductions in fecundity may not be shown to be statistically significant. They rely heavily on the arguments of Stephan and Rogers (1985) that hypothesis-testing to define chronic effect benchmarks have important undesirable features since some MATCs have been set at levels associated with greater than 50% mortality.

This debate over whether to use regression techniques or hypothesis testing to determine endpoints for MATCs is of considerable practical importance. Stephan and Rogers (1985) argue that there are numerous computational and conceptual advantages using regression analysis over hypothesis testing for calculating results of chronic toxicity tests with aquatic animals (Table 4.11). A critical factor here is that most toxicity tests with aquatic animals are highly suited for regression analysis since they typically involve six treatments, including a control and five concentrations. This is in marked contrast to most mammalian studies which involve a control and only two treatments. It should be emphasized that in 1984 Crump proposed a comparable scheme for determining allowable daily intakes for humans based on mammalian toxicology studies.

In addition to statistical considerations, Suter et al. (1987) argue that even though the MATC is believed to be the threshold for fish populations, no thresholds or even negligible effects for most of the published chronic tests have been provided. Even the least sensitive endpoint, which was hatching success, displayed a 12% average reduction at the MATC, as determined by regression analysis. The most sensitive overall response (i.e., fecundity) displayed a 42% reduction at the MATC, as determined by regression analysis. These treatment effects, judged significant by regression analysis, were not deemed statistically significant via hypothesis testing.

The arguments concerning both sensitive endpoint and statistical method selection raised by Suter et al. (1987) are substantial both theoretically and practically with respect to how ecological toxicology studies are designed, conducted, and interpreted. The information also has a considerable relevance for multiple extrapolation issues, including acute to chronic UF, LOAEL to NOAEL UF, interspecies UF, and less-than-lifetime UF, since the use of the regression technique provides a direct estimate of the 95% UF discussed above.

c. Recommendation for Sensitive Life-Stage UF

The size of the sensitive life-stage UF which should be seen as a component of an overall intraspecies UF for use in ecological risk assessment may be argued as being in the range of 2- to 7-fold (McKim, 1977). However, the recent findings of Suter et al. (1987) concerning sensitive endpoint identification argue for a

Table 4.11. Advantages for Using Regression Analysis to Estimate MATCs**Computational Advantages**

1. Regression analysis provides a well-defined procedure for interpolation of effect to untested concentrations, whereas hypothesis testing provides quantitative information concerning only the concentrations that were actually tested.
2. Estimates of toxicity calculated using hypothesis testing are sensitive to the care with which the test was conducted and to the number of replicates used, whereas estimates of toxicity calculated using regression analysis are not.
3. The choice of "alpha" does not affect the estimate of toxicity obtained using regression analysis.
4. The estimate of the endpoint concentration obtained using regression analysis is independent of the concentrations actually used in the test.
5. Changes in the statistical procedure can affect the results of hypothesis testing more than comparable changes can affect the results of regression analysis.
6. Regression analysis can accommodate unexpected inversions in the data.
7. Regression analysis does not require treating experimental units as replicates if, in fact, they are not.

Conceptual Advantages

1. Use of regression analysis will encourage aquatic toxicologists to consider the real-world importance of the observed effects.
2. It is easier for toxicologists and others to make decisions about the adequacy of a toxicity test in terms of confidence limits on endpoint concentrations than in terms of a minimum statistically significant difference.
3. Use of regression analysis will encourage aquatic toxicologists to think of chronic toxicity in terms of a concentration-effect relationship.
4. Use of regression analysis will discourage people from thinking that hypothesis testing identifies "no effect" concentrations.
5. Use of regression analysis will discourage people from thinking that the most sensitive hypothesis test is the best hypothesis test.

Source: Stephan and Rogers, 1985.

somewhat larger UF. Support for this position is found in Table 4.12 (Barnthouse et al., 1990), which indicates that the 95% UF for Larval Mortality EC25, Hatch EC25, and EGG EC25 when compared to parent mortality EC25 range from 8-to 16-fold. These findings, while qualitatively similar to the McKim (1977) findings, support a rounded value of 10-fold for the sensitive life stage 95% UF.

Table 4.12. Life-Stage Extrapolation: Means and Weighted Means Calculated for the 95% and 99% Prediction Intervals for Uncertainty Factors Calculated from Regression Models

X Variable	Y Variable	n	Uncertainty Factor		
			Prediction Interval		
			90%	95%	99%
Life-Stage Extrapolation					
Larval Mort EC25	Parent Mort EC25	16	6	8	11
Larval Mort EC25	Hatch ^a EC25	28	11	13	17
Hatch EC25	Parent Mort EC25	7	10	13	20
Hatch EC25	Eggs ^b EC25	6	10	13	21
Eggs EC25	Parent Mort EC25	27	13	16	21
Eggs EC25	Larval Mort EC25	25	6	7	9
Mean				11.7	16.5
Weighted Mean				11.6	15.7

Source: Barnthouse et al., 1990.

^aFraction of eggs failing to produce normal larvae.

^bNumber of eggs produced per female fish surviving to the beginning of spawning.

2. Intraspecies UF for Protected Species

a. Background

While the pervasive approach inherent in ecological risk assessment is that of protection of the population (in contrast to the individual), this perspective is altered markedly when consideration is given to species protected by law under the Endangered Species Act and the Migratory Bird Treaty Act. In the case of specially protected species, the environmental legislation has the intention of ensuring protection for individuals as well as the population. Thus, the growth, maintenance, and reproduction triad, as previously discussed, may not be fully adequate to ensure protection of such species. In such cases it may be necessary to address additional toxic endpoints not usually considered in ecological risk assessment, such as chronic toxicities and interindividual variation in susceptibility. It may also be necessary to incorporate the use of larger UFs in the derivation of acceptable exposures for such species. This area is clearly one in which additional toxicologically based risk assessment criteria are needed for development.

While no specific guidance exists on UFs for endangered species, it bears considerable similarity to the human intraspecies UF

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rtainty Factors

tainty Factor	
tion Interval	
95%	99%
8	11
13	17
13	20
13	21
16	21
7	9
11.7	16.5
11.6	15.7

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intraspecies UF

where the goal is to protect susceptible subgroups within the population as well as developmental and reproductive domains. There are some relevant distinctions to be made, however, between the use of the intraspecies (i.e., interindividual) UF for humans and possible UFs for endangered species. First, the ostensible goal of the human intraspecies UF is to protect susceptible, yet reasonably sizeable, "subgroups" above a certain proportion in the population (e.g., 1%) while the Endangered Species Act is specifically concerned with protecting all individuals. This is interpreted to mean that uniquely sensitive humans or sensitive humans in small subgroups (e.g., 1% of the population) may not be specifically intended for protection. Second, the size of the distribution of humans is huge, while that of an endangered species would be expected to be quite small (dozens to several hundred). The degree of interindividual variation would be expected to increase as the population itself increases. For example, the variability could be expected to be larger in a population of 200 individuals as compared to a population of 20 individuals. A larger sized UF would be derived for the larger population if the goal were to protect *all* individuals. On the other hand, if only 20 individuals exist there is considerably less room for error of losing the entire species! Thus, since the stakes are so high (at least in a legislative sense) it is reasonable to err on the side of safety in such cases. This would tend to be the case for all endangered species evaluations, but it could be more pronounced in cases such as the 20 individuals example. Perhaps this is a situation (i.e., where the population is quite low, such as 20) where a modifying factor would be appropriate.

Should the size of the intraspecies UF for ecological risk assessments dealing with endangered species be the same as used in human risk assessment? It is argued here that the UF for Endangered Species should be larger than the 10-fold factor used in human risk assessment. This is based on the goal that each individual needs to be protected, and that the 10-fold factor may not address the full range of human interindividual variation in response to toxic agents, even when only relatively small sample sizes (i.e., several hundred) are used. It is highly uncertain what type of variation to expect for Endangered Species and it is likely to be considerably different, depending on the specific species.

Should each intraspecies UF for a protected species be the same? Ideally, it would be expected that protected species should have their own uniquely tailored UF; however, there is no obvious means

to determine how to derive such a value. Unfortunately, it is highly likely that no toxicological information will be available for many Endangered Species.

b. Recommendation

It would appear reasonable for each protected species to have the same intraspecies UF due to a lack of species-specific data in this area. While the magnitude of this UF would be expected to be greater than the 10-fold factor used in the human risk assessment, how much greater? In the absence of an adequate database, it would appear that the present UF of 10-fold factor should be increased by a factor of 2, making it 20-fold. This is sufficiently large as to provide an apparent additional margin of safety, while at the same time not being unnecessarily conservative. It is a tentative judgment that needs to be subsequently reevaluated so that adjustments could be made.

F. LESS THAN LIFETIME (LL) UF

1. Nonendangered Species: Rationale and Recommendation

The use of a LL-UF is standard practice in human risk assessment processes; however, the concept of a chronic bioassay and its utility in ecological risk assessment theory and practice concentrates on the species rather than the individual. It is proposed that a "chronic" study in ecological risk assessment for nonendangered species be 15% of the normal adult life-span after weaning. This duration was selected since it would provide an adequate opportunity for reproductive success by permitting the animal the opportunity to achieve reproductive maturity. [When a species becomes reproductively mature, relative to their adult life-span, is variable according to the species and breed.]

Some would argue that the LL-UF for nonendangered species is already incorporated within the sensitive lifestage (i.e., intraspecies) UF and is unnecessary. We believe this argument is not compelling, since fecundity* is often the most sensitive endpoint for MATC derivation (Suter et al., 1987), and that it is uncertain in most

*Fecundity is defined by Suter et al. (1987) as viable eggs produced per female surviving to the initiation of reproduction.

instances whether these effects are principally the result of debilitation of the adults or to direct effects on reproductive process such as oocyte development.

Within the percentage of life-span context, a LL-UF of >1 would not be necessary if a study of $\geq 15\%$ of a normal adult life-span after weaning has been achieved. This would essentially conform to a 90-day study in rodents and up to a 9-12 month study in a longer lived species such as the dog. These studies are designed to ensure that growth, maintenance, and reproductive functions would be sustained. Studies of a duration $< 15\%$ in rodents would likely be an acute toxicity assessment, involving the derivation of an LD_{50} . This study would be best handled within the context of a frank effect level (FEL) to NOAEL UF extrapolation. Studies of $< 15\%$ in dogs, such as those of 3 or 6 months, would not likely be of an acute toxicity nature. Such studies would need to be handled within the context of a LL-UF. The size of the LL-UF in ecological risk assessment is proposed to be 10 and would be consistent with that used in human risk assessment.

2. Endangered Species: Rationale and Recommendation

The concept of a LL UF changes when endangered species are considered. In this case, one is guided by the premise that not only is reproductive success important, but also the health of individual animals. Based on the current dictum that individuals of endangered species need to be protected, it is recommended that procedures by which a LL UF are derived in human risk assessment be adopted for endangered species. Guidance that exists on this issue is as follows:

1. Rodent studies of a typical "experimental" lifetime are for two years, which is about 50-70% of the expected average life-span of the mouse/rat, depending on the strain.
2. Generally, if the duration of a rodent study is less than a year, a case can be made for the use of a LL UF. The case has historically been much less compelling if the duration of the study is ≥ 1 year, but < 2 years. This would essentially indicate that in mammalian toxicology if the duration of the rodent study were 25-35% of the expected average life-span for the studies, then the UF would be 1. If the study were $< 25\%$ of the expected average life-span for the endangered species the UF would be 10, as could happen in human risk assessment.

3. In a practical sense it is unlikely that adequate data would exist on various endangered species. In cases of inadequate data on the species of concern, standard procedures used in human risk assessment, therefore, would be used (i.e., use of surrogate species).

G. LACK OF ACHIEVEMENT OF STEADY-STATE (SS) UF

1. Concept

It has been argued that agents requiring a long time to achieve steady-state may have their chronic toxicity underestimated in short-term aquatic (McCarty et al. 1985) and mammalian (Mosberg and Hayes 1989) toxicity studies. In order to prevent such underestimates of toxic responses, the risk assessor must assure that the compound under study has achieved approximate steady-state for the duration of the study. This will assure that the available data will have considered toxicity during both uptake (i.e., kinetic-phase toxicity) and steady-state (i.e., inherent toxicity) phases of exposure.

The concepts of kinetic-phase and inherent-phase toxicity have implications for the derivation of the ACR. The data suggest that compounds which achieve steady state (SS) quickly are more likely to have a lower ACR than those agents which take a long time to achieve SS. This suggests further that the magnitude of the average ACR is likely to be influenced by the selection of chemicals employed to construct the distribution. If the agents selected for the ACR achieve SS quickly, a lower ACR would be predicted and vice versa. It should be emphasized that factors other than achieving SS may be more important in the causation of toxicity. This discussion is not designed to minimize this possibility, but to ensure that the time to achieving SS concept is given proper consideration in the interpretation of the ACR.

While the % SS UF has a role in overall UF consideration in the process of ecological risk assessment, it is limited because of potential for interdependence with other UFs, such as the LL-UF and the ACR UF.

2. Potential Interdependence of ACR UF and % SS UF

In most circumstances it would be expected that the acute to chronic UF should have taken the % SS UF at least partially into

account since some degree of contaminant uptake would have occurred. In such cases there would be potential for an error of double counting (i.e., interdependence of UFs) if both UFs are employed. Prior to determining the potential size of the % SS UF it would be necessary to estimate the % of SS achieved in the chronic study. At that point it may be possible to address the question of whether a % SS UF may be necessary and what its size should be.

3. Potential Interdependence of the LL-UF vs % SS UF

The LL UF should be partially interdependent with the % SS UF. This conclusion derives from the belief that the LL UF takes into account generally those agents that continue to accumulate, but that do not achieve SS after the end of the LL study. Thus, when a LL UF is used, the % SS UF should not be used to normalize the LL study to one of a chronic nature. The question which then emerges is: when (if at all) should the % SS UF be used?

1. It could be used in chronic studies where SS has not been achieved. However, the size of this UF would need to be addressed on a case-by-case basis.
2. The LL UF should account for the % SS UF for the time period dealing from the completion of the LL study to the completion of a chronic study; however, there would remain concern for that period of life after the completion of the normal chronic study to the average expected life span.

4. Recommendation

The only time the % SS UF should be employed is for that time period after the end of a normal chronic study (as achieved by a chronic study via the use of a LL-UF or A/C UF) when the concentration of the toxicant continues to increase in bodily tissues. However, this type of information would generally not be available and, if it existed at all, would likely be modeled predictions. Consequently, we believe that while the concept of a % SS UF is theoretically valid, it has limited utility and would normally not be employed. If it were ever to be employed, it would be on a case-by-case basis.

H. MODIFYING FACTOR (MF)

This factor will be handled in a similar fashion as seen in human risk assessment (see Table 4.1).

I. LABORATORY—FIELD EXTRAPOLATION UF

1. Rationale and Recommendation

Whether and to what extent a separate UF should be used for extrapolation from the laboratory to the field has been a much discussed (Slooff et al. 1986; Van Straalen and Denneman 1989), but essentially unresolved issue. It has been argued that laboratory studies have the potential to both under- and overestimate field-based responses (Table 4.13). Thus, a laboratory-to-field extrapolation factor, if adopted, could be either greater or smaller than one. According to Van Straalen and Denneman (1989) no convincing case has yet been made concerning the magnitude of the laboratory-to-field UF and, at least for the foreseeable future, a factor of one should be applied. If one were to be adopted, it should be approached on a case-by-case basis.

J. INTERDEPENDENCE OF UFs: AVOIDING ERRORS IN OVER-CONSERVATIVE APPLICATION OF UFs

For UFs to be properly employed it is assumed that they are independent of each other and, therefore, have a multiplicative interaction. However, several instances of interdependence of UFs exist, so that their joint use should be avoided.

1. Acute to Chronic UF and the LL UF

If an acute to chronic UF is used it is assumed that the UF will estimate the response over a normal adult life span. Thus, use of a LL UF in this instance would be an error in double counting.

Table 4.13. Arguments Used in Establishing a Laboratory-Field Extrapolation Factor

-
- +1. In the laboratory, organisms are tested under optimal conditions.
 - 2. In the field, biological availability of chemicals is lower than in laboratory tests.
 - +3. In the field, organisms are exposed to mixtures of many chemicals.
 - 4. In the field, ecological compensation and regulation mechanisms are operating.
 - 5. In the field, adaptation to chemical stress may occur.
 - +6. Adaptation often entails costs in ecological performance.
-

Source: Van Straalen and Denneman, 1989.

Note: A plus sign indicates a positive argument to maintain an extrapolation factor greater than one; a minus sign indicates a negative argument.

2. Acute to Chronic UF and Intraspecies (i.e., Sensitive Life-stage) UF

If the A/C UF is based on complete life-stage data then the intraspecies UF should not be employed. This concern with the interdependence of UFs would not apply to protected species. In the case of endangered species the use of the A/C UF would not preclude the use of an intraspecies UF. This is because the typical chronic stage would not address the interindividual variation as required for protection of endangered species.

3. Interspecies UF and Intraspecies UF

The interspecies UF in human risk assessment is generally recognized as providing an extrapolation from the average animal to the average human, assuming that humans may be 10-fold more sensitive. The interindividual UF assumes that most (not necessarily all) human responses to an agent fall within approximately a 10-fold range. Given this assumption, the application of a 10-fold interindividual UF should begin with the average person and extend to cover the higher risk segments of the population. Consequently, an UF of 5 would be expected to protect most humans (Figure 4.4).

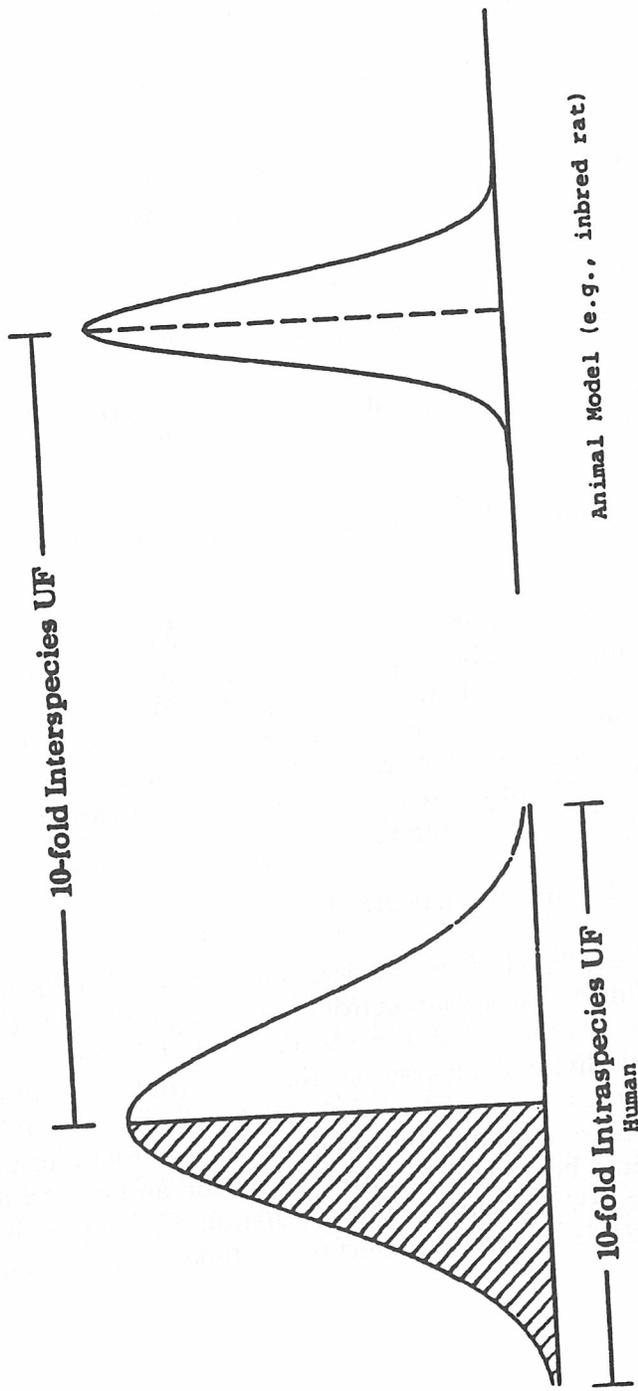


Figure 4.4. Interdependence of Uncertainty Factors (UF).

The application of a 10-fold UF for humans would be more justified if it were based on an occupational epidemiological study. This type of study does not consider the most sensitive humans and is likely to involve principally healthy workers and a self-selection component that consists of the less sensitive members of the population (Figure 4.5). Therefore, it is concluded that the current use of a 10-fold factor for interindividual variation, as typically applied to animal toxicological studies used in risk assessment, represents an important deviation from the original intention of uncertainty factor use. This intention for interindividual variation is satisfied with an UF of 5 when based on animal studies, but with a factor of 10 when based on occupational epidemiological studies. It should be emphasized that this argument would apply to the basic relationship between the interspecies and intraspecies UF. The UF values of 10 and 5 are used here because of their relationship to current EPA practice and for illustrative purposes. This concept would be applicable whether the size of the UFs were larger or smaller than 10. *Therefore, when both of these UFs are present the size of the intraspecies UF should be reduced by 50%.*

K. ALTERNATIVE TO THE USE OF UFs

In the face of mounting costs associated with remedial actions at hazardous waste sites, there is great incentive to find ways to reduce toxicological uncertainties with realistic testing so that the magnitude of traditionally combined UFs and, therefore, costs can be mitigated. With this as their goal, the Department of Defense has set forth on a program to develop fast and relatively inexpensive nonmammalian toxicity assessment techniques that can be employed not only in the laboratory, but also at field sites having contaminated water (Van der Schalie and Gardner 1989; Gardner 1990). The advantage of such a system is that data can be obtained on realistic exposures within the context of multiple dilutions with large numbers of fish per exposure level. The system is also set up to consider a broad spectrum of toxic endpoints, including immunological alterations, tumor promotion, and organ specific toxicities. The plan is unique in that NOAELs for sensitive endpoints may be obtained with the toxic mixture of concern. This type of approach has the capacity to significantly reduce some of the uncertainties associated with site assessments, especially those dealing

Human
Figure 4.4. Interdependence of Uncertainty Factors (UF).

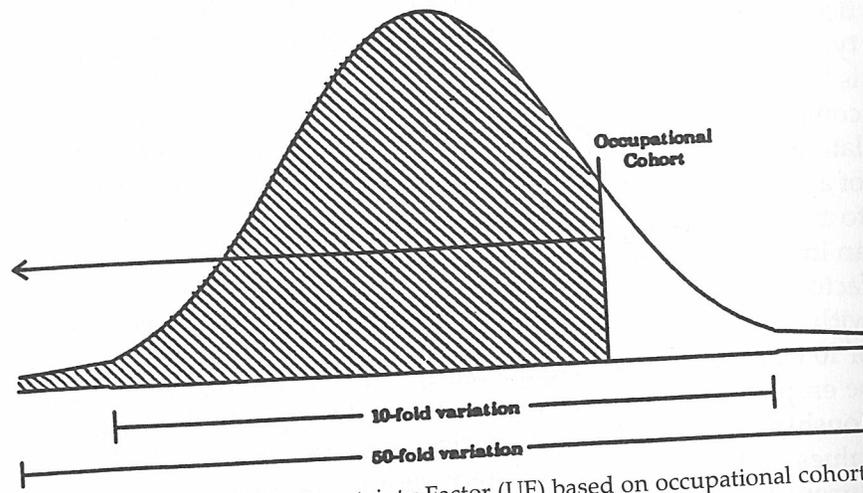


Figure 4.5. Intraspecies Uncertainty Factor (UF) based on occupational cohort.

with high to low dose concerns, identification of NOAELs, and possible additive or synergistic effects. It also can be applied so that sensitive life stages could be tested within the context of defining chronic toxicities. The methodology, however, would still need to assess the issue of interspecies uncertainty.

L. SUMMARY

In conclusion, the concept of UFs in ecological risk assessment is conceptually well established. While no widespread agreement exists concerning their magnitude, a series of recommendations for UF size (Table 4.14), along with the biological basis to support such decisions, is provided. Even though a number of similarities exist between the use of UFs for noncarcinogens in human and ecological risk assessment, major differences exist with respect to the types of UFs and their magnitude. The driving force for variation between the two schemes relates to the goal of human risk assessment to protect individuals, while the goal of ecological risk assessment is to protect populations. Other factors contributing to variability in the size of UFs between ecological and human risk assessment procedures relate to the need of ecological risk assessment to address multispecies variability and ecosystem health instead of only one species (i.e., humans). In addition, variation in

Table 4.14. Recommended UFs in Ecological Risk Assessment

Types of UFs	Size of UFs
1. Interspecies Uncertainty	
a. Species with genus	10
b. Genera within family	30
c. Families within order	60
d. Orders within class	100
e. Classes within phylum	1000
2. Intraspecies Uncertainty	
a. Nonendangered Species (addresses developmental/reproductive endpoints)	10 ^a
b. Endangered Species (addresses interindividual variation including sensitive life-stages)	20 ^a
3. Less-than-Lifetime at Steady State	
i. ≥15% of normal adult life span.	1
ii. <15% of normal adult life span (but not an acute toxicity test)	10
iii. <25% of normal adult life span for an endangered species	10
4. Acute Toxicity to Chronic NOAELS	
i. Lethality (LD to LD ₅₀ range)	50 at 95% 100 at 99%
ii. If nonlethal but frankly toxicity effects occur:	>10- <50
5. LOAEL to NOAEL	10
6. Modifying Factor	up to 10

^aThe values of the intraspecies UF will be reduced by 50% when used in conjunction with interspecies UF.

usual testing protocols has implications for how LOAEL/NOAELS may be estimated between the two approaches.