Distributions of Individual Susceptibility among Humans for Toxic Effects

How Much Protection Does the Traditional Tenfold Factor Provide for What Fraction of Which Kinds of Chemicals and Effects?

DALE HATTIS,[a] PRERNA BANATI, AND ROBERT GOBLE

Center for Technology, Environment, and Development, George Perkins Marsh Institute, Clark University, Worcester, Massachusetts, USA

ABSTRACT: A significant data base has been assembled on human variability in parameters representing a series of steps in the pathway from external exposure to the production of biological responses: contact rate (e.g., breathing rates/body weight, fish consumption/body weight); uptake or absorption (mg/kg)/intake or contact rate; general systemic availability net of first pass elimination and dilution; systemic elimination or half-life; active site availability/general systemic availability; physiological parameter change/active site availability; functional reserve capacity—change in baseline physiological parameter needed to pass a criterion of abnormal function or exhibit a response. This paper discusses the current results of analyzing these data to derive estimates for distributions of human susceptibility to different routes of exposure and types of adverse effects. The degree of protection is tentatively evaluated by projecting the incidences of effects that would be expected for a tenfold lowering of exposure from a 5% incidence level if the population distribution of susceptibility were truly log-normal out to the extreme tails, and if the populations, chemicals, and responses that gave rise to the underlying data were representative of the cases to which traditional uncertainty factor is applied. The results indicate that, acting by itself, a tenfold reduction in dose from a 5% effect level is associated with effect incidences ranging from slightly less than one in ten thousand, for a median chemical/response, to a few per thousand, for chemicals and responses that have greater human interindividual variability than 19 out of 20 typical chemicals/responses. In practice, for many of the cases where the traditional tenfold factor is applied, additional protection is provided by other uncertainty factors. Nevertheless, the results generate some reason for concern that current application of traditional safety or uncertainty factor approaches may allow appreciable incidences of responses in some cases.

[a]Address for correspondence: Center for Technology, Environment, and Development, George Perkins Marsh Institute, Clark University, 950 Main Street, Worcester, MA 01610, USA. 508-751-4603 (voice); 508-751-4600 (fax).
e-mail: dhattis@clarku.edu

INTRODUCTION

This paper is one of several efforts[1–7] that are attempting to help build the basis for improved quantitative assessment of the noncancer effects of chemicals. Much has changed since the landmark paper of Lehman and Fitzhugh[8] in 1954, which set the paradigm for traditional analyses with the original *100-fold safety factor* (of which 1/10 is allocated to possible differences in sensitivity among people). Today we have the experience and the computational capabilities to employ distributional approaches in place of simple rule-of-thumb formulæ. We also have the benefit of an enormous flowering of biomedical science over the last few decades from which we can draw helpful data (although many of the data are not ideal for our purposes). Finally, we live in an age where the questions for analysis have broadened beyond the main issues confronting the U.S. Food and Drug Administration of 1954. In contexts as diverse as occupational safety and health, general community air pollution, drinking water contaminants, and community exposures from waste sites decision makers and the public ask questions like "does exposure to *X* at fraction *Y* of an estimated no-adverse-effect level really pose enough of a risk of harm as to merit directing major resources to prevention?" On the other hand, are questions such as "would it not be more prudent to build in additional safety factors to protect against effects to people who may be more sensitive than most because of young or old age, particular pathologies, or other causes of special vulnerability?" In the U.S., the Occupational Safety and Health Administration may only promulgate a new permissible exposure level for a chemical if can produce a credible estimate that the risk under the pre-existing standard is *significant* by some broadly defined quantitative criteria. To address these questions, we need to make at least quantitative estimates of the risks that result from current approaches.

One basic concept that lies at the heart of this analysis has not changed from the time of Lehman and Fitzhugh; the idea that many toxic effects result from placing a chemically-induced stress on an organism that exceeds some homeostatic buffering capacity. From this follows an expectation that there should be individual thresholds for such effects. An individual will show a particular response (or a response at a specific level of severity) only when the individual threshold exposure level for the chemical in question has been exceeded.

Now consider a population of individuals, each of whom has a different threshold for a particular response. How many people in a mixed group are affected depends on the fraction of people whose individual thresholds are exceeded at each exposure level. The broader the distribution of thresholds in the population—the greater the individual variability of the thresholds—the more gradual will be the decrease in the proportion of people showing a specific response as dose is lowered below the levels where effects can be readily observed in small test populations. For this reason, quantifying the functional form and degree of spread (interindividual variability) for individual threshold exposure levels is a key issue in quantitative risk assessment for this kind of biological response.[3]

Imagine, for purposes of illustration, that the distribution is log-normal; that is, that the logarithms of the individual thresholds have a normal Gaussian distribution. (This is the standard assumption that we use in our analysis below. Such a distribution would be expected if there are many factors, each contributing modestly to the

individual variability in threshold doses, and if each factor tends to act multiplicatively to affect individual thresholds. This assumption of log-normality of population distributions of thresholds is by no means new—it is the basis for traditional probit analysis of toxicological data that predates Lehman and Fitzhugh.[9]) For example, consider a log-normal distribution with a Log_{10}(geometric standard deviation) of 0.5. (We abbreviate variability estimates in this form to Log(GSD).) This means that one standard deviation of the threshold dose population distribution corresponds to $10^{0.5}$ or just over a threefold change in dosage, and of course two standard deviations would correspond to a tenfold change in dosage. If 1 mg/kg of such a chemical causes an effect in 5% of the population (corresponding to a point in a cumulative log-normal distribution that is 1.645 standard deviations below the mean) then a tenfold reduction in dosage to 0.1 mg/kg would place us at a point 1.645 + 2 = 3.645 standard deviations below the mean. From normal curve area tables (or, in Microsoft Excel, by using the *normsdist* function) one can easily determine that in this case the 0.1-mg/kg dose would be expected to affect about one in ten thousand of the population—again assuming that the distribution of thresholds is log-normal. If there were much less variability than this, a Log(GSD) of 0.25, the same tenfold reduction in dose to 0.1 mg/kg would yield a 1/0.25 = 4 standard deviation difference in the population distribution, to a point 5.645 standard deviations below the mean. In this case the calculated risk would be very small; much less than one in a million. By a similar calculation, a higher Log(GSD) of 0.75 would imply a risk of 1.4 per thousand at 0.1 mg/kg.

To further illustrate the significance of log-normal variability, TABLE 1 shows the implications of various Log(GSD) variability values for the multiplicative difference

TABLE 1. A scale for understanding log-normal variability differences between particular percentiles of log-normal distributions[a]

Log_{10}(GSD)	Probit slope $1/Log_{10}$(GSD)	Geometric standard deviation	5%–95% Range (3.3 standard deviations)	1%–99% Range (4.6 standard deviations)
0.1	10	1.26	2.1-fold	2.9-fold
0.2	5	1.58	4.5-fold	8.5-fold
0.3	3.33	2.0	10-fold	25-fold
0.4	2.5	2.5	21-fold	73-fold
0.5	2	3.2	44-fold	210-fold
0.6	1.67	4.0	94-fold	620-fold
0.7	1.43	5.0	200-fold	1800-fold
0.8	1.25	6.3	430-fold	5,300-fold
0.9	1.11	7.9	910-fold	15,000-fold
1	1.0	10.0	1,900-fold	45,000-fold
1.1	0.91	12.6	4,200-fold	130,000-fold
1.2	0.83	15.8	8,900-fold	380,000-fold

[a]Adapted from Hattis.[10]

spanned by 3.3 standard deviations. If human susceptibility distributions were truly log-normal out to the extreme tails, then 3.4 standard deviations would be expected to be the difference between 20% and a 10^{-5} incidence of effect; 3.1 standard deviations would be expected to be the difference between a 5% and a 10^{-6} incidence of effect. Thus, the dosage spreads shown in TABLE 1 can be used as a crude first guess at the dose reduction that would be needed to take a typical LOAEL or NOAEL effect incidence (not incompatible with a 5% incidence of effect in typical cases) down close to or into the frequency region that has been considered *acceptable* for some general population exposures for the serious outcome of cancer.

Making calculations of this type, of course, begs the question of how well log-normal distributions actually describe real variability distributions out to the extreme tails. In this paper we do not examine the possible effects of departures from log-normality. However FIGURE 1A shows a comparison of 2700 individual data points from our pharmacokinetic data base with expectations under a log-normal distribution. In this figure, the *ordinal Z-score* is the inverse of the cumulative normal distribution calculated solely from the order statistics of the data using the formula of Cunane.[10]

$$\frac{i - 3/8}{N + 1/4}$$

where N is the number of data points in the data set, and i is the order of each data point in the data set (1 for the lowest and N for the highest). The log-normal Z-score for each data point is

$$\frac{\text{Log(data value)} - \text{mean of all Log(data values)}}{\text{standard deviation of all Log(data values)}}.$$

In all cases shown in FIGURE 1 the data points have been arranged so that the points to the right indicate relatively greater potential for toxicity (e.g., longer half-lives, smaller distribution volumes). FIGURE 1B shows an analogous comparison under the hypothesis that the data are normally distributed. It can be seen that the log-normal distribution provides a much better description of the data than does a normal distribution. Nevertheless, there appears to be some tendency for the data points at the extreme right of FIGURE 1A to be above, rather than below the line, indicating the log-normal expectation. This suggests that there may be some tendency toward bimodality, or other departures from log-normality for the larger data sets in the direction of having somewhat larger numbers of high risk values than would be expected. The statistical significance of this apparent tendency and possible implications for risk will be explored in future work. It is clear, however, that these data exhibit no apparent tendency for the distributions to be truncated at the high risk end, as might be expected if the variability in susceptibility due to these parameters were to be constrained to a defined upper limit.

We first briefly describe our data base of variability observations. Then we give our approaches for estimating the statistical uncertainties in our estimates of variability from individual data sets. These estimates of uncertainty are used in the following section to develop a set of statistically weighted estimates of the median amounts of variability associated with various steps in the causal pathway from external exposure to end-effects. From these estimates we derive estimates for the overall variability in susceptibility for median chemicals, with responses of different types and with different modes of exposure. Subsequently, we assess the spread of

variability values for individual chemicals from the median-chemical predictions, after control for toxicity type, route of exposure, and statistical uncertainties in the derivation of the Log(GSD) estimates. Finally, based on the spread of likely Log(GSD) variability among chemicals/responses of a given type, we draw inferences about the degree of protection likely to be provided by the standard tenfold uncertainty factor, and arithmetic mean *expected value* estimates of risk at various fractions of a dose that produces a 5% response in a mixed human population. These results update those in a previous report[11] to the U.S. Occupational Safety and Health Administration based on unweighted analyses of a portion of the present data base.

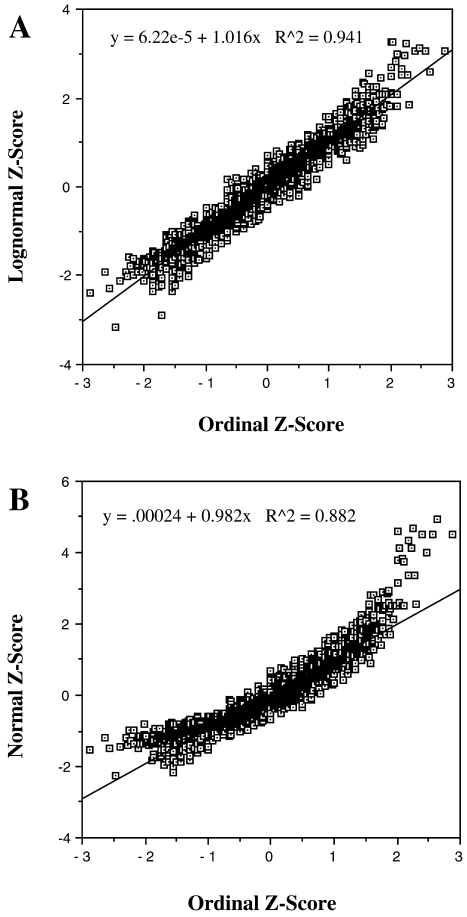

FIGURE 1. Comparison of 2700 pharmacokinetic data points with expectations: **A.** log-normal distribution; **B.** normal distribution.

DESCRIPTION OF THE DATA BASE

Screening criteria and basic approaches for analyzing many of the individual observations of variability have been described in previous papers,[2–4,11–16] of which the most comprehensive and recent summary can be found in Reference 16. By an *observation* of variability, we do not mean a single measurement of a relevant parameter in an individual, but the variability within a data set of separate values for at least five people, summarized by a Log(GSD) value. The full data base, including detailed analyses and references, is available in the form of Microsoft Excel spreadsheets from the first author of this paper. Documentation can also be obtained via our website, www.clarku.edu/~dhattis.

For cases for which the data were in the form of individual measurements of a continuous parameter, Log(GSD) values were calculated directly as the standard deviations of the Log_{10}–transformed parameter values. This was done for all the pharmacokinetic data and for a few cases where parameters with pharmacodynamic information were presented in the form of continuous parameter values (e.g., internal concentrations causing 50% of some specified maximal effect). Additionally, for pharmacokinetic observations where the same parameter had been measured in more than one independent study for a particular chemical, we pooled the observed within-study variances to derive a combined estimate of a Log(GSD). Thus, some of the individual *observations* reflect information from several different data sets.

For the great majority of observations of pharmacodynamic variability, the data were given in the form of the fraction of an exposed group that met some criterion of physiological parameter change or response. In these cases we used a spreadsheet system described by Haas[17] to make maximum likelihood Log(GSD) estimates from a probit[4,9] population dose-response model. Where the data included a control group with a finite incidence of the effect being studied, the models included a background term whose value was also estimated by likelihood maximization. In addition, where age-related information was given that seemed to be important in determining the response, the background response term was made dependent on the average age of each group in the analysis. Finally, for some large data sets of the variability of contact rates (e.g., breathing rates and tap water ingestion rates), where the original data were presented as the values at various percentiles of a population distribution, Log(GSD) values were calculated as the slopes of regression lines from probability plots.[16]

The different parameters whose variability has been measured incorporate variability for different portions of the pathway, from external exposure to end effects. Therefore each parameter is assigned a set of *dummy*-variable classifications of (0 or 1) that indicate the kinds of variability that are included. For example, measurement of the integrated area under the curve (AUC)—the product of internal concentration and time per mg/kg of administered dose, includes variability in steps #2-#5 in the following schema:

1. Contact rate: breathing rates/body weight; fish consumption/body weight (subclassified by oral, inhalation, or other route).
2. Uptake or absorption (mg/kg)/intake or contact rate (subclassified by oral, inhalation, or other route).

3. General systemic availability net of first pass elimination and dilution via distribution volume (subclassified by oral versus inhalation/other route).
4. Dilution via distribution volume.
5. Systemic elimination/clearance or half-life.
6. Active site availability/general systemic availability.
7. Physiological parameter change/active site availability.
8. Functional reserve capacity: change in baseline physiological parameter needed to pass a criterion of abnormal function.

Measurements of the fraction of people who experience a given percentage change in the amount of air they can exhale in one second (FEV_1) in relation to an exposure to ozone in external air, are classified as having variability types 1–7; whereas, measurements of the fraction of patients who suffer dose-limiting toxic symptoms in relation to plasma concentrations of an administered drug, are considered to include variability types 6–8.

In addition to these sources of real variability in items that are relevant to susceptibility distributions, some data sets implicitly included variability and/or uncertainty of other types. Four observations resulted from epidemiological studies of occupational or community groups for which there was considerable uncertainty about individual exposure levels. For these cases we included a dummy variable, indicating the additional source of apparent variability in order to isolate uncertainty in individual dosimetry from the estimates of real variability affecting estimates of risk. In a few other cases, C_{max} (maximum blood or plasma concentrations) and AUC pharmacokinetic parameters were measured after administering a dose of a drug expressed in weight units (e.g., a 200 mg pill), but there was no accompanying information about individual body weights to permit normalization of the results per dose in mg/kg body weight. In these cases we included an additional dummy variable to represent the fact that the data set included variability in body weights in the test population. Although this variable is needed to help explain the aggregate variability seen in some of the observations, it is not relevant to the variability in susceptibility per unit mg/kg dose and will not be included in later summary calculations of risks related to the usual application of the tenfold uncertainty factor.

Given this classification, TABLE 2 offers a simple unweighted summary of the variability data for pharmacokinetic and contact rate parameters. TABLE 3 does the same for parameters that include pharmacodynamic variability. As noted in the table footnotes, the 10%–90% ranges in each cell are calculated by assuming that the Log(GSD) observations within each grouping are themselves log-normally distributed. FIGURES 2–4 show probability plots that indicate rough correspondence of the distributions of Log Log(GSD) values to regression lines for log-normal expectations.

Of these types, pharmacodynamic variability data are by far the most difficult to find. To convey a clearer impression of the nature of pharmacodynamic observations, TABLES 4 and 5 list the individual measurements included in this group. TABLE 4 gives observations of variability in parameter change and response susceptibility at sites of direct contact with an agent (e.g., eye, skin, and respiratory system irritation). TABLE 5 shows cases where the toxicant travels systematically before reaching the site of action. (Derivation of the confidence limits for individual data points is described in the next section.) It can be seen that the pharmacodynamic observations

TABLE 2. Summary of unweighted Log(GSD) variability observations for different types of uptake and pharmacokinetic parameters in adults (data for groups including children under 12 excluded)

Parameter type	Oral	Intravenous	Inhalation	Other routes	All routes + route-nonspecific data
Blood concentration for toxicant delivered mainly by indicated route	0.322[a] (3) 0.295–0.351				0.322 (3) 0.295–0.351
Body weight (adults only)					0.086 (2) 0.065–0.113
Contact rate/body weight	0.257 (1—tap water daily intake)		0.108 (2—daily) 0.094–0.125	0.168 (1) (time showering)	0.150 (4) 0.088–0.256
Volume of distribution/body weight					0.128 (16) 0.058–0.284
Volume of distribution with no control for body weight					0.092 (1)
C_{max}/(dose/body weight)	0.147 (20) 0.059–0.367	0.154 (1)	0.071 (1)	0.224 (1)	0.145 (23) 0.060–0.350
C_{max}/dose with no control for body weight	0.225 (2) 0.133–0.379	0.177 (1)		0.238 (3) 0.169–0.334	0.222 (6) 0.156–0.315
Elimination half-life or clearance/body weight					0.112 (70) 0.058–0.214
Clearance with no control for body weight					0.116 (2) 0.046–0.289
AUC/(dose/body weight)	0.147 (20) 0.072–0.301	0.118 (9) 0.071–0.197	0.149 (1)	0.132 (4) 0.052–0.336	0.137 (34) 0.070–0.269
AUC/dose with no control for body weight	0.187 (11) 0.107–0.326	0.073 (1)		0.271 (2) 0.200–0.367	0.184 (14) 0.099–0.344
Total adult uptake and pharmacokinetic observations	(57)	(12)	(4)	(11)	(175)

[a]Within each cell of this table, the geometric mean of the Log(GSD) observations is given on the first line, the number of observations appears on the second line, and the third line gives a 10%–90% range of the observations calculated assuming that the Log(GSD) values themselves are log-normally distributed. Each *observation* consists of one or more data sets where the variability of a particular parameter was measured. In cases where the same pharmacokinetic parameter was measured for the same chemical in different groups of people, the variance was pooled to form a single *observation*.

TABLE 3. Summary of unweighted Log(GSD) variability observations for different types of pharmacodynamic parameters

	GI Tract	Nervous system	Respiratory system	Cardiovascular renal system + receptor-based effects	Other (e.g., eye, skin irritation)	All effects
Local (contact site) parameter change/external exposure or dose			0.357 (4) 0.272–0.468			0.357 (4) 0.272–0.468
Local (contact site) response/external exposure or dose	0.325 (1—stomach pH)		0.475 (7) 0.208–1.087		0.481 (6) 0.238–0.972	0.465 (14) 0.226–0.959
Physiological parameter change/internal concentration after systemic delivery		0.252 (5) 0.191–0.331		0.056 (2—Na^+ or K^+ excret./drug excret.) 0.042–0.075		0.164 (7) 0.062–0.434
Physiological parameter change/external (IV) systemic dose		0.195 (1—cisplatin *significant* hearing loss)				0.195 (1)
Response/blood level or internal concentration after systemic delivery		0.206 (7) 0.103–0.412		0.519 (3) 0.375–0.720	0.502 (1— cataracts)	0.288 (11) 0.128–0.647
Response/external dose (IV or oral admin.) without large dosimetric uncertainty		0.497 (1—haloperidol dose limiting tox)		0.546 (1—ibuprophen dental pain analgesia)		0.521 (2) 0.479–0.568
Response/external dose with large dosimetric uncertainty (e.g., workplace epidemiology)			1.33 (1—talc lung disease)	0.684 (3) 0.430–1.09		0.807 (4) 0.456–1.43
Total observations including pharmacodynamic variability	(1)	(14)	(12)	(9)	(7)	(43)

NOTE: Within each cell of this table, the geometric mean of the Log(GSD) observations is given on the first line, the number of observations appears on the second line, and the third line gives a 10%–90% range of the observations calculated assuming that the Log(GSD) values themselves are log-normally distributed. For example, differences in the internal concentration needed to produce a specific fraction of an individual's maximal response in a measured parameter, such as specific changes on an electroencephalograph.

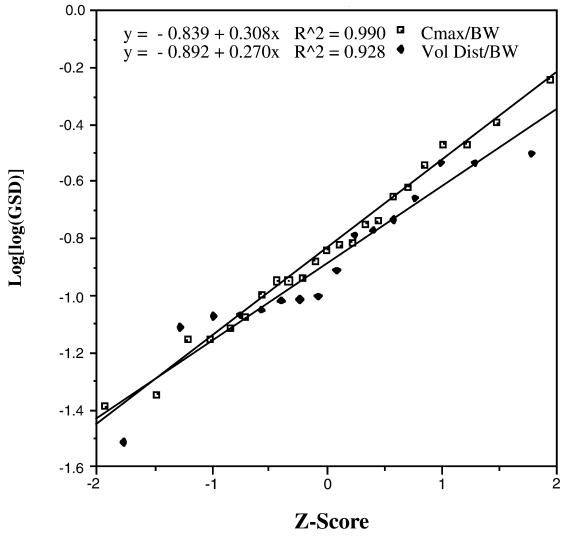

FIGURE 2. Log-normal plots of 23 C_{max}/body weight and 16 volume of distribution/body weight interindividual variability observations.

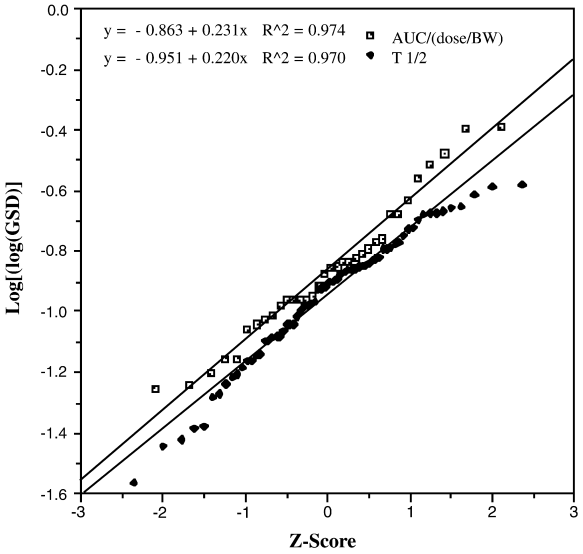

FIGURE 3. Log-normal plots of 34 AUC/body weight and 70 T1/2 or clearance/body weight interindividual variability observations.

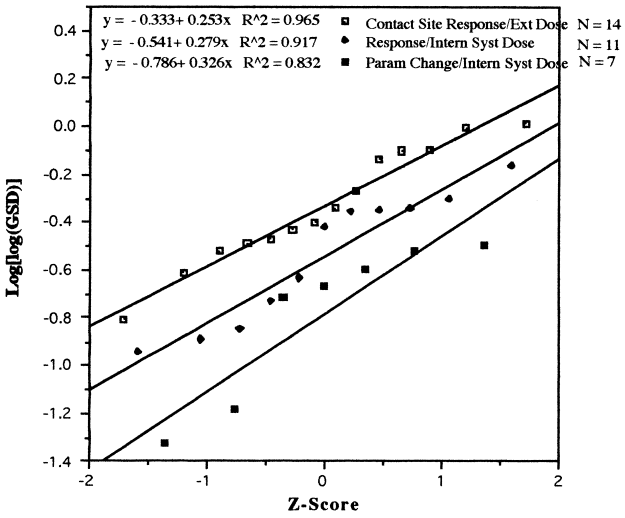

FIGURE 4. Log-normal plots of Log(GSD) values for three types of parameters that include pharmacodynamic variability.

tend to include much larger estimates of interindividual variability than the pharmacokinetic observations. Furthermore, among the pharmacodynamic observations, cases for which *response* is measured tend to show more variability than do cases for which the endpoint is some degree of change in a physiological parameter. In our schema, this difference is interpreted as indicating variability among people in functional reserve capacity; the amount of change in a physiologic parameter needed to cause different individuals to show a response—Step 8 in the outline given above.

STATISTICAL UNCERTAINTY IN THE ESTIMATES OF INTERINDIVIDUAL VARIABILITY

For continuous parameters, a standard statistical text[33] gives a formula for 95% confidence limits on the variance, σ^2, of a normally distributed parameter as:

$$\frac{(n-1)\hat{S}^2}{a} \text{ and } \frac{(n-1)\hat{S}^2}{b},$$

where n is the number of data points, a and b are the 0.025 and 0.975 fractiles, respectively, of a chi-squared distribution with $n-1$ degrees of freedom, and $\hat{S}^2$ is the observed unbiased estimator of the variance—the square of the ordinary standard deviation with $n-1$ weighting. In general, any fractile of the confidence distribution for σ^2 can be calculated similarly by adjusting the fractile of the chi-squared distribution.

TABLE 4. Detailed listing of pharmacodynamic variability observations at sites of direct contact with the toxicant

Parameter and reference	Chemical	Route	Log(GSD)	5%–95% conf. limits on Log(GSD)	Statistical weight = 1/variance of Log Log(GSD)
Long term FEV1 change/ pack-year of smoking[5]	cigarette smoking	inhalation	0.279	0.25–0.31	1101
Specific airway resistance—conc. needed for 100% increase in individual baseline value[18]	methacholine	inhalation	0.421	0.39–0.46	1986
FEV1 change in relation to CXT of ozone exposure (clinical)[4]	ozone	inhalation	0.321	0.28–0.37	761
FEV1 increase by antiasthmatic[15]	salbutamol	inhalation	0.431	0.31–0.61	120
Lowering of gastric pH below 2[19]	pantoprazole	oral	0.325	0.09–1.20	8
Nasal dryness[20]	ammonia	inhalation	0.340	0.18–0.64	36
Throat irritation[20]	ammonia	inhalation	0.156	0.10–0.25	67
Olfactory cognition—air concentrations needed to produce three levels of smell perception[21]	diallylamine	inhalation	0.369	0.27–0.51	142
Nose irritation—slight or moderate[21]	diallylamine	inhalation	0.803	0.49–1.33	57
Nose irritation—slight or moderate[21]	mono-allylamine	inhalation	0.459	0.26–0.82	42
Nose irritation—slight or moderate[21]	triallylamine	inhalation	0.735	0.59–0.91	310
Pulmonary discomfort—*slight* and *moderate* or more[21]	triallylamine	inhalation	1.038	0.78–1.38	180
Eye irritation—external air concentration causing four levels[21]	acrolein	air—direct contact	0.301	0.23–0.39	229
Eye irritation[20]	ammonia	air—direct contact	0.243	0.13–0.45	39
Skin hypersensitivity to chromium (VI)[3]	chromium VI	skin	0.989	0.84–1.17	511
Eye irritation—slight or moderate and above[21]	diallylamine	air—direct contact	0.398	0.28–0.56	122
Skin irritation response to sodium laurel sulfate applied via skin patch[22]	sodium lauryl sulfate	skin	0.797	0.53–1.20	87
Eye irritation—slight or moderate and above[21]	triallylamine	air—direct contact	0.539	0.48–0.60	1228
Pneumoconiosis (two levels) in relation to cumulative talc air exposure (inc. dosimetry)[23]	talc	inhalation	1.330	0.78–2.25	52

TABLE 5. Detailed listing of observations of systemic pharmacodynamic variability

Parameter and reference	Chemical	Route	Log(GSD)	5%–95% conf. limits on Log(GSD)	Statistical weight = 1/variance of Log Log(GSD)
Diuretic efficiency (ml/μg) (Drug induced urine flow/drug excretion rate)[24]	furosemide	IV	0.048	0.03–0.07	74
Natriuretic efficiency (ml/μg) (drug induced response/drug excretion rate)[24]	furosemide	IV	0.066	0.04–0.10	74
EC50-effect site concentration producing 50% of predetermined maximal EEG changes[25]	alfentanil	IV	0.214	0.12–0.38	43
EC50-concentration producing 50% max. monoamine oxidase-A inhibition[26]	befloxatone	oral	0.194	0.14–0.28	117
EC50-effect site concentration producing 50% of a predetermined maximal EEG change[25]	fentanyl	IV	0.302	0.17–0.54	43
Proportion of patients receiving more than 95% of their individual maximal response in relation to plasma conc.[15]	imiprimine	oral	0.253	0.20–0.33	224
EC50-effect site concentration producing 50% of a predetermined maximal EEG change[25]	trefentanil	IV	0.319	0.20–0.51	64
Significant hearing loss/one dose of cisplatin[15]	cisplatin	IV	0.195	0.13–0.29	99
Haloperidol toxicity (minimum of four other signs mostly neurological)[27]	haloperidol	oral	0.115	0.06–0.22	36
Ataxia/blood level[28]	MeHg	diet	0.232	0.16–0.34	99
Deaths/blood level[28]	MeHg	diet	0.128	0.06–0.28	24
Disarthria/blood level[28]	MeHg	diet	0.186	0.08–0.45	19
Hearing defects/blood level[28]	MeHg	diet	0.143	0.09–0.23	60
Paresthesia/blood level[28]	MeHg	diet	0.382	0.27–0.53	127
Visual effects/blood level[28]	MeHg	diet	0.458	0.33–0.63	135
High β2M urinary excretion vs. occupational blood conc X time[4]	cadmium	inhalation	0.697	0.50–0.97	129
High β2M urinary excretion vs. urinary Cd[4]	cadmium	diet	0.445	0.37–0.53	442
High β2M urinary excretion vs. urinary Cd[4]	cadmium	diet	0.452	0.37–0.55	353
Cataracts in relation to TNT hemoglobin adducts[4]	trinitro-toluene	inhalation	0.502	0.37–0.69	144
Dose-limiting toxicity including malaise, neurotoxicity, pericardial effusion[29]	suramin	IV	0.497	0.19–1.27	16
Analgesia from dental pain (not taking medication at three and six hours after procedure)[30]	ibuprofen	oral	0.546	0.36–0.82	85
High β2M urinary excretion in relation to diet, controlling for age (inc. dosimetry)[31,32]	cadmium	diet, females	0.499	0.37–0.66	175
High β2M urinary excretion in relation to diet, controlling for age (inc. dosimetry)[31,32]	cadmium	diet, males	0.631	0.42–0.95	86
High β2M urinary excretion vs. occupational air conc X time (inc. dosimetry)[4]	cadmium	inhalation	1.016	0.73–1.42	129

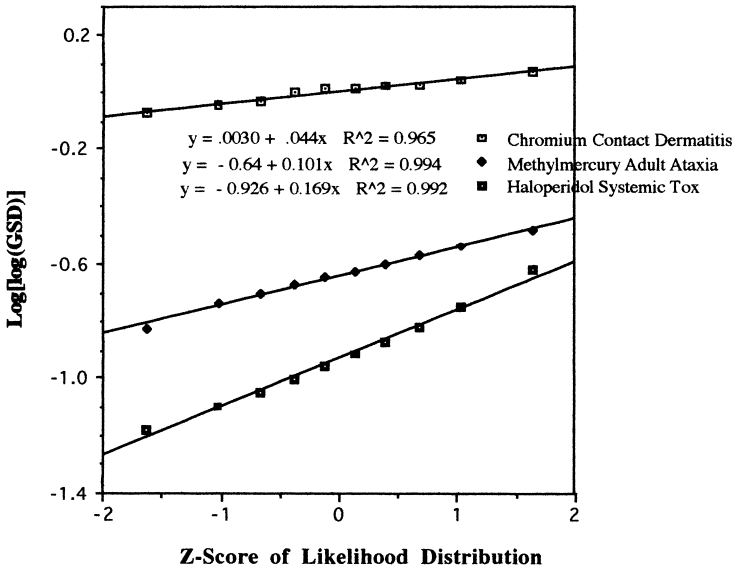

FIGURE 5. Log-normal probability plots of the likelihood distributions for quantal pharmacodynamic interindividual variability observations.

In model calculations we computed a large number of points on confidence distributions for log-normal distributions with different absolute values of Log(GSD) and n. We found that the desirable *statistical weight* for our analysis, the reciprocal of the variance of the LogLog(GSD) for each data set, was not affected by the absolute value of the Log(GSD) estimates but could be simply described by an empirical formula depending only on n:

$$\text{Weight} = 10.6n - 10.33$$

(approximately proportional to $n - 1$).

For quantal response parameters we used the Haas[17] spreadsheet-based likelihood fitting system cited earlier to calculate ten equally spaced fractiles (from 0.05 through 0.95) of the confidence distribution for each Log(GSD). As can be seen in the examples plotted in FIGURE 5, these confidence distributions appear to be well described as log-normal. We simply used these values to derive the variance of the corresponding LogLog(GSD) values. As for the continuous parameters, the reciprocal of this variance was used as the statistical weight in our later modeling.

MODELING THE COMBINED SUSCEPTIBILITY VARIABILITY FOR MEDIAN CHEMICALS—DEPENDENCE ON TYPES OF TOXICITY AND ROUTE OF EXPOSURE

If we assume that the interindividual variability, for each of several different steps in the causal sequence, from contact rate to effect, is independent and log-normal,

then the population distribution of the overall variability in susceptibility can be described simply as a log-normal distribution with variance equal to the sum of the log-normal variances at the component steps. For example, for an inhaled chronic systemic toxicant,

$$\text{Log(GSD)}_{\text{total}} = \sqrt{(\text{Log(GSD)}_{\text{total}})^2 + (\text{Log(GSD)}_{\text{fraction absorb}})^2 + \ldots + (\text{Log(GSD)}_{\text{functional reserve}})^2}$$

Based on this approach, we have developed a simple spreadsheet optimization model to estimate the median-chemical Log(GSD) values for each causal step, from external exposure to end response, that best correspond to our 226 observations. Given a set of starting values for the median-chemical Log(GSD) values for each causal step, and the set of dummy variables assigned to characterize which kinds of variability are included in each observation, the model makes a *prediction* of the expected median-chemical Log(GSD) for that observation. Then, in a series of iterative trials, the system calculates the set of median-chemical Log(GSD) values for each causal step that minimize the sum of the squares of the observed versus the predicted LogLog(GSD) values for all observations combined. This quantity is chosen for minimization because of the earlier finding that both the variability (FIGS. 2–4) and the uncertainty (FIG. 5) in Log(GSD) values appear to be reasonably described as log-normal. Parallel analyses are conducted by minimizing the sum of squares with and without the statistical weights derived in the previous section. In all cases the Log(GSD) values for each step are constrained to be nonnegative, because a negative values for a step-specific estimate of variability would be meaningless. TABLES 6–8 show the median-chemical Log(GSD) values for individual steps between contact rate and end effects that result from our model. For each table, the individual steps representing specific types of variability are shown in the first column. Each subsequent column represents a set of median-chemical Log(GSD) estimates that results from a progressive series of selections from the data base of variability observations. For comparison, the second column in each table gives results from a previous unweighted analysis[11] of the 126 variability observations that were available as of May, 1997. TABLE 6 shows results of analyses that only include physiological parameter changes and responses at sites of direct contact with external agents (i.e., those observations that were individually listed in TABLE 4). TABLES 7 and 8 show analyses of the full data base with progressive exclusions so that the final three columns combine the contact-rate and pharmacokinetic observations only with pharmacodynamic data on systemic toxic responses (excluding the direct-contact observations). TABLE 7 and the upper part of TABLE 6 show the results of unweighted analyses, in which each observation is treated equally in the optimization process. TABLE 8 and the lower part of TABLE 6 show the results using the statistical weights, in which the deviation of each observation from the corresponding model prediction is weighted in proportion to the inverse of the variance of the primary observation in the optimization.

Comparing the first numerical column with the subsequent columns in these tables, it can be seen that the expansion of the data base from 126 to 226 observations has not, in itself, given rise to major changes in the overall picture of step-specific

TABLE 6. Summary of median variability for specific steps for direct contact physiological parameter change and response

	Previous unweighted results[11]	Data only including direct contact observations	Data only including direct contact respiratory system observations	Direct contact observations for non-respiratory responses
		A. Unweighted Analysis		
Number of observations	6	18	11	7
All steps up through physiological parameter change/active site availability	0.393	0.357	0.357	allocation not meaningful—all observations are responses
Functional reserve capacity—change in baseline physiological parameter needed to pass a criterion of abnormal function	0.499	0.298	0.314	allocation not meaningful—all observations are responses
Summary Log(GSD) for direct contact effects	0.635	0.465	0.475	0.455
		B. Weighted Analysis		
Number of observations	6	18	11	7
All steps up through physiological parameter change/active site availability	0.393	0.357	0.357	allocation not meaningful—all observations are responses
Functional reserve capacity—change in baseline physiological parameter needed to pass a criterion of abnormal function	0.499	0.455	0.470	allocation not meaningful—all observations are responses
Summary Log(GSD) for direct contact effects	0.635	**0.578**	**0.590**	**0.574**

NOTE: The bold-face numbers are used for subsequent risk calculations in TABLE 11.

TABLE 7. Unweighted analysis: summary of median estimates of human interindividual variability for various steps in the pathway from external exposure to response

	Data Inclusions/Exclusions						
	Previous unweighted results[11]	All data, incl children and var. inflation	All adult data, including var. inlation	All adult data excluding var. inflation	Uptake, PK and 21 systemic PD obs. excluding direct contact PD obs.	Uptake, PK and only 14 systemic neurological PD obs.	Uptake, PK and 7 systemic non-neurological PD obs.
Number of variability observations included	126	226	218	214	196	189	182
Oral contact rate (tap water, fish consumpt/Kg BW)	0.286	0.275	0.257	0.266	0.264	0.264	0.264
Inhalation contact rate (breathing rate/Kg BW)	0.286	0.103	0.174	0.170	0.108	0.108	0.108
Other contact rate	0.286	0.168	0.168	0.168	0.168	0.168	0.168
Oral uptake or absorption (mg/Kg)/intake or contact rate	0.117	0.000	0.000	0.000	0.000	0.000	0.000
Inhalation fraction absorbed	0.117	0.103	0.000	0.000	0.000	0.000	0.000
Other route fraction absorbed	0.117	0.113	0.113	0.112	0.000	0.000	0.000
Oral systemic availability net of local or first pass liver metabolism	0.000	0.057	0.073	0.073	0.080	0.080	0.080
Systemic availability after absorption by inhalation or other route	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Body weight correction	not included	0.083	0.083	0.083	0.089	0.089	0.089
Dilution via distribution volume/BW	0.075	0.121	0.113	0.113	0.113	0.113	0.113
Systemic elimination half life or clearance/BW	0.110	0.110	0.107	0.107	0.107	0.107	0.107
Active site availability/general systemic availability	0.000	0.000	0.000	0.000	0.071	0.000	0.347
Physiological parameter change/active site availability	0.079	0.186	0.179	0.180	0.158	0.227	0.056
Functional reserve capacity—change in physiological parameter needed for effect	0.338	0.316	0.316	0.316	0.252	0.000	0.445
Likely inflated variability— imperfect epidemiological estimation of exposure/dose	0.753	0.691	0.688				

TABLE 8. Weighted analysis: summary of median estimates of human interindividual variability for various steps in the pathway from external exposure to response

	Data Inclusions/Exclusions						
	Previous unweighted results[11]	All data, inc. children and var. inflation	All adult data, including var. inlation	All adult data excluding var. inflation	Uptake, PK and 21 systemic PD obs. excluding direct contact PD obs.	Uptake, PK and only 14 systemic neurological PD obs.	Uptake, PK and 7 systemic non-neurological PD obs.
Number of variability observations included	126	226	218	214	196	189	182
Oral contact rate (tap water, fish consumpt/Kg BW)	0.286	0.261	0.261	0.261	0.261	0.261	0.261
Inhalation contact rate (breathing rate/Kg BW)	0.286	0.090	0.117	0.117	0.117	0.117	0.117
Other contact rate	0.286	0.168	0.168	0.168	0.168	0.168	0.168
Oral uptake or absorption(mg/Kg)/intake or contact rate	0.117	0.000	0.000	0.000	0.000	0.000	0.000
Inhalation fraction absorbed	0.117	0.276	0.263	0.259	0.000	0.000	0.000
Other route fraction absorbed	0.117	0.072	0.068	0.068	0.000	0.000	0.000
Oral systemic availability net of local or first pass liver metabolism	0.000	0.091	0.107	0.107	0.110	0.110	0.109
Systemic availability after absorption by inhalation or other route	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Body weight correction	not included	0.087	0.087	0.087	0.087	0.087	0.087
Dilution via distribution volume/BW	0.075	0.124	0.113	0.113	0.112	0.112	0.112
Systemic elimination half life or clearance/BW	0.110	0.136	0.135	0.135	0.135	0.135	0.135
Active site availability/general systemic availability	0.000	0.087	0.082	0.080	0.145	0.000	0.350
Physiological parameter change/active site availability	0.079	0.175	0.177	0.180	0.146	0.233	0.056
Functional reserve capacity—change in physiological parameter needed for effect	0.338	0.461	0.460	0.460	0.367	0.149	0.444
Likely inflated variability— imperfect epidemiological estimation of exposure/dose	0.753	0.405	0.408				

variabilities. The largest single contributor to overall variability is the last step or two in the process, representing pharmacodynamic variability (2–4 lines from the bottom in TABLES 7 and 8). What is somewhat different is that the weighted analyses, done here for the first time (TABLE 8), indicate somewhat larger variability than the unweighted analyses. Evidently the statistically stronger data sets happened to indicate larger amounts of variability than some of the statistically weaker data sets.

Progressing to the third numerical column in TABLES 7 and 8, it can be seen that excluding the very small number of data sets that have values for young children does not materially change the overall results. Furthermore, excluding the four data points that are likely to include substantial uncertainty in individual dosimetry (fourth numerical column) results in very little difference in the estimates. By contrast, excluding the direct contact observations, moving from the fourth to the fifth numerical columns in these tables, does cause a noticeable change in the variability allocated to the final three steps. A modest increase in variability for active site availability/general systemic availability is more than offset by reductions in the two last steps. This is further modified when systemic neurological and non-neurological observations of pharmacodynamic observations are segregated in the final two columns (although it should be stressed that the data are too few at this stage for us to be confident that the suggestion that non-neurological endpoints are more variable will survive as additional information accumulates).

One advantage of having these variability results disaggregated by causal steps in the pathway from contact to effect, is that one can recombine the step-specific results to estimate overall variability in susceptibility for different types of toxicants presented to people in different media. This is done by simply combining the logarithmic variances for the relevant steps, as illustrated in the previous section with the equation for the overall variability of an inhaled chronic systemic toxicant. TABLES 9 and 10 show the overall Log(GSD) values that result from a variety of such combinations in the same format that was previously used for TABLES 7 and 8. The aggregate Log(GSD) values for agents causing effects at the sites of direct contact with external agents were given previously in TABLE 6.

The bold face entries in TABLES 6 and 10 represent the *bottom line* results that we believe are most salient as points of departure for estimating risks for different categories of toxicants. These are used in later risk calculations. Of these, the results in the second line of TABLE 10 (for an oral agent whose dose is expressed in mg/kg, without allowing for contract rate variability) provide the single most relevant set of variability estimates for comparison with expectations for the original Lehman-Fitzhugh food additive/pesticide residue context. Without further calculation, however, it can be seen that, because most of the interindividual variability indicated by the present data base is associated with the pharmacodynamic steps, the details of route of exposure for systemic toxicants exert mainly second-order effects. Comparing TABLE 6 with TABLE 10, however, it can be seen that there is an appreciable tendency for the direct-contact responses to be associated with greater overall variability than the systemic toxic responses.

TABLE 9. Unweighted analysis: summary aggregate Log(GSD) estimates for different types of toxicants delivered in different ways

Type of agent and mode of administration	Previous unweighted results[11]	All data, incl. children and var. inflation	All adult data, including var. inlation	All adult data excluding var. inflation	Uptake, PK and 21 systemic PD obs. excluding direct contact PD obs.	Uptake, PK and only 14 systemic neurological PD obs.	Uptake, PK and 7 systemic non-neurological PD obs.
Ingested systemic chronic toxicant (including variability in ingestion behavior)	0.483	0.489	0.477	0.482	0.441	0.400	0.656
Chronic toxicity from an orally administered drug with perfect compliance (no contact rate variabity)		0.405	0.402	0.402	0.353	0.287	0.593
Inhaled chronic systemic toxicant		0.427	0.431	0.430	0.360	0.296	0.598
Chronic systemic toxicant delivered by other route		0.449	0.444	0.444	0.382	0.323	0.611
Ingested systemic acute toxicant (no elimination rate variability)		0.477	0.465	0.470	0.428	0.375	0.641
Acute toxicity from an orally administered drug with perfect compliance (no contact or elim. rate variabity)		0.390	0.387	0.388	0.336	0.266	0.584
Inhaled systemic acute toxicant		0.412	0.418	0.417	0.344	0.276	0.588
Systemic acute toxicant delivered by other route		0.435	0.430	0.431	0.367	0.304	0.602

TABLE 10. Weighted analysis: summary aggregate Log(GSD) estimates for different types of toxicants delivered in different ways

Type of agent and mode of administration	Previous unweighted results[11]	All data, incl. children and var. inflation	All adult data, including var. inlation	All adult data excluding var. inflation	Uptake, PK and 21 systemic PD obs. excluding direct contact PD obs.	Uptake, PK and only 14 systemic neurological PD obs.	Uptake, PK and 7 systemic non-neurological PD obs.
Ingested systemic chronic toxicant (including variability in ingestion behavior)	0.483	0.601	0.600	0.600	**0.536**	0.441	0.664
Chronic toxicity from an orally administered drug with perfect compliance (no contact rate variability)		0.541	0.541	0.541	**0.469**	**0.345**	**0.605**
Inhaled chronic systemic toxicant		0.607	0.603	0.602	**0.470**	**0.347**	**0.606**
Chronic systemic toxicant delivered by other route		0.564	0.560	0.560	**0.485**	0.368	0.618
Ingested systemic acute toxicant (no elimination rate variability)		0.585	0.585	0.585	**0.519**	0.411	0.645
Acute toxicity from an orally administered drug with perfect compliance (no contact or elim. rate variability)		0.524	0.524	0.524	**0.449**	0.318	0.590
Inhaled systemic acute toxicant		0.592	0.588	0.586	**0.451**	0.320	0.591
Systemic acute toxicant delivered by other route		0.547	0.544	0.544	**0.466**	0.342	0.603

NOTE: THE bold-face numbers are used for subsequent risk calculations in TABLE 11.

ASSESSING THE SPREAD OF VARIABILITY VALUES AMONG CHEMICALS

Policies that utilize safety/uncertainty factors as a guide to risk management do so repeatedly for many chemicals with different toxic effects. Each risk management choice under such a system essentially makes a random draw from a group of chemicals and effects for which the mixed human population is likely to have different amounts of real interindividual variability in susceptibility. It is therefore important to assess the extent of real variation among chemicals/effects in the Log(GSD) values for human susceptibility.

One indicator of the possible extent of this variation is the spread of Log(GSD) values for similar types of parameters, such as the distributions plotted in FIGURES 2-4. The slopes of the regression lines in these figures indicate Log Log(GSD) standard deviations within different parameter types in the range of 0.22–0.33. Unfortunately, these spreads include both real Log(GSD) variability among chemicals and additional spread due to uncertainties in the estimation of the individual Log(GSD) values from the samples of people studied. The real variability is, therefore, likely to be somewhat smaller.

To distinguish real variability among chemicals from uncertainties in the estimation of the individual Log(GSD) values we borrow a technique from meta analyses and array the observed minus model predicted Log(Log(GSD) value deviations by the statistical strength of the individual data points, in the form of *funnel* plots.[34] The

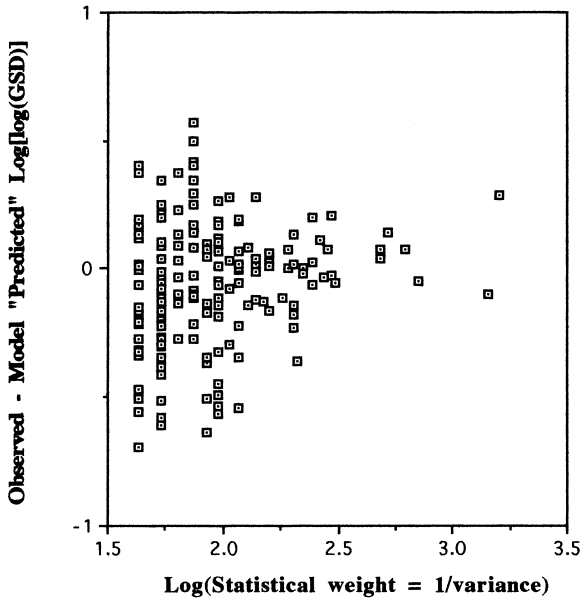

FIGURE 6. Funnel plot for pharmacokinetic interindividual variability observations.

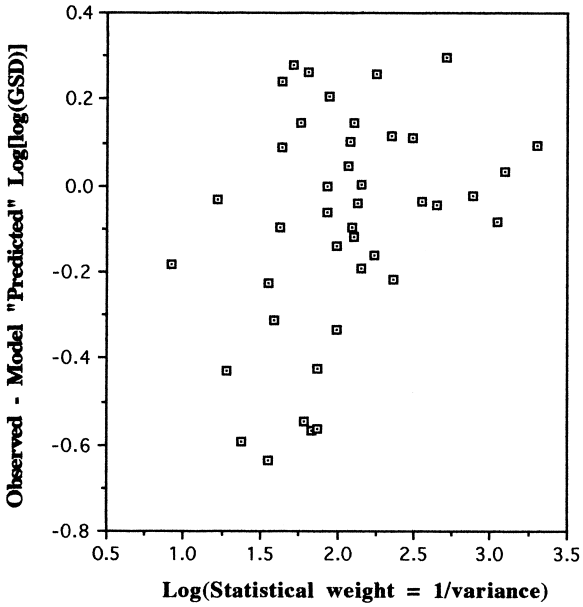

FIGURE 7. Funnel plot for pharmacodynamic interindividual variability observations.

expectation here is that the points will form a funnel shape with a wider variation in observed minus predicted results for the weaker data points on the left side of these plots, narrowing to a smaller residual variation (small part of the funnel) for the stronger points at the right. The basic idea is that the spread at the wider end of the funnel includes both real and chemical variation in Log(GSD) for a given parameter and measurement errors. At the narrower end of the funnel, however, the statistically stronger data points may have measurement errors that are small relative to the real variability among chemicals. FIGURES 6 and 7 show such plots for the individual pharmacokinetic and pharmacodynamic observations, respectively. FIGURES 8 and 9 show the observations grouped together to better reveal numerical trends in the spread among chemicals, quantified as the root mean square error (equivalent to a standard deviation) of the observed minus predicted LogLog(GSD) values. It can be seen that in each case the plots appear to converge on the right to a between-chemical standard deviation of about 0.14 (the weighted average of all the data in the indicated regions from both plots is 0.138). This number is considerably less than the 0.22–0.32 range for the raw standard deviation of all the LogLog(GSD) values within various parameter types. In subsequent risk calculations we will therefore assume that the susceptibility Log(GSD) values for different chemicals are characterized by log-normal distributions with geometric means equal to the bold face values in TABLES 6 and 10, and a geometric standard deviation equal to $10^{0.138} = 1.37$.

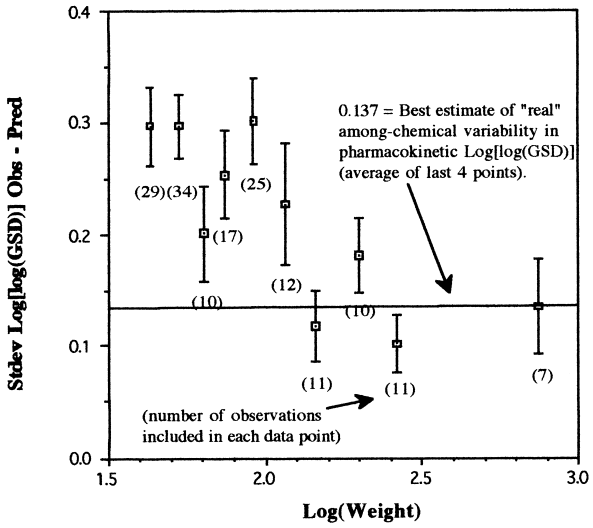

FIGURE 8. Relationship between root mean square prediction error and Log(statistical weight) for pharmacokinetic interindividual variability observations.

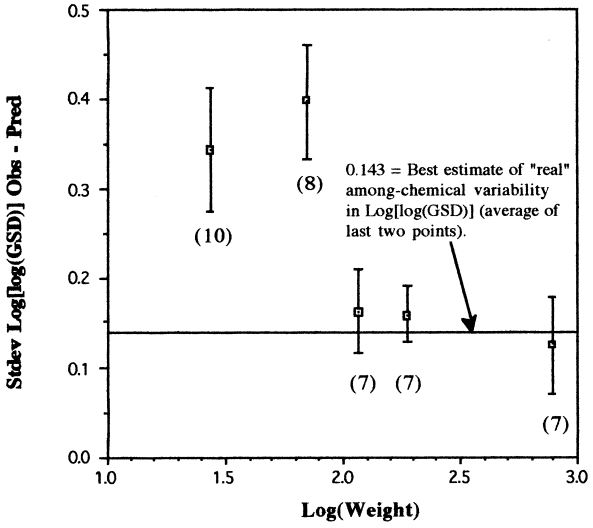

FIGURE 9. Relationship between root mean square prediction error and Log(statistical weight) for observations with pharmacodynamic interindividual variability.

TABLE 11. Weighted analysis: implications of the spread of variability results among chemicals; expected fraction of people showing a response at one tenth of the dose that produces the response in 5% of exposed people

	50% confidence (median chemical) risk	Arithmetic mean (expected value)	95th percentile chemical risk
Ingested systemic chronic toxicant (including variability in ingestion behavior)	2.2E–04	6.8E–04	3.0E–03
Chronic toxicity from an orally administered drug with perfect compliance (no contact rate variabity)	7.9E–05	3.7E–04	1.8E–03
Inhaled chronic systemic toxicant	8.1E–05	3.8E–04	1.8E–03
Chronic systemic toxicant delivered by other route	1.1E–04	4.4E–04	2.1E–03
Ingested systemic acute toxicant (no elimination rate variability)	1.8E–04	5.9E–04	2.7E–03
Acute toxicity from an orally administered drug with perfect compliance (no contact or elim. rate variabity)	5.4E–05	3.0E–04	1.5E–03
Inhaled systemic acute toxicant (no elimination rate variability)	5.6E–05	3.1E–04	1.5E–03
Systemic acute toxicant delivered by other route	7.6E–05	3.6E–04	1.8E–03
Chronic systemic neurological toxicity for an ingested drug with perfect compliance	2.8E–06	7.0E–05	3.9E–04
Chronic systemic non-neruological toxicity for an ingested drug with perfect compliance	4.9E–04	1.1E–03	4.3E–03
Chronic systemic neurological toxicity for an inhaled toxicant	3.1E–06	7.3E–05	4.1E–04
Chronic systemic non-neurological toxicity for an inhaled toxicant	4.9E–04	1.1E–03	4.4E–03
Acute systemic neurological toxicity for an inhaled toxicant	9.4E–07	4.3E–05	2.4E–04
Acute systemic non-neurological toxicity for an inhaled toxicant	4.2E–04	1.0E–03	4.1E–03
All direct contact effects	3.7E–04	9.2E–04	3.8E–03
Direct-contact respiratory effects	4.2E–04	1.0E–03	4.0E–03
Direct-contact non-respiratory effects	3.5E–04	8.9E–04	3.7E–03

IMPLICATIONS FOR RISK AT ONE TENTH OF AN ED05 DOSE

On this basis, TABLE 11 shows the incidences of response that are expected for exposure of populations at one tenth of an ED05 dose for different chemicals/responses within and among different exposure and toxicity types. For the second line of the table, the case that most resembles the original Lehman-Fitzhugh context of an orally-administered drug or food additive that causes chronic systemic toxicity after presentation at a defined mg/kg dose, the risk for a median chemical is expected to be slightly less than one in 10,000; but a chemical that has more variability than 95% of other chemicals would be expected to cause an incidence of effect exceeding one in 1,000. Risks for some other categories of exposure mode and response extend up to several per 1,000 at the 95% confidence level. Thus, if the underlying estimates of the extent of log-normal response variability are approximately correct, use of the traditional tenfold safety/uncertainty factor, without any other protective factors, would appear to run risks of response incidences that are large enough to be of some concern, although they would generally be difficult to detect directly at those exposure levels in any but the largest and best controlled epidemiological studies of effects with low background levels of response.

In general, however, the tenfold uncertainty factor for interindividual variability is not used in isolation, but is combined with other uncertainty factors (e.g., for interspecies projections or use of subchronic data to predict chronic response levels) many of which may tend to provide additional protection in the cases of typical chemicals.[1,7,35] Full quantitative assessments of the incidences of response expected in these cases must take the uncertainty distributions of these other factors into account.

IMPLICATIONS FOR MEAN EXPECTED VALUE INCIDENCES OF RESPONSE AT VARIOUS FRACTIONS OF ED05 EXPOSURES

In a number of cases, legislative and administrative authorities concerned with the economic impacts of measures intended to protect human health have requested that quantitative analyses be done that would facilitate juxtapositions of health and economic effects of proposed actions.[36] For such comparisons, it is desirable to have arithmetic mean *expected value* estimates of health response and health benefits of control, in addition to the *upper confidence limit* estimates that others may desire in order to make judgments of the equity of the risks imposed on protected parties.[37] FIGURE 10 shows log-log plots of the results of these arithmetic mean calculations for various exposure mode and response categories as a function of dose reductions below a defined 5% incidence level at the ED05. From the correspondence of the points to the straight lines, it can be seen that these risk versus dose functions are well described as power-law relationships with exponents ranging from about 1.6 to 3.2 for the different cases shown.

In conclusion, the generic analysis of the ensemble of all studied chemicals and toxic responses provided here permits preliminary pathway-specific estimates to be made of likely health benefits in the absence of detailed information about the Log(GSD) values associated with a particular chemical and toxic response.

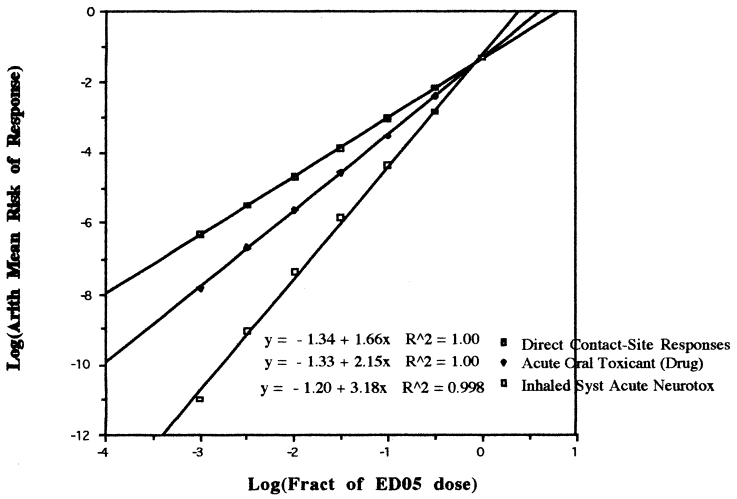

FIGURE 10. Log Log plots of model projections of the mean risk of toxicant exposures at various fractions of an ED05 dose or exposure level.

CAVEATS AND LIMITATIONS

This analysis should be understood as an early effort on the road toward quantitative analyses of effects that are produced by *threshold* (homeostatic system overwhelming) mechanisms. Not all non-cancer effects may be best treated in this way. Several other strategies for quantification dependent on different features of causal mechanisms were summarized in a previous paper.[4] Additionally, even within the context of effects whose mechanisms lend themselves to treatment as individual threshold responses, several notes of caution are in order:

- First, we have assumed that the data base of variability observations, for a highly diverse set of chemicals and toxic responses, is reasonably representative of the interindividual variability in cases that might be presented for evaluation by agencies charged with managing specific types of non-cancer risks. Some chemicals for which we have pharmacodynamic adverse effect information may have had that information collected and interindividual variability quantified just because there has been some visible toxic problem to be investigated by epidemiologists or toxicologists. The current data base may not be an unreasonable reflection of the spectrum of chemicals and effects encountered by an agency such as the U.S. Occupational Safety and Health Administration, which generally deals with problem chemicals for which toxicity of some sort has usually been noticed in human workers at not-uncommon exposure levels. However, these sets may not be entirely similar to the general purpose chemicals that are likely to be presented for decision-making by a

regulator of food additives, for example; or even for the EPA Office of Toxic Substances, that evaluates new general industrial chemicals.

- Second, throughout this analysis we have assumed log-normal distributions of individual susceptibility in people, and, in the final analysis, log-normal distributions for the Log(GSD) values themselves. These assumptions appear to be generally compatible with the available data, but when projections are made to very low effect levels, the unsuspected presence of discrete subpopulations with unusual sensitivity could cause departures from population log-normality that would add uncertainty to the estimates of low dose risks.
- We have also implicitly assumed that each parameter included in our variability observations has a direct proportionate and independent effect on individual susceptibility (the dose at which an individual will experience a response), and that the combined effects of all the variability parameters are simply multiplicative. Correlations (positive or negative) between contact rate, pharmacokinetic, and pharmacodynamic variability parameters could appreciably modify the expected proportions of people who appear at the extreme tails of the population distribution of susceptibilities.
- Finally, we have not analyzed the measurement error and short term within-individual variability implicit in the individual estimates of human Log(GSD) values for various parameters. This could lead to a tendency to estimate higher risks than are actually likely to be present for chronic exposures. On the other hand, the populations studied for the original observations were generally less diverse than actual human populations likely to be exposed to toxicants. Investigators rarely include in their study groups very old or very young people, or people known to be suffering from serious pathologies that might make them specially vulnerable to the toxicants. This would be expected to result in understated risks relative to those likely to be experienced by more diverse groups of exposed people.

Nevertheless, recognizing these limitations, later efforts can strive to gather more extensive and better data, quantify as yet unanalyzed sources of uncertainty and variability, and eventually provide the foundation for risk analyses that can more frankly and fairly inform decision-makers, and the public, about the likely benefits of alternative policies to control exposures to chemicals posing toxic hazards.

ACKNOWLEDGMENTS

The analysis reported in this document was supported by a purchase order (#B9F74428) from the U.S. Occupational Safety and Health Administration. Construction of the underlying data base was supported by Grant # R825360 from the Office of Research and Development of the U.S. Environmental Protection Agency. The views expressed, however, are solely those of the authors and do not necessarily reflect either the technical or the policy judgments of either agency.

REFERENCES

1. BAIRD, S.J.S., J.T. COHEN, J.D. GRAHAM, A.I. SHLYAKHTER & J.S. EVANS. 1996. Noncancer risk assessment: A probabilistic alternative to current practice. Hum. Ecol. Risk Assess. **2:** 78–99.
2. HATTIS, D., L. ERDREICH & M. BALLEW. 1987. Human variability in susceptibility to toxic chemicals—a preliminary analysis of pharmacokinetic data from normal volunteers. Risk Analysis **7:** 415–426.
3. HATTIS, D. & K. SILVER. 1994. Human interindividual variability—a major source of uncertainty in assessing risks for non-cancer health effects. Risk Analysis **14:** 421–431.
4. HATTIS, D. 1998. Strategies for assessing human variability in susceptibility, and using variability to infer human risks. *In* Human Variability in Response to Chemical Exposure: Measures, Modeling, and Risk Assessment, D.A. Neumann and C.A. Kimmel, Eds.: 27–57. CRC Press, Boca Raton.
5. SWARTOUT, J.C., P.S. PRICE, M.L. DOURSON, H.L. CARLSON-LYNCH & R.E. KEENAN. 1998. A probabilistic framework for the reference dose (probabilistic RfD). Risk Anal. **18:** 271–282.
6. RENWICK, A.G. & N.R. LAZARUS. 1998. Human variability and noncancer risk assessment—an analysis of the default uncertainty factor. Regul. Toxicol. Pharmacol. **27:** 3–20.
7. RHOMBERG, L., S.J.S. BAIRD, G.M. GRAY, J.S. EVANS & J.T. COHEN. 1997. Framing for development of data-derived probability distributions in workshops of experts. Final Report for Health Canada, Priority Substances Section, Harvard Center for risk Analysis, Harvard School of Public Health, 718 Huntington Ave., Boston, MA.
8. LEHMAN, A.J. & O.G. FITZHUGH. 1954. 100-fold margin of safety. Assoc. Food Drug Off. U.S. Q. Bull. **18:** 33–35.
9. FINNEY, D.J. 1971. Probit Analysis, 3rd ed. Cambridge University Press, London.
10. CUNNANE, C. 1978. Unbiased plotting positions—a review. J. Hydrol. **37:** 205–222.
11. HATTIS, D., P. BANATI, I. SIROVIC & R. GOBLE. 1997. Preliminary analysis of a data base of human interindividual variability observations--implications for generic occupational health risk assessments for chronic toxic responses, Report to the Occupational Safety and Health Administration, Clark University, Worcester, MA.
12. HATTIS, D. 1997. Variability in susceptibility—how big, how often, for what responses to what agents? Environmental Toxicology and Pharmacology **4:** 195–208.
13. HATTIS, D. 1994. The importance of exposure measurements in risk assessment of drugs. Archives of Toxicology, Suppl. **16:** 201–210.
14. HATTIS, D. 1994. The use of well defined biomarkers (such as blood lead) in risk assessment. Environmental Geochemistry and Health **16:** 223–228.
15. HATTIS, D. 1996. Variability in susceptibility—how big, how often, for what responses to what agents? Environmental Toxicology and Pharmacology **2:** 135–145.
16. HATTIS, D., P. BANATI, R. GOBLE, & D. BURMASTER. 1999. Human interindividual variability in parameters related to health risks. Risk Analysis **19:** 711–726.
17. HAAS, C.N. 1994. Dose response analysis using spreadsheets. Risk Analysis **14:** 1097–1100.
18. BALMES, J.R., R.M. ARIS, L.L. CHEN, C. SCANNELL, I.B. TAGER, W. FINKBEINER, D. CHRISTIAN, T. KELLER, P.Q. HEARNE, R. FERRANDO & B. WELCH. 1997. Airway inflammation and responsiveness to ozone in normal and asthmatic subjects. *In* Effects of Ozone on Normal and Potentially Sensitive Subjects. Health Effects Institute Research Report Number 78, Cambridge, MA.

19. KOOP, H., S. KULY, M. FLUG, R. EISSELE, H. MONNIKES, K. ROSE, R. LUHMANN, A. SCHNEIDER, R. FISCHER & R. ARNOLD. 1996. Intragastric pH and serum gastrin during administration of different doses of pantoprazole in healthy subjects. Eur. J. Gastroenterol. Hepatol. **8:** 915–918.
20. INDUSTRIAL BIOTEST. 1973. International Institute of Ammonia Refrigeration irritation threshold evaluation study with ammonia. IBT Report No. 663-03161.
21. HINE, C.H., F.H. MEYERS, F. IVANHOE, S. WALKER & G.H. TAKAHASHI. 1961 Simple tests of respiratory function and study of sensory response in human subjects exposed to respiratory tract irritants. Fifth Air Pollution Medical Research Conference.
22. JUDGE, M.R., H.A. GRIFFITHS, D.A. BASKETTER, I.R. WHITE, R.J.G. RYECROFT & J.P. MCFADDEN. 1996. Variation in response of human skin to irritant challenge. Contact Dermatitis **34:** 115–117.
23. WILD, P., M. REFREGIER, G. AUBURTIN, B. CARTON & J. J. MOULIN. 1995. Survey of the respiratory health of the workers of a talc producing factory. Occup. Environ. Med. **52:** 470–477.
24. WALKELKAMP, M., G. ALVAN, J. GABRIELSSON & G. PAINTAUD. 1996. Pharmacodynamic modeling of furosemide tolerance after multiple intravenous administration. Clin. Pharmacol. Therapeut. **60:** 75–88.
25. LEMMENS, H.J.M., J. B. DYCK, S. L. SHAFER & D.R. STANSKI. 1994. Pharmacokinetic-pharmacokinetic modeling in drug development: application to the investigational opioid trefentanil. Clin. Pharm. Ther. **56:** 261–271.
26. PATAT, A., F. LECOZ, C. DUBRUC, J. GANDON, G. DURRIEU, I. CIMAROSTI, S. JEZEQUEL, O. CURET, I. ZIELENIUK, H. ALLAIN & P. ROSENZWEIG. 1996. Pharmacodynamics and pharmacokinetics of two dose regimens of befloxatone, a new reversible and selective monoamine oxidase inhibitor, at steady state in healthy volunteers, J. Clin. Pharmacol. **36:** 216–229.
27. DARBY, J.K., D.J. PASTA, L. DABIRI, L. CLARK & D. MOSBACHER. 1995. Haloperodol dose and blood level variability: toxicity and interindividual and intraindividual variability. J. Clin. Pharmacol. **15:** 334–340.
28. INSTITUTE OF MEDICINE. 1991. Seafood Safety Committee on the Evaluation of the Safety of Fishery Products, Food and Nutrition Board, Institute of Medicine. Farid E. Ahmed, Ed.: National Academy Press, Washington, D.C.
29. KOBAYASHI, K., E. VOKES, N. VOGELSANG, L. JANISCH, B. SOLIVEN & M. RATAIN. 1995. Phase I study of suramin given by intermittent infusion without adaptive control in patients with advanced cancer. J. Clin. Oncol. **13:** 2196–2207.
30. SCHOU, S., H. NIELSEN, A. NATTESTAD, S. HEILLERUP, M. RITZAU, P.E. BRANEBJERG, C. BUGGE & L.A. SKOGLUND. 1998. Analgesic dose-response relationship of ibuprofen 50, 100, 200, and 400 mg after surgical removal of third molars: a single-dose randomized placebo-controlled and double-blind study of 304 patients. J. Clin. Pharmacol. **38:** 447–454.
31. HOCHI, Y., T. KIDO, K. NOGAWA, H. KITO & Z. SHAIKH. 1995. Dose-response relationship between total cadmium intake and prevalence of renal dysfunction using general linear models. J. Appl. Toxicol. **15:** 109–116.
32. NOGAWA, K., R. HONDA, T. KIDO, I. TSURITANI, Y. YAMADA, M. ISHIZAKI & H. YAMAYA. 1989. A dose-response analysis of cadmium in the general environment with special reference to total cadmium intake limit. Environ. Res. **48:** 7–16.
33. WINKLER, R.L. & W.L. HAYS. 1975. Statistics: Probability, Inference, and Decision, second ed. 381–385, Holt, Rinehart and Winston, New York.
34. BHATIA, R., P. LOPIPERO & A.H. SMITH. 1998. Diesel exhaust exposure and lung cancer. Epidemiol. **9:** 84–91.

35. KODELL, R. 1999. Combining uncertainty factors in setting allowable exposure levels. Ann. N.Y. Acad. Sci. **895:** this volume.
36. HATTIS, D. & W.S. MINKOWITZ. 1996. Risk evaluation: criteria arising from legal traditions and experience with quantitative risk assessment in the United States. Environ. Toxicol. Pharmacol. **2:** 103–109.
37. HATTIS, D. & E. ANDERSON. 1998. What should be the implications of uncertainty, variability, and inherent 'biases'/'conservatism' for risk management decision making? Risk Analysis. **19:** 95–107.