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Health Risk above the Reference Dose for Multiple Chemicals

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Recent work indicates that the regression of toxicity data viewed as categories of pathological staging is useful for exploring the likely health risk at doses above a Reference Dose (RfD), which is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Toxic effects, which may include both quantal and continuous data, are classified into ordered categories of total toxic severity (e.g., none, mild, adverse, severe). These severity categories are regressed on explanatory variables, such as dose or exposure duration, to estimate the probability of observing an adverse or severe effect. In this paper, categorical regression has been expanded to compare the likely risks across multiple chemicals when exposures are above their RfDs. Existing health risk data for diazinon, disulfoton, *S*-ethyl dipropylthiocarbamate, fenamiphos, and lindane were analyzed. As expected, the estimated risks of adverse effects above the RfD varied among the chemicals. For example, at 10-fold above the RfD these risks were modeled to be 0.002, 0.0001, 0.0007, 0.002, and 0.02, respectively. The results and impacts of this analysis indicate that categorical regression is a useful screening tool to analyze risks above the RfD for specific chemicals and suggest its application in evaluating comparative risks where multiple chemical exposures exist.

INTRODUCTION

The use of a "safe"-dose concept in noncancer risk assessment has been employed by expert risk assessors throughout the world (Lu and Sielken, 1991). An example of this is the United States Environmental Protection Agency's (EPA) current practice of expressing noncancer toxicity as Reference Doses (RfDs) (Barnes and Dourson, 1988). The RfD is "an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime" (U.S. EPA, 1998). An analogous value for inhalation exposures is EPA's Reference Concentration (RfC) (Jarabek *et al.*, 1990).

An RfD is often calculated by dividing an experimental or epidemiologic no-observed-adverse-effect level (NOAEL) for the critical effect (i.e., usually the first adverse effect or its known precursor as dose or concentration increases) by one or more uncertainty factors (UFs). (More recently, the NOAEL has in some cases been replaced by a benchmark dose, a modeled value that is most commonly defined as the statistical lower confidence limit on the dose estimated to produce a predetermined level of change in response relative to controls.) UFs have in practice been used to extrapolate the NOAEL from an animal experimental dose level (or rarely from human data) to a human safe dose based on what is unknown (e.g., differences in pharmacokinetics and pharmacodynamics across species, duration of exposure, protection of sensitive subpopulations). The NOAEL procedure for calculating the RfD does not include the estimation of error or variability in the RfD; thus, it is unclear how to express the potential consequences of excess exposures.

During the process of choosing a critical effect, the available toxicity data are sometimes classified into ordered categories of severity (DeRosa *et al.*, 1985; Dourson *et al.*, 1985); at the very least, NOAELs and lowest-observed-adverse-effect levels (LOAELs) are identified. An expanded version of this classification process, useful for categorical regression, is to employ four ordered categories: no effects, nonadverse effects, adverse effects, and frank effects, which correspond to the more traditional no-observed-effect level (NOEL), NOAEL, adverse-effect level (AEL), and frank-effect level (FEL), respectively.

The use of a categorical regression procedure to express the risk of adverse health effects from chemical

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exposures in excess of the RfD was first proposed by Hertzberg and Miller (1985) and Hertzberg (1989) and then demonstrated with several chemicals (Farland and Dourson, 1992; Rao *et al.*, 1993; Dourson *et al.*, 1997). The regression procedure accommodates both quantal and continuous data and data that are reported both quantitatively and qualitatively, as well as incorporating different end points representing various levels of effect severity. In addition to regressing on dose, other explanatory (independent) variables such as exposure duration can be included, and analyses can be stratified by species (Guth *et al.*, 1991, 1996, 1997). Thus, models may be developed to estimate risk for a variety of exposure scenarios.

The purpose of this paper is to compare the results of categorical regression analysis on five pesticides of high interest: diazinon, disulfoton, *S*-ethyl dipropylthiocarbamate (EPTC), fenamiphos, and lindane. Because this analysis includes a number of diverse data sets that cross several species, toxic end points, and study types, this comparison is only meant as a broadly based screening tool for ascertaining the relative potency of the five chemicals being modeled.

METHODS

Analysis of Toxicity Data

Existing oral toxicity data for diazinon, disulfoton, EPTC, fenamiphos, and lindane were identified from available reviews, reports of studies submitted to the EPA Office of Pesticide Programs under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), and computer searches of TOXLINE (1981 to July, 1993), RTECs, and TSCATS data bases. Experimental animal chronic, subchronic, and acute toxicity studies, in addition to developmental and reproductive toxicity studies, were included in the analyses, but cancer studies (which provided no information on systemic toxicity) or systemic toxicity studies with nonoral routes of exposure were not included. Human studies were reviewed as available. Toxicity studies were reviewed and summarized in tables for each of the pesticides (see Results).

Categories of response, no effects (NE), no-adverse effects (NAE), adverse effects (AE), and frank effects (FE), were assigned to each exposure level in each of the summarized studies based on the description of the nature of the observed effects. It was recognized that these categories are broad and that certain effects are not easily classified into such categories. (This uncertainty must be kept in mind when drawing conclusions based on these regressions.) Because most toxicity studies report the types of effects observed at the dose-group level and not at the individual animal level, the requisite unit of study in the analysis was the dose group. Two studies of fenamiphos, however, were located that provided individual animal responses (cholinesterase inhibition), thus allowing a possible comparison of the application of categorical regression analysis at the individual animal level to analysis at the dose-group level.

Inhibition of cholinesterase activity was the most sensitive identified toxicological end point for three of the five pesticides studied herein (diazinon, disulfoton, and fenamiphos). Adverse health effects resulting from the inhibition of acetylcholinesterase in the nervous system included excessive and/or deregulated stimulation of the parasympathetic nervous system, skeletal muscle, and autonomic ganglia. High levels of inhibition of acetylcholinesterase produce clinical signs of cholinergic deregulation including tremors or twitching, salivation, and diarrhea and can be fatal. While the toxicological significance of inhibition of nonneuronal cholinesterases, such as RBC and plasma cholinesterases, is not completely understood, activities of these enzymes have been used as biomarkers for acetylcholinesterase activity. For the analyses described herein, the following scheme was adopted in judging the adversity of inhibition of cholinesterase activities (neuronal or nonneuronal): NOEL, no inhibition or a decrease in activity $<5\%$ of control; NOAEL, decrease in activity ≥ 5 and $<20\%$ of control; and AEL, decrease in cholinesterase $\geq 20\%$ of control. The observation of clinical cholinergic symptoms was assigned an AEL designation; these symptoms were assigned a FEL designation only when they were accompanied with deaths. The only exception to these rules was the assignment of a FEL to one diazinon dose level that produced no measurable blood cholinesterase activities in a rat study by Hazleton Laboratories (1955).

Categorical regression analysis was used to model the relationship between the logarithm of human equivalent doses and response category for each of the pesticides. Human equivalent doses were calculated based on the assumptions that doses are equivalent between species on a surface area basis and that surface area is approximated by body weight to the 2/3 power [human equivalent dose = animal dose $\times$ (animal body weight/human body weight)$^{1/3}$] (U.S. EPA, 1980). Please note that other scaling procedures are possible (Chappell, 1989; Travis and White, 1988; U.S. EPA, 1996). Male animal and human reference body weights for chronic exposure were used as given by U.S. EPA (1997) or from individual animal studies as appropriate.

The Categorical Regression Model

Categorical regression is a mathematical tool that can be adapted to estimate potential health risk from chemical exposures. By regressing ordered categories of toxic severity or pathological staging on exposure dose, this method can estimate the likelihood of observ-

ing any of the categories of severity at any dose level. Depending on the nature of the available data, these estimates can take the form of incidence rates for any of the categories in an exposed population or the probability of observing effects of a particular severity at a specified dose level for a new study.

For this model, it is assumed that the toxic response (or its absence) is related to the explanatory variables, dose and duration, by using a cumulative logistic function. Also, p is defined as the probability of observing a response of a certain severity or a lessor response, and the values generated for p must remain between 0 and 1. The logistic function that expresses the relationship between p and the explanatory variables is given by Eq. (1),

$$p_i(s \leq i) = \frac{\exp(\alpha_i + \beta_{1x1} + \beta_{2x2})}{1 + \exp(\alpha_i + \beta_{1x1} + \beta_{2x2})}, \qquad (1)$$

where p_i is the probability of observing an effect of severity i or less; i is the severity category 1, 2, or 3; α_i is an unknown intercept parameter associated with severity i; x_1 is the dose of the chemical; β_1 is an unknown slope parameter associated with the exposure to dose; x_2 is the duration of the exposure to the chemical; and β_2 is an unknown slope parameter associated with the duration of exposure. (Note that there are only three cumulative probabilities for four severity categories because $p(s \leq 4)$ is equal to 1 by definition.) Using algebra, this logistic function is easily converted to a linear relationship by the logit transformation as in Eq. (2):

$$L_i = \log [p_i (s \leq i)/(1 - p_i (s \leq i))] = \alpha_i + \beta_1 x_1 + \beta_2 x_2. \qquad (2)$$

The cumulative logit in this case is the log of the odds associated with a given category i of response or less. This model specifies that the relationship between the cumulative logits and the response variable is determined by a series of parallel straight lines (for a model with dose only as an explanatory variable) or planes (for more than one explanatory variable) with a common slope parameter(s) across severity categories. In addition, the log odds ratio for two different vectors of the explanatory variables is proportional to the difference between these vectors with the same proportionality constant for every category. This proportional odds (i.e., equal slopes) assumption can be tested for using a χ^2 test. In this application, the model was considered valid only when the test was significant. The output from the model using cumulative logits is the probability of a given category i of response or less; thus, some simple algebra $[1 - p(s \leq i)]$ yields the probability of an effect greater than severity category i. Additional descriptions of this method with greater detail on the statistical theory can be found in Hertzberg (1989) and Dourson *et al.* (1997).

Modeling of the dose–category data for each of the compounds began by fitting the four-category regression model to all of the available data with the logarithm of the human equivalent dose as the explanatory variable and the response category as the dependent variable (NOEL, NOAEL, AEL, FEL). If the model failed to satisfy the proportional odds assumption, NOELs and NOAELs were combined into one class and a model with three categories (NOEL + NOAEL, AEL, FEL) was applied to the data. Grouping NOELs and NOAELs in one class is paralleled in the current RfD methodology in which these two effect levels are functionally equivalent.

If the three-category model still failed to satisfy the proportional odds assumption, the data set was examined to identify biological reasons that could explain a poor fit of the whole data set to a single model and the data set was censored accordingly. The censored data were then fit to the four-category model, followed by fitting to the three-category model if necessary. "Unreliable" NOELs or NOAELs were censored from the data sets for diazinon, disulfoton, and fenamiphos; such NOELs or NOAELs were identified in experiments that did not include measurement of the most sensitive toxicological end point of interest for these compounds, namely cholinesterase inhibition. Three NOELs from one developmental toxicity study (PPG Industries, 1985) were censored from the data set of EPTC because the species (rabbit) was clearly less sensitive than rats, which showed toxicity at the same and lower doses. Data records from the lindane data set were censored on the basis of irrelevance to humans ($\alpha_{2\mu}$-globulin nephropathy in male rats) and unreliability of certain NOELs or NOAELs (see Results for further details).

Once the proportional odds assumption was satisfied, further analyses examined whether the addition of exposure duration (expressed as a proportion of life span) as an explanatory variable improved the model significantly. The final categorical regression model equations were used to estimate the risks of the occurrence of an AE or FE (i.e., an adverse effect or greater) at doses 10-fold above the RfD. The modeling results were graphed and compared as a method for screening the relative potencies of these chemicals. All analyses were completed using SAS Institute Inc. software on an IBM-compatible personal computer. Categorical regression analyses were done with the LOGISTIC procedure in SAS (1990).

RESULTS

Categorical regression models were successfully generated for the five pesticides using the logarithm of the human equivalent dose as the only explanatory variable. The proportional odds assumption was met using

TABLE 1
Frequency Distribution (%) of Data Records Among Response Categories for Five Pesticides

Pesticide	Response categories				Total number of data records
	NOEL	NOAEL	AEL	FEL	
Diazinon	17.4	16.5	52.1	14.0	121
	6.5	18.2	62.3	13.0	77
Disulfoton	6.0	14.0	68.0	12.0	50
	2.1	14.9	70.2	12.8	47
EPTC	19.7	32.8	42.6	4.9	61
	15.5	34.5	44.8	4.5	58
Fenamiphos	16.9	25.4	44.1	13.6	59
	4.5	27.3	50.0	18.2	44
Lindane	18.7	25.2	36.4	19.6	107
	20.2	26.3	32.3	21.2	99

Note. The first line of entries for each pesticide is for the whole data set; the second line of entries is for the censored data set. See Methods for explanation of censored data sets.

three-category models for each pesticide. The P values from χ^2 tests for the duration coefficient were not significant for any of the data sets ($P > 0.092$). The P values for dose were significant in all data sets ($P \leq 0.001$). Thus, adding duration to the model did not contribute to explaining the severity categories.

Diazinon Analysis

Diazinon is an organophosphorus compound that is used as an insecticide and nematicide (U.S. EPA, 1986, 1989b). Data regarding adverse effects in humans following exposure to diazinon are limited, but suggest that the characteristic effects of diazinon observed in animals and insects, cholinesterase inhibition and nervous system disturbance, also occur in humans. The complete data set for diazinon consisted of 38 studies and provided 121 data records with dose–category information (see Table 1).

The EPA's Integrated Risk Information System (IRIS) (U.S. EPA, 1998) does not list an RfD for diazinon. However, an RfD of 9×10^{-5} mg/kg/day can be calculated, based on a NOEL of 0.009 mg/kg/day for plasma cholinesterase inhibition in rats fed diazinon in the diet subchronically (Davies and Holub, 1980) and an uncertainty factor of 100 for inter- and intraspecies variability in the toxicity of this chemical in the absence of chemical-specific data. This calculated RfD will be used in this paper for the purpose of comparing risks across pesticides. Cumulative probabilities of an adverse effect or greater [P(AE) + P(FE)] as a function of the logarithm of the human equivalent dose are graphed in Fig. 1 for the censored diazinon data set. The estimated risk of a dose group that is 10 times the

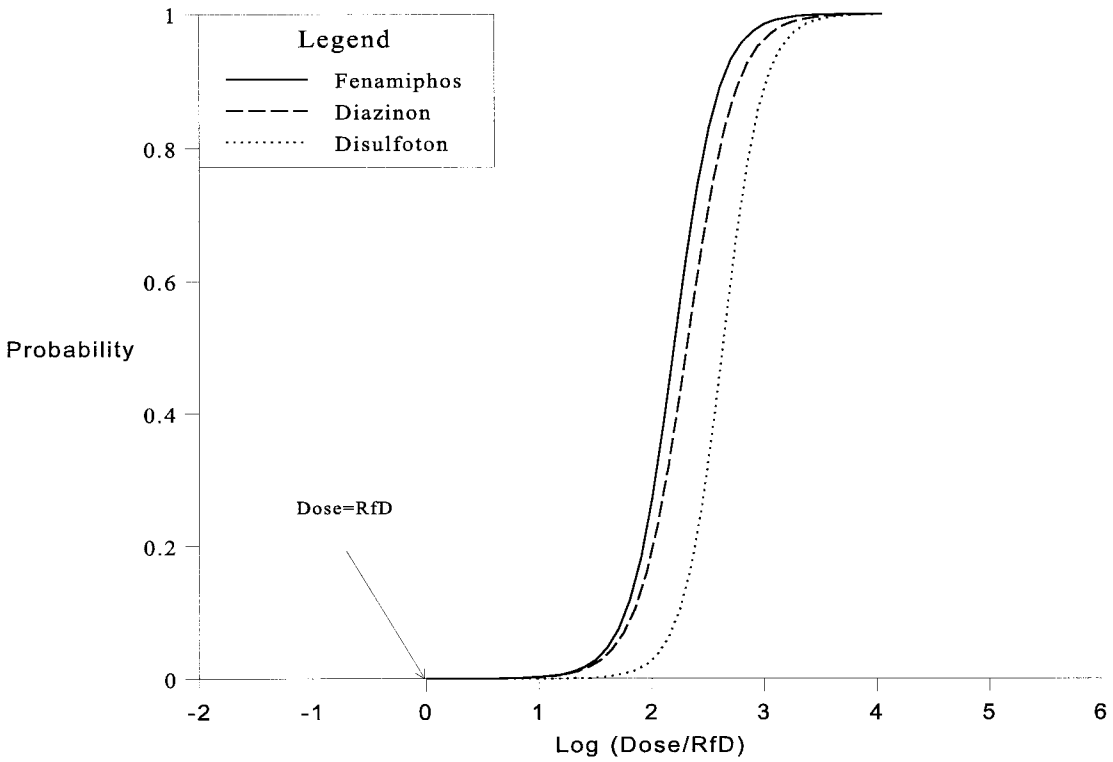

FIG. 1. Predicted probabilities of adverse or frank effects in humans after oral exposure to three pesticides. Three-category regression model. Doses scaled to human doses based on equivalence of (body weight)$^{2/3}$.

TABLE 2
Reference Doses for Two Sets of Chemicals and Their Underlying Data[a]

Chemical	Critical effect	NOAEL (mg/kg/day)	UF	RfD	Risk at RfD × 10
Diazinon	Cholinesterase inhibition	0.009	100	9×10^{-5}	0.002
Disulfoton	Cholinesterase inhibition	0.8	1000	4×10^{-5}	0.0001
EPTC	Muscle and nerve degeneration	2.5	100	2.5×10^{-2}	0.0007
Fenamiphos	Cholinesterase inhibition	0.025	100	2.5×10^{-4}	0.002
Lindane	Neurological signs, liver changes	0.33	1000	3×10^{-4}	0.02

[a] Data taken from U.S. EPA (1998), except for the diazinon RfD that was calculated for this paper using data from Davies and Holub (1980).

RfD being judged as exhibiting adverse or frank health effects is 2×10^{-3} (see Table 2).

Disulfoton Analysis

Disulfoton is an organophosphate thioester compound that is used as a systemic insecticide. Dose–response data for humans exposed to disulfoton were not located. Available toxicity data for animals following oral exposure include chronic feeding studies with rats, mice, and dogs; subchronic feeding studies with rats; developmental toxicity studies with rats and rabbits; a three-generation reproduction performance study with rats; and six acute studies including three LD_{50} studies. Cholinesterase inhibition appears to be the most sensitive adverse effect produced by oral exposure to disulfoton; repeated oral exposures also have been associated with myopia and degenerative ocular effects in the ciliary muscle and optic nerve, impaired reproductive performance, and impaired fetal development. The complete data set for disulfoton used for categorical regression contained 50 records with dose–category information (see Table 1).

The current oral RfD for disulfoton (U.S. EPA, 1998), 4×10^{-5} mg/kg/day, is based on a LOAEL of 0.8 ppm disulfoton (0.04 mg/kg/day) for cholinesterase inhibition and optic nerve degeneration identified in a 2-year rat dietary study. An uncertainty factor of 1000 (100 for "interspecies differences and the spectrum of sensitivity in the human population" and 10 for the use of an adverse-effect level in deriving the RfD) was applied to the LOAEL to obtain the RfD.

Figure 1 graphs the cumulative probability of an adverse effect or greater [P(AE) + P(FE)] as a function of the logarithm of the human equivalent dose using the censored data set for disulfoton. The estimated risk of a dose group that is 10 times the RfD being judged with adverse or frank health effects is 1×10^{-4} (see Table 2).

EPTC Analysis

EPTC is a pre- and postemergence herbicide which is used on a wide variety of agricultural commodities (U.S. EPA, 1984). Information on the toxicity of EPTC in humans was not located. Oral subchronic, chronic, and two-generation reproduction studies in rats have been performed which indicate that effects of EPTC include decreased weight gain and muscle and nerve degeneration. Some studies also observed testicular effects in rats and dogs, but the reproduction studies in rats showed no effects on reproductive function. The entire data set for EPTC consisted of 11 studies providing 61 records with dose–response category information (Table 1).

The current RfD for EPTC, 2.5×10^{-2} mg/kg/day (U.S. EPA, 1998), is based on a NOAEL of 2.5 mg/kg/day for degenerative cardiomyopathy, observed in offspring of rats in one of the two-generation reproduction studies, and an uncertainty factor of 100 to account for inter- and intraspecies differences. The relationship between the logarithm of the human equivalent dose of EPTC and the cumulative probability of adverse effects or greater [P(AE) + P(FE)] is graphed in Fig. 2. The estimated risk of a dose group that is 10-fold higher than the RfD being judged with adverse or frank health effects is estimated as 7×10^{-4} (see Table 2).

Fenamiphos Analysis

Fenamiphos is an organophosphorus compound used as a systemic nematicide (U.S. EPA, 1989a). Oral systemic toxicity data for fenamiphos are restricted to animal studies; data from human clinical studies, epidemiological studies, or reports of incidental poisonings in humans were not located. The data set includes 14 studies and provided 59 records with dose–response category information (see Table 1). The existing animal data suggest that inhibition of cholinesterase activity is the most sensitive adverse effect produced by oral exposure to fenamiphos.

The current RfD for fenamiphos, 2.5×10^{-4} mg/kg/day (U.S. EPA, 1998), is based on a NOEL of 0.025 mg/kg/day for plasma and red blood cell cholinesterase inhibition in dogs exposed to fenamiphos in the diet for 2 years and an uncertainty factor of 100 (to account for intra- and interspecies differences). Cumulative probabilities of an adverse effect or greater [P(AE) + P(FE)] as a function of the log of the human equivalent dose

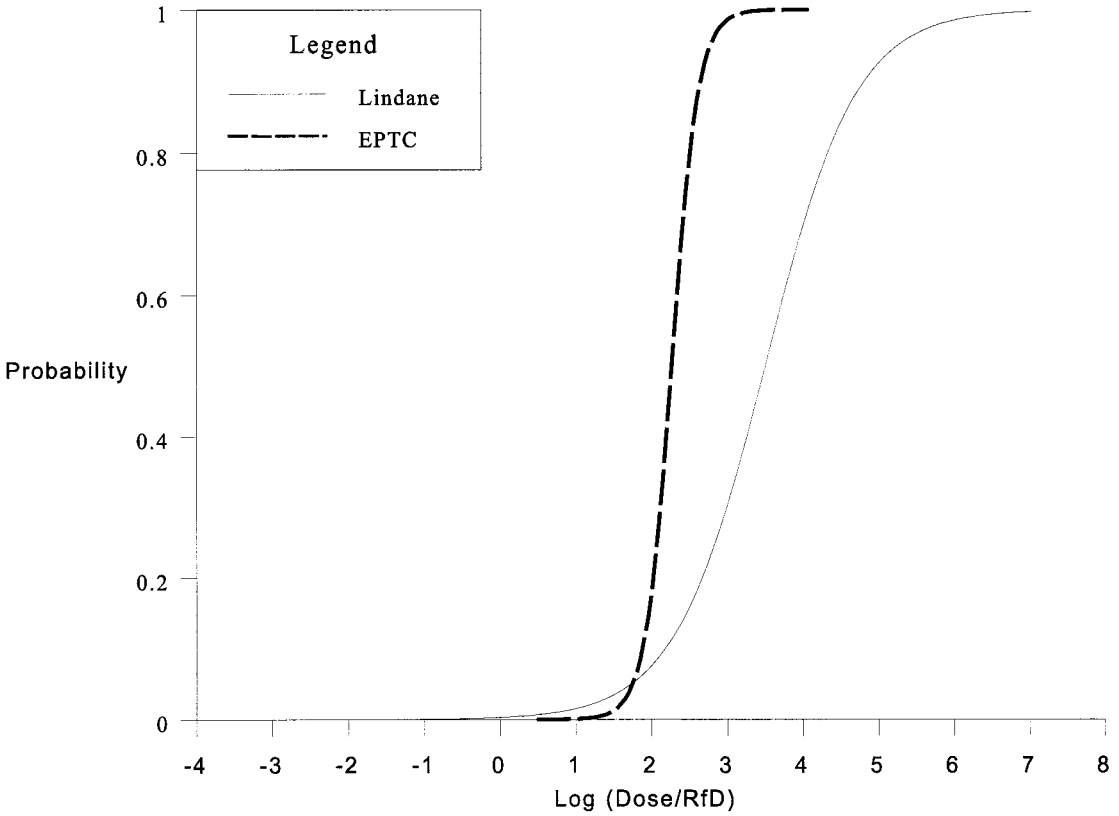

FIG. 2. Predicted probabilities of adverse or frank effects in humans after oral exposure to three pesticides. Three-category regression model. Doses scaled to human doses based on equivalence of $(\text{body weight})^{2/3}$.

are graphed in Fig. 1 for the censored data set. The estimated risk of a dose group that is 10-fold higher than the RfD being judged with adverse or frank health effects is 2×10^{-3} (see Table 2).

Lindane Analysis

Lindane is an insecticide to control various soil-dwelling and phytophagous insects, particularly for seed treatment, and various species of wood-inhabiting beetles (U.S. EPA, 1988). Information on the oral toxicity of lindane in humans is limited to observations following acute ingestion of large doses (U.S. EPA, 1988). The CNS appears to be the primary target of acute oral toxicity. Effects of chronic occupational exposure to lindane include neurological signs, pathological changes in the liver, and irritation of the skin, eyes, and respiratory tract mucosa. Oral toxicity data for lindane in animals have been investigated in chronic, subchronic, acute, developmental, and reproductive effects studies. Sensitive end points include kidney pathology, immunosuppressive effects, decreased adrenocortical function, and reproductive and fetal viability effects. The complete lindane data set used for categorical regression analysis consisted of 35 studies in five species providing 107 data records (see Table 1).

The current RfD for lindane, 3×10^{-4} mg/kg/day (U.S. EPA. 1998), is based on a NOAEL of 0.33 mg/kg/day for liver and kidney toxicity in rats exposed for 12 weeks and an uncertainty factor of 1000 (for use of a subchronic study, to account for interspecies variation and to protect sensitive human subpopulations). Figure 2 graphs the cumulative probabilities of an adverse effect [P(AE) + P(FE)] as a function of the logarithm of the human equivalent dose using the censored data set for lindane. The estimated risk of a dose group that is 10 times the RfD being judged with adverse or frank health effects is 2×10^{-2} (see Table 2).

DISCUSSION

Table 2 and Figs. 1 and 2 illustrate how toxicological judgment and statistical analyses can be used as a screening tool to compare risks at 10-fold above the RfD across multiple chemicals. These comparisons are dependent on several factors including, the severity category judgments made by the toxicologist, the underlying mechanism of action for each chemical, the application of UFs, the choice and combination of studies used in the regression, and the method for derivation of a human equivalent dose for the various animal studies. Because of the variety of species, effects, and

exposure durations that have been combined in this analysis, it is clear that the results are useful only as a method for screening and comparison and are not meant as reliable estimates of actual risk; this can be achieved, however, for the individual chemicals by narrowing the scope of the analysis (see Dourson *et al.*, 1997) and by using stratification techniques (see Guth, 1996).

Figure 1 shows the results of categorical regressions for the three organophosphate insecticides. These regressions have been normalized in relation to each chemical's RfD, so that the risks above the different RfDs can be readily compared. Because the regression categories are based on judgment, the risks shown in Fig. 1 (and Fig. 2) refer to the probability that a dose group will be judged as having adverse or frank health effects. Risk in these figures does not refer to incidence of effects.[2]

Note what appear to be parallel dose–response curves for these three insecticides. In addition, the regression curves for fenamiphos and diazinon are relatively close (the RfDs for these two chemicals are also close: 2.5×10^{-4} and 9×10^{-5} mg/kg/day, respectively). The regression curve for disulfoton is displaced about one-half order of magnitude to the right of the other two curves, or about 3-fold. This could be due to several reasons. The RfD for disulfoton (i.e., 4×10^{-5} mg/kg/day) is lower by about a factor of 3 when compared to the other two insecticides. The UF used to estimate the RfD for this chemical is 10-fold higher than the other two because the RfD was based on a LOAEL rather than a NOAEL. [See Barnes and Dourson (1988) or Dourson *et al.* (1997) for a description of uncertainty factor choice.]

Figure 2 shows the results of categorical regressions for EPTC and lindane. These regressions have also been normalized in relation to each chemical's RfD, so that the risks above the different RfDs can be readily compared. Unlike for the "similar" insecticides, the regression curves are not parallel nor close for these latter two chemicals. This could be due to several reasons, including diverse mechanisms of toxic action. Furthermore, the RfDs are not close for these two chemicals (3×10^{-4} mg/kg/day for lindane compared to 2.5×10^{-2} mg/kg/day for EPTC).

It is interesting to note with the cholinesterase inhibitors that as smaller UFs are used to estimate these RfDs, a tendency exists for the categorical regressions to indicate higher risks at given doses above the RfD. For example, it could be argued that for the diazinon RfD, an additional UF of 10 should be added for extrapolation from a subchronic study to a chronic study. If this were done, then the RfD would be lowered to 9×10^{-6} mg/kg/day with a UF of 1000, causing the curve in Fig. 1 to be shifted to the right while maintaining the same shape and lowering the risk at 10-fold above the RfD. Another illustration is to compare the UFs for disulfoton with those for fenamiphos (UF of 1000 with the smaller UF of 100) in contrast with their respective risks at 10-fold above the corresponding RfDs (1×10^{-4} with the larger risk of 2×10^{-3}). This is not the case, however, when one compares the uncertainty factors for lindane and EPTC (UF of 1000 with the smaller UF of 100). Here the risk at 10-fold above the corresponding RfD for lindane (2×10^{-2}) is higher than the corresponding risk for EPTC (7×10^{-4}). There are not enough data to pose a hypothesis, but the notion in the general literature that UFs are conservative would suggest results similar to those of the three cholinesterase inhibitors.

Also of interest, these regressions may provide a method to choose among those RfDs that need to be revisited. For example, the higher risk associated with the lindane RfD when compared to the other risks at the same 10-fold excess level would suggest an evaluation here first when compared to the other four pesticides.

As with any empirical modeling effort, this application of categorical regression is somewhat model dependent and does not fully express all of the uncertainties or resolve all of the judgmental issues. Nonetheless, the technique is a promising tool for screening the relative potencies of chemicals and for evaluating and expressing the uncertainties in potential risks associated with doses above the RfDs. It offers a more complete use of the available toxicity data for risk management decisions.

[2] To determine incidence at doses above the RfD, incidence data are needed as inputs to this regression model and equivalence in incidence between experimental animals and humans must be assumed. See, for example, Dourson *et al.* (1997) where incidence data were available in humans for aldicarb.

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