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ESTIMATING LIMITING RISK LEVELS FROM ORALLY INGESTED DDT AND DIELDRIN USING AN UP-DATED VERSION OF THE MANTEL-BRYAN PROCEDURE

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16. ABSTRACT

Mathematical extrapolations of the upper limits on risk of cancer at various low levels of exposure to dieldrin and DDT are presented. The statistical model used is that described by Mantel, et al., Cancer Research, 35, 865-872, 1975, the so-called "updated" Mantel-Bryan procedure. The data upon which the extrapolations are based are derived from the studies by Tomatis, et al., International Journal of Cancer, 10, 489-506, 1972 for DDT and by Walker, et al. Food and Cosmetics Toxicology, 11, 415-432, 1972 for dieldrin.

Several alternative methods of treating the data are presented, and pesticide levels associated with various levels of risk are estimated. Certain precautions which must be observed in applying the "updated" Mantel-Bryan technique are discussed.

17. KEY WORDS AND DOCUMENT ANALYSIS

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This report has been reviewed by the Office of Toxic Substances, EPA, and approved for publication. Approval does not signify that the contents necessarily reflect the views and policies of the Environmental Protection Agency, nor does mention of trade names or commercial products constitute endorsement or recommendation for use.

I will give below a description of the up-dated Mantel-Bryan procedure and the rationale for such up-dating. Let me begin however, with a description of the data to which the Mantel-Bryan method was applied.

DATA EVALUATED

DDT

The basic DDT data came from a report by Tomatis, Torusov, Day, and Charles appearing in the International Journal of Cancer (The Effect of Long-Term Exposure to DDT on CF-1 Mice, Vol. 10, 489-506, 1972). In this work 6-to 7-week old CF-1 mice received dietary DDT at levels up to 250 ppm for their remaining life span. One-third of the females in each group were mated when 9 to 10 weeks old, and their offspring were given similar dietary levels of DDT. Only sufficient first generation offspring were added to the treatment group as approximately to double the total— there would thus be something on the order of 120 mice of a sex on a treatment level, and the authors report in many instances only combined results for both parents and offspring. (Results are also given for a positive control group receiving urethane in their drinking water.) Except for a few mice with tumors killed early for transplantation tests and two mice per sex-generation-DDT level-group killed for study of DDT levels in their tissues, mice were kept until natural death or killed when moribund. At experiment termination all survivors were killed and autopsied, the parent generation having been carried to 140 weeks of age, the offspring to 130 weeks. The data reported include: number of survivors at the end

of each ten-week period; the total number of tumors and of tumor-bearing animals; the total number of tumors at a specific site. For liver tumors, lung tumors and lymphomas data are given separately for three time periods of tumor occurrence: between 0 and 69 weeks of age; between 70 and 94 weeks; from age 100 weeks on. Data are not given on the instances where mice fell into more than one of these tumor groups, and the total of such tumors frequently exceeds the total number of mice under study.

I note that the total number of tumor-bearing animals is likely unsuitable for analysis since many non-malignant tumors are included in any case this is such a broad catch-all category that upwards of 80% of control animals developed some kind of tumor. The main tumor of interest seems to be those of the liver which the authors report to be metastatic and dose-dependent in frequency. (Transplantation of such tumors was unsuccessful in 2 cases with young adult recipients, successful in 1 of 2 newborn recipients.) For these reasons, I have made a "safe"* dose analysis using liver tumor data. In this analysis, I have alternatively included or excluded tumors arising from 100 weeks on, with the exclusion giving less weight to the late-appearing tumors and minimizing any spontaneous tumor effects. I have made a similar analysis relative to lung tumors, but indicate the "safe" doses resulting as not reliable. The cause of unreliability is that at high dose levels of DDT liver tumors arise so early that the mice do not have a chance to develop lung tumors.

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*The word "safe" as used in this report is not necessarily meant to imply complete absence of hazard or risk. The "safe" dosages obtained are ones for which, by the procedures used and under the assumptions made, the true risk does not exceed some pre-specified low level.

This competitive effect from liver tumors is largely responsible for the failure of the authors to detect any dose-progressiveness in their occurrence.

The consequent data going into my analysis are shown in table 1.

I have additionally examined a report by Tarján and Kemeny in Food and Cosmetics Toxicology (Multigeneration Studies on DDT in Mice, vol. 7, 215-222, 1969) on the effects of dietary DDT. The multigeneration study in BALB/c mice was unsuitable for "safety" analysis for a variety of reasons. For one thing, DDT was fed for only 6 months, and at only comparatively low levels, about 3 ppm. (But the data do seem suggestive of tumorigenic and leukemogenic effects at this time- and dose-restricted treatment. The authors attribute this to the generational method of their study which could have permitted fetal exposure to DDT.) Nextly, while the authors do give separate data on tumors by sex, they do not give a corresponding sex breakdown on the number of animals examined. The real curiosity about the data, however, is that no data on tumors arising during the course of the study are provided—what the investigators report are their findings on an examination of surviving animals 26 months after the study began, at which time the fifth-generation mice were typically 4-6 months younger than the first generation mice. The data to me seem to show about the same tumor rates for all generations (which might indirectly indicate higher rates for the later generations since they are younger) so I am surprised to see the authors claiming almost logarithmic increase in tumor incidence with tumor generation. The number of animals with tumors does increase with generation, but so do the number of mice examined so that incidence rates remain stable, in which case the authors' remarks on fetal exposure become less meaningful.

Dieldrin

These data came from a report by Walker, Thorpe, and Stevenson appearing in Food and Cosmetics Toxicology (The Toxicology of Dieldrin (HEOD). 1. Long-Term Oral Toxicity Studies in Mice, vol. 11, 415-432, 1972). Here in various experiments and subexperiments CF-1 mice received dietary dieldrin at levels ranging as high as 20 ppm, for variously 104, 128, or 132 weeks, ADAB being used as a positive control treatment. Treatment was initiated in the week following the period in which the mice as 3-week-old weanings were housed together so as to accustom them to the change from the breeding to the experimental unit. In the first study, experiment 1, dose levels used varied by 10-fold increments; experiment 2.1, of study 2, directed to elucidating dose response relationships involved 2-fold dose increments of dieldrin, the diet being sterilized by use of ethylene oxide; in experiment 2.2, a single dose level of dieldrin was used, interest focussing on the influence of radiation-sterilization of diet and use of litter. For the present analysis I have ignored manipulations of sterilization in experiment 2.2 and of litter, combining all control groups into one, and all dieldrin-treated groups into one.

The report gives the percentage of animals with tumors of various sites but does not permit identification of instances of mice with tumors of several sites. Here I have chosen liver tumor data as the basis for "safety" analysis, making alternate determinations according to whether all liver tumors (a+b) or only those showing areas of papilliform or adenoid growth (b) are considered. I do not use the data from two additional experiments reported, one directed to

getting at the combined effect of dieldrin and DDT, the other to the effect of changing the duration of dieldrin treatment.

I note that the data published in this report were incomplete in that they represent percentages of animals with tumors, not actual numbers as I would have needed. In table 2, I give my best efforts reconstruction of the actual data, which reconstruction I used in my analysis. An uncertainty results from situations like that in which 20% of 288 mice are shown to have liver tumors — I took this as 58 tumorous mice, but 57 or 59 are alternative values which would have rounded off at 20%. My analysis is probably not critically dependent on which of these alternative values I used. I note that in experiment 2.1, liver tumor frequency at the two highest dose levels was reduced suggesting that lethal toxicity of treatment had interfered with tumor appearance. Such lethality is further indicated by the reduced numbers of animals shown as at risk which are less here (and also elsewhere in the table) than those the authors describe in their text as being allocated to each group. I would judge that the authors reasonably reduced the numbers of animals considered at risk so as to allow for mortality occurring before any tumors were likely to occur. But they nowhere make clear just how they did this. It may be that the reduction in tumor incidence at high dose levels would not have occurred if the author used a more effective method of reducing the numbers considered at risk. For example, at 20 ppm, the report shows that nearly 50% of female mice died within 3 months (all were dead within a year), yet the number of such mice for which tumor incidence was calculated is 21, or 70% of the original number. While the authors accept that their

data demonstrate the induction of liver lesions, it seems to me that they are concerned with the failure to induce other lesions like sarcomas, which ADAB(but tested at 600 ppm) seems to induce. They indicate that their results support the idea that the mouse may be unsatisfactory for testing compounds which induce hepatic microsomal enzymes.

THE UP-DATED MANTEL-BRYAN "SAFETY" PROCEDURE

In the original publication by Mantel and Bryan in the Journal of the National Cancer Institute ("Safety" Testing of Carcinogens, vol.27, 455-470, 1961) two particular qualifications are noted. One point is that the procedure is overconservative in the handling of spontaneous tumor rates, a minor point when control tumor rates are low. In more recent long-term testing of carcinogens the occurrence of high spontaneous rates, say on the order of 40% is not uncommon, and overconservatism by the original Mantel-Bryan procedure can become extreme.

An up-dating of the procedure to remove this conservatism has been prepared by a cooperative effort of investigators at several institutions and will in the near future be prepared for publication and it is this up-dated method that I applied to the instant data. The method formally takes care of spontaneous responses by formulating a model, implicitly suggested in the Mantel-Bryan paper, that the response at a dose level reflects the independent addition of probabilities — observed proportion = induced proportion + spontaneous proportion - product of induced and spontaneous proportions.

The up-dated procedure further incorporates a second modification, the need for which Mantel and Bryan indicate in an appendix as superior to the method of "justifiable" combined results described

in the text — that modification was suggested in part by Cornfield. The "justifiable" combined results approach has a kind of bending-over-backward aspect in that it permits treating any outcome observed at a higher dose as though it had in fact occurred at a lower dose — this sometimes could result in a higher estimate of the "safe" level by the Mantel-Bryan method since that method could be used only for the outcome at a single dose level. What this second modification does is to permit the simultaneous handling of data at several dose levels so that the outcome at a higher dosage is not artificially treated as an outcome at a lower dosage. In applying the method a principle suggested by Mantel and Patwary at the 32d session of the International Statistical Institute (Interval Estimation of Single Parametric Functions, Tokyo, Japan, 1960) is employed. A maximum likelihood estimate is made of all the parameters of the system, that is the spontaneous tumor rate or rates, and of the "safe" dose, or equivalently, the intercept for the induced tumor rate since the probit slope is conservatively fixed at unity, or some other prespecified value. (The intercept parameter is the normal deviate corresponding to the induced rate at unit dose, i.e. log dose equal to zero.) The next step is to find an alternate "safe" dose or intercept value such that when a conditionally maximum likelihood estimate of the remaining unspecified parameters is made, the fit is just significantly worsened. A consequence here however, is that use of exact binomial probabilities as Mantel and Bryan espouse is no longer feasible, and the up-dated Mantel-Bryan procedure instead relies on use of -2 loglikelihood ratio taken as following an asymptotic chi-square distribution for setting limits. Of interest, it is not essential under the modifications incorporating the handling both of spontaneous response and multiple dose levels that control data be available. If the data available over several non-zero dose levels suggest that there is spontaneous response

this will be automatically weighed into the analysis.

There is one basic way in which both standard and up-dated Mantel-Bryan procedures remain the same relative to the use of data at several dose levels. Suppose we have determined the "safe" level using all the data up to a certain dose level, and then add the data for the next higher dose level, calculating a new "safe" level. If the new "safe" level is higher we accept it, otherwise not. The logic here is that the assumed probit slope of unity is conservatively shallow, the true slope in the observable region somewhat steeper. A decrease in the "safe" level can accordingly be explained away — but an increase is accepted because this means that the added information relative to safety has outweighed the tendency for use of higher dose level data to reduce the calculated "safe" dose.

This rule for using higher "safe" levels when they arise, discarding lower ones must be used with judgement. The rule should not be used where the increase has occurred because the response at higher doses has flattened out or turned down — it should be reserved for the case where the increase in "safe" dose has occurred despite a rapidly rising response rate with dose. As I noted above, and will refer to again below, the case of DDT elicited lung tumors is one where responses may turn down at high levels because of earlier-appearing liver tumors. For the liver tumors elicited by high doses of dieldrin in one experiment there also was a reduction, but this perhaps could have been avoided by reducing further the number of mice considered as at risk.

In general the "safe" dose procedure has to be used with care and with thoughtful interpretation. It may be, for example, if an extended time study is conducted with late-appearing tumors getting full weight that an agent may appear tumorigenic by virtue of its life-

prolonging qualities. This is the reverse of the situation where tumorigenicity is masked by early lethal toxicity. It is thus important to check whether higher tumor frequencies in treated animals might not be due to increased longevity, whether only a chance increase or one actually attributable to treatment. This is an added reason for not giving great emphasis to late-appearing tumors—the other reasons are that they magnify the spontaneous-response problem and that anyway they are less important.

Up-dating of the Mantel-Bryan procedure is characterized by a novel feature—it permits handling independent sets of data. If an agent has been tested independently on two or even more occasions, how do you get the "safe" dose? If you calculate a "safe" dose for each separate test, which do you use or how do you use them? If you calculate one "safe" dose for males and one for females using data obtained at the same occasion, how use or combine them? It would seem improper to use the higher of the separate "safe" doses, because this may be too high for the other sex—also biases could result if we permitted repeated testing, then selecting the highest individual "safe" dose. Yet if individually calculated "safe" doses are about equal, somehow the appropriate pooled "safe" dose should be higher than either one alone because of the reduced statistical variability and increased information available.

Our new feature accomplishes this kind of thing. If we want to come out with a single number for the "safe" dose albeit we have data from several experiments, we should postulate that a single common "safe" dose exists, then proceed to estimate it, then finally putting a statistical lower limit on that estimate.

This we do by fitting a joint model to all the data under which the intercept parameter is common to the various data sets but each data set has its own spontaneous response parameter — the slope parameter remains fixed for all the data sets at its specified conservatively low value.

In application to the DDT and dieldrin data described above, the combined "safe" dose was consistently higher than the (geometric) average of the separate "safe" doses, and substantially higher than either "safe" dose when the individual "safe" doses were about equal. As between sexes, note that the model postulates males and females to differ only in their spontaneous tumor rates but to be identical in their "safe" dose values—if this premise is unacceptable, then separate "safe" doses would be required and in practice the lower of the two would have to be used. An incidental consequence of the added feature is that it can permit combining results, but with caution, from several test species if we are willing to commit ourselves to a particular way of scaling dosages, e.g. mg/m^2—milligrams of agent per square meter of surface area of the test animal.

RESULTS OF ANALYSIS

Tables 3 and 4 give certain summary analyses of the DDT and dieldrin tumorigenicity data. These summary analyses are premised on use of a unit probit slope, an assurance level of 99% and a "safety" level of 10^{-8} as initially illustrated by Mantel and Bryan. Results of additional computations and manipulations will be given in a supplementary report rather than in an appendix to the present one,

so that it can be self-contained.

"Safe" levels shown in Tables 3 and 4 are expressed in parts per trillion (parts per 10^{12} or ppt). These can be converted to 10^{-7} or 10^{-6} "safe" levels by multiplying respectively by either 2.59 or 7.23. Use of a higher probit slope of 1.5 would likely result in "safe" levels upwards of 20 times greater, the respective multipilication factors for 10^{-7} or 10^{-6} risk then being 1.88 and 3.74. I would recommend against use of such a steeper slope as being inadequately conservative. With a slope of 1, the 10^{-8} risk dose level is 1/1930th the 1% risk dose level. If we should have used the one-hit model for extrapolation our apparent 10^{-8} risk dose would represent a risk of 1/193,000. With a change in slope to 1.5, the 10^{-8} risk dose level is 1/155th the 1% risk dose so that the true risk if the one-hit model obtained would be 1/15,500. (For a slope of 2 the fraction and one-hit model risk would be 1/44 and 1/4400 respectively. Note that use of a slope somewhere between 1.5 and 2 gives results on the order of the standard practice of using 1% of the apparent no risk dose.) Another modification which could lead to an increase in the "safe" dose would be that of reducing the assurance level, say from 99% to 95%.

Inspection of Table 3 shows that the combined data "safe" dose of DDT relative to liver tumors ranges from 506-2390 ppt depending on whether all tumors or only tumors within 99 weeks are considered and on whether the risks for all mice or only for those surviving 70 weeks are considered. As illustration of how the procedure combines independent data I show in Table 3 the separate results for male and female mice. The combined "safe" level is much closer to the higher female values of 670-3270 ppt than they are to those

for male mice, 50-420 ppt. The lower "safe" level values for male mice do not necessarly presage greater vulnerability of males to DDT—it could also reflect that in some way the data for male mice are less informative. A possible way for such reduced information to come about is through a high spontaneous rate, a situation true for males but not for females, as then the effect of treatment cannot be measured as precisely. Calculated estimates of the spontaneous rates associated with each set of data analyzed are also shown as a matter of interest—these should be given limited credence since they are based on use of all the data and with the acceptance of a unit probit slope. Inclusion of the data at the dose level of 250 ppm would have resulted in overestimates of the spontaneous rates as the responses at that dose level were higher than the unit slope would have called for. In support of this, in 11 of 12 instances related to liver tumors the highest "safe" dose level of DDT resulted with the analysis of data up to 50 ppm; the dose level at which this maximum occurred is designated in Table 3 as the "highest influential dose", signifying that incorporation of data at the next higher dose level would have resulted in a reduction in the calculated "safe" dose.

In the lower half of Table 3 I show the "safe" levels for lung tumors. The combined "safe" levels range from 1820 – 19,100 ppt and I show them in parentheses in order to convey that they cannot be reliably accepted. This is due to the fact that at high DDT levels many mice get early liver tumors and so fail to display lung tumors—the fact that the highest influential dose is the highest dose employed reflects this in part. An interesting feature in the lung tumor analysis, however, is that it shows the combined "safe" dose to be higher, sometime much so, than the separate sex "safe" doses where the separate "safe" levels

differ only moderately.

The dieldrin "safe" levels in Table 4 relate only to the combined analysis, individual analyses by sex and/or experiment being reserved for the supplemental report. These "safe" levels are 11 ppt relative to all tumors, 87 ppt relative to liver tumors showing areas of papilliform or adenoid growth. In both cases the "safe" dose occurred at an intermediate value for the highest influential dose, 1.25 ppm and 5 ppm respectively, notwithstanding the reversal at high dose levels in experiment 2.1. The sharp increase in response at 10 ppm in the other two experiments apparently more than compensated for the reversal. Recall, also, that the authors apparently dropped early deaths from the number of mice at risk and so avoided extreme reductions in response rates at high dose levels. As a point of interest I include two sets of estimated spontaneous tumor rates in Table 4, one based on all the available data, the other based only on data at dose levels up to and including the highest influential dose.

Let me now come to question of how the "safe" dose values can be used. First, note that they are in this case expressed in parts per trillion of diet. The dietary intake of a mammal is, to an approximation, proportional to its surface area. Thus no further adjustment need be made if we extrapolate to another species, as to man. There could be some point, if we wished, to use an additional safety factor (as distinct from an extrapolation factor) to cover the possibility that even after species size adjustment man is still more sensitive than mouse. (There is a curiosity about use of one-hit "safety" determination methods. By its underlying logic the absolute safe dose in man should be the same

as for mouse with no further adjustment permitted for species size. In fact the absolute daily "safe" dose would be lower for a man than for a mouse because of his greater longevity—lifetime "safe" doses would remain the same.)

Daily food and water intakes of a mammal are, in many cases, approximately equal. Thus the dietary "safe" levels can be interpreted as drinking water "safe" levels if drinking water is anticipated to be the source of human exposure to DDT or dieldrin. But a "safe" level in water actually drunk, which is limited in quantity, should not be loosely interpreted as a permitted level in water available for drinking, as in water supply systems, which is a much larger quantity. Much less should it be interpreted as a permitted level in water supply sources which vastly exceed the amount of water actually drunk. The adverse effects of permitting in all fresh water bodies in the United States chemical levels seemingly safe for humans is not immediately predictable. One likely consequence could be extreme harm for fish and other animals inhabiting the water since their total exposure at a given water concentration would be much higher than for man or other animals which consume only limited amounts of water each day.

Table 1. Data from Tomatis, et al., on the occurrence of liver and of lung tumors in CF-1 mice receiving varying levels of dietary DDT, parent and first generation offspring combined. Results are shown separately for all mice and for those surviving to the 70th week of age.

	All Mice					Mice surviving to week 70 only				
		With Liver Tumors		With Lung Tumors			With Liver Tumors		With Lung Tumors	
DDT Dietary Dose Level ppm	Number at Risk	Within 99 Weeks	At Any Time	Within 99 Weeks	At Any Time	Number at Risk	Within 99 Weeks	At Any Time	Within 99 Weeks	At Any Time
				Male Data Only						
0	125	7	24	18	42	94	7	24	16	40
2	126	22	57	34	70	104	20	55	27	63
10	111	25	50	33	58	85	25	50	25	50
50	135	31	66	36	64	110	30	65	34	62
250	117	72	81	35	42	72	60	69	29	36
				Female Data Only						
0	117	0	4	12	35	94	0	4	8	31
2	110	1	4	11	30	91	1	4	10	29
10	126	1	11	23	50	107	1	11	21	48
50	109	3	13	21	40	85	2	12	18	37
250	105	43	60	20	30	76	39	56	18	28

Table 2. Reconstructed data from Walker et al. on the occurrence of liver tumors in CF-1 mice receiving varying levels of dietary dieldrin. Results are shown separately for three experiments.

Dieldrin Dietary Dose Level, ppm	Experiment 1			Experiment 2.1			Experiment 2.2		
	Number at Risk	Liver Tumors		Number at Risk	Liver Tumors		Number at Risk	Liver Tumors	
		Total	With Papilliform and Adenoid Growth		Total	With Papilliform and Adenoid Growth		Total	With Papilliform and Adenoid Growth
Male Data Only									
0	288	58	12	78	9	0	77	25	2
0.1	124	32	5	—	—	—	—	—	—
1	111	34	9	—	—	—	—	—	—
1.25	—	—	—	30	6	2	—	—	—
2.5	—	—	—	30	13	1	—	—	—
5	—	—	—	30	26	3	—	—	—
10	176	165	100	11	5	1	56	45	13
20	—	—	—	17	12	9	—	—	—
Female Data Only									
0	297	39	0	78	8	0	74	12	0
0.1	90	25	4	—	—	—	—	—	—
1	87	32	5	—	—	—	—	—	—
1.25	—	—	—	30	5	0	—	—	—
2.5	—	—	—	28	12	1	—	—	—
5	—	—	—	30	18	5	—	—	—
10	148	136	81	17	9	2	65	36	12
20	—	—	—	21	8	3	—	—	—

Table 3. "Safety" analysis of the data from Tomatis et al. shown in Table 1. A combined analysis is shown for males and females as well as separate sex analyses. Analyses use a slope of unity, an assurance level of 99%, and a "safety" level of 10^{-8}.

Data Analyzed	Combined Sex Analysis				Separate Sex Analyses					
					Males			Females		
	DDT "Safe" Dose ppt	Highest Influential Dose ppt	Estimated Spontaneous Response Using All Data %		DDT "Safe" Dose ppt	Highest Influential Dose ppm	Estimated Spontaneous Rate %	DDT "Safe" Dose ppt	Highest Influential Dose ppm	Estimated Spontaneous Rate %
			Males	Females						
Liver Tumors										
All Mice										
Tumors Within 99 Weeks	2390	50	14.3	0	420	50	10.3	3270	50	0
All Tumors	697	50	34.7	2.4	191	250	31.7	891	50	2.7
70 Week Survivors Only										
Tumors Within 99 Weeks	2130	50	17.5	0	271	50	10.6	3110	50	0
All Tumors	506	50	44.4	2.3	50	50	33.2	670	50	2.9
Lung Tumors										
All Mice										
Tumors Within 99 Weeks	(4540)	250	23.7	13.5	(2920)	250	23.6	(3590)	250	13.6
All Tumors	(19,100)	250	45.0	32.6	(11,600)	250	45.0	(7400)	250	32.6
70 Week Survivors Only										
Tumors Within 99 Weeks	(1820)	250	24.5	12.8	(966)	250	23.5	(1800)	250	13.4
All Tumors	(5080)	250	54.0	38.2	(2690)	250	54.0	(2650)	250	38.2

*Figures in parentheses represent "safe" dose estimates which are considered unreliable, as indicated in the text, because of the high frequency of early liver tumors.

Table 4. "Safety" analysis of the data from Walker et al. shown in table 2. Only the combined analysis for both sexes, all three experiments, is shown. Analysis uses a slope of unity, assurance level of 99%, and a "safety" level of 10^{-8}.

	All Liver Tumors	Tumors With Papilliform and Adenoid Growth
Dieldrin "Safe" Dose, ppt	11	87
Highest Influential Dose, ppm	1.25	5
Estimated Spontaneous Rates, %		
Using All Data		
Expt. 1, Males	20.3	4.4
Females	15.6	0.3
Expt. 2.1, Males	9.6	0
Females	6.9	0
Expt 2.2, Males	32.6	2.0
Females	13.3	0
Up To Influential Dose Only		
Expt. 1, Males	20.7	4.2
Females	16.7	0.9
Expt. 2.1, Males	10.5	0
Females	9.0	0
Expt. 2.2, Males	32.5*	2.6*
Females	16.2*	0*

*Represents tumor rates among controls. There were no actual test groups in this experiment below the highest influential dose.

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NOTICE

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The accompanying tables show the results of application of the "safe"* dose determination procedure with varying specification of the assurance level (95% or 99%) and varying specification of the postulated shallow slope (1.0 or 1.5 normal deviates per 10-fold dose increase). Yet another variation, but one readily obtainable, was that of alternative limitations on the risk level, specifically 10^{-8}, 10^{-7}, 10^{-6}, 10^{-5}. For each of the two agents overall "safe" levels were determined using all available data and separate "safe" levels were determined for certain data subsets. Relative to DDT there were only two data subsets, male or female. But for dieldrin there were eleven such data subsets—two for sexes, three for experiments, six for each sex in each experiment.

Other variants in the analyses made have been indicated in the initial report. For DDT the variants included whether data for all animals or only for 70-week survivors should be considered, and whether all tumors or only those occurring within 99 weeks should be considered. In the present report relative to DDT, I am showing "safe" level determinations only for liver tumors, since I do not consider the lung tumor determinations to be reliable, for reasons indicated in my initial report—at increasing dose levels lung tumor rates fail to increase because of the earlier occurrence of liver tumors. The added variant relative to dieldrin was only that of alternatively considering all liver tumors or only those liver tumors displaying areas of papilliform or adenoid growth.

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*The word "safe" as used in this report is not necessarily meant to imply complete absence of hazard or risk. The "safe" dosages obtained are ones for which, by the procedures used and under the assumptions made, the true risk does not exceed some pre-specified low level.

The several variant analyses of the DDT liver tumor data are given in tables 1A, 1B, 1C, and 1D, the tables varying in the postulated assurance levels and slopes. The column headings in the tables indicate whether results relate to combined data or to sex-specific data, whether all tumors or only early tumors are considered, and whether data for all animals or only for 70-week survivors are considered. Tables 2A, 2B, 2C, and 2D relate similarly to the dieldrin data on all liver tumors, the column headings indicating to which subset of the data the results shown relate. This pattern is repeated in tables 3A, 3B, 3C, and 3D which related to the dieldrin data on liver tumors showing papilliform and adenoid growth.

Specifically what is shown in the various tables is this. All the non-zero dose levels, in parts per million (ppm) in the experiment or experiments are arranged in ascending order at the left end of the table. The row entry in a column represents the computed upper limit on the intercept parameter (see initial report) using data obtaining for dose levels at or below the dose level shown for that row—the entry, however, relates to the analysis indicated by the column heading. Where no entry would be appropriate because of unavailability of data a dash is used. The dash is also used to indicate instances where the entry should be the same as at a preceding lower dose level, since no new data have been introduced which could influence the analysis. In each column, the lowest of the upper limits on the intercept parameter has been routinely (but see discussion below) underlined. Those lowest upper limits on the intercept parameter are decoded into "safe" level estimates, expressed in parts per trillion (ppt) which are shown in the lower portion

of each table, for the alternative limitations on the risk level as designated in the left most column of the table. No attempt is made in this report to give estimates of the spontaneous tumor rate for each experiment, though such estimates are available if desired. My reason for this is the multiplicity of such estimates which can be made. A different estimate can be made for each analysis into which a data set is entered, for each different progressively increasing dose level, and for each of the two specified slope values.

DISCUSSION OF DDT RESULTS, TABLES 1A, 1B, 1C, 1D.

Table 1A duplicates in large part the liver tumor results given in table three of the initial report. Overall "safe" doses at the 10^{-8} risk level range from 500-2390ppt depending on which of the four alternative sets of data is considered. The overall "safe" doses are heavily weighted toward the higher female "safe" doses which range between 670-3270 ppt, while the lower male "safe" levels range between 50-420 ppt. (Note that in only 1 of 12 instances does the "safe" dose shown result from the inclusion of data at the highest dose level of 250 ppm.) As the limiting risk level is increased in stages from 10^{-8} to 10^{-5}, the "safe" level can be seen to increase by a factor of approximately 3 for each 10-fold increase in risk.

The altered assurance level of 95% used in Table 1B produces no great changes from the results of Table 1A—typically the "safe" levels of Table 1B are about 30% larger than those of Table 1A. Much more profound effects on the "safe" dose are evidenced in Table 1C in which the slope parameter has been increased from 1 to 1.5. "Safe" doses are now 20 to 100 times greater than those of Table 1A at the 10^{-6} risk level.

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The altered assurance level of 95% used in Table 1B produces no great changes from the results of Table 1A—typically the "safe" levels of Table 1B are about 30% larger than those of Table 1A. Much more profound effects on the "safe" dose are evidenced in Table 1C in which the slope parameter has been increased from 1 to 1.5. "Safe" doses are now 20 to 100 times greater than those of Table 1A at the 10^{-8} risk level.

At higher risk levels the multiplicative factor is somewhat reduced since at the slope of 1.5, each 10-fold increase in the animal risk level results in only about a 2-fold increase in the "safe" dose. (In these analyses with a slope of 1.5 there are 2 added instances in which the "safe" dose results from inclusion of the data at 250 ppm, but these are marginal cases, and, in fact, disappear in the Table 1D analyses in which the assurance level is changed to 95%.) When the assurance level is altered to 95% using the 1.5 slope, the effect, as shown in Table 1D, is even more moderate than before, the "safe" dose level being increased by only about 20%, or even less.

DISCUSSION OF DIELDRIN RESULTS, ALL LIVER TUMORS, TABLES 2A, 2B, 2C, 2D.

The overall "safe" dose at the 10^{-8} risk level shown in Table 2A is 11 ppt with only a moderate difference between 13 ppt for males, 6 ppt for females. The range of the variously determined "safe" levels is from 2-16 ppt. In only one instance is the "safe" level associated with the inclusion of data at the highest of several dose levels employed. This instance relates to the data of experiment 2.1 which, as described in my first report, show a questionable inversion at the two highest dose levels. Since in experiment 2.2 only a single non-zero dose level was employed, any "safe" levels calculated specifically for that experiment must employ data at the highest dose level therein. And as the overall calculated "safe" dose results from data at dose levels of 1.25 ppm. or less, there can be no ambiguous effects due to data inversion.

As in the case of the DDT data analysis (Table 1A), each 10-fold increase in the risk level results in about a 3-fold increase in the "safe" level. Table 2B, shows, as before, that change in the assurance level to 95% produces only a moderate increase in the "safe" level, again about 30%.

Changing of the slope parameter, Table 2C, again produces dramatic increases in the "safe" dose, in one instance by a factor in excess of 100. The increase in the "safe" dose per 10-fold increase in the risk level is again about 2 at the higher slope of 1.5. A particular effect of use of the higher slope is that it has allowed the data inversions of experiment 2.1 to dominate certain analyses. Thus, all "safe" dose determinations for experiment 2.1 and the overall female "safe" dose are based on the use of all data including that at the highest dose level of 20 ppm. An anomalous consequence is that the overall "safe" dose of 580 ppt is lower than that of either 590 ppt for males or 620 ppt for females. The anomaly disappears, however, if we discount the high "safe" level for females as attributable in part to the data inversion at the highest dose levels of experiment 2.1. With such discounting the overall female "safe" dose would be reduced to 450 ppt. The same kind of pattern occurs in Table 2D in which the assurance level has been altered to 95%, the effect of the change in assurance level being only to increase the "safe" levels by a moderate 10-20%.

DISCUSSION OF DIELDRIN RESULTS, LIVER TUMORS SHOWING AREAS OF PAPILLIFORM AND ADENOID GROWTH, TABLES 3A, 3B, 3C, 3D.

The results of these analyses parallel those for all liver tumors obtained with dietary dieldrin, but at somewhat increased "safe" levels. Thus at the 10^{-8} risk level with slope of one the overall "safe" dose is raised from 11 to 87 ppt, while that for males is raised from 13 to 78 ppt, and that for females from 6 to 57 ppt. There is again a pattern of moderately increased "safe" doses as the assurance level is changed to 95%, of sharply increased "safe" doses as the slope is increased to 1.5 and of 2 or 3-fold increases in the "safe" dose with 10-fold increases in the risk level. Again the data inversions of

experiment 2.1 give rise to some instances of estimated "safe" doses which should perhaps be discounted, but these are not so pronounced as in the preceding analyses.

GENERAL DISCUSSION AND SOME INTERPRETATIONS

From the foregoing the pattern of effect of altered assurance levels, slope parameters, or risk levels seems somewhat evident and I will not dwell on these here. A particularly interesting point however, to which I specifically alluded in my first report, was the large difference between males and females in their "safe" DDT doses, with the combined "safe" dose somewhat closer to the higher of the two. I suggested that this could reflect a difference in the relative amounts of information available for the two sexes, rather than any true difference in their susceptibilities to DDT.

I give next a simple hypothetical example which brings out my point. It consists of five experiments in which the control spontaneous rate, based on 50 animals, increases progressively from 0 to 50%, while the apparent induced rate (measured by (Pt - Pc)/(1 - Pc)) remains constant at 10% . The following table shows the "safe" doses for the separate experiments and the combined "safe" dose as determined by the method I have used, employing an assurance level of 99%, a slope of unity, and a limiting risk level of 10^{-8}.

Experiment	Controls	Treated 100ppm	"Safe" Dose, ppt
1	0/50	5/50	1380
2	10/50	14/50	700
3	20/50	23/50	400
4	30/50	32/50	220
5	40/50	41/50	90
Combined	-	-	1700

What is curious about this result is that the highest "safe" dose attaches to the first experiment which is the one exhibiting the most clear evidence for a carcinogenic effect. Yet only a low "safe" dose attends the results for experiment 5 which displays questionable evidence of carcinogenicity. The explanation is that in the first experiment, though the data suggest a carcinogenic effect to exist, the upper limit on that effect is probably limited to something under about 20%, say as due to a zero control rate and a 20% treated rate. The upper limit on the tumor induction rate for experiment 5 is considerably higher—the data, for example, are not too inconsistent with true rates of 70% for controls, 90% for treated, for an induction rate of 67%. The high spontaneous rate in experiment 5 led to such an imprecise estimate of the induced rate that the data in it are consistent with the possibility either of a zero induction rate and of a rather high induction rate. Interestingly, the combined "safe" dose is higher than the individual experiment "safe" doses—in fact the data for the last few experiments, while not so informative in themselves, did add to the total information available and so did serve to raise the "safe" dose estimate.

The lesson here is the need to avoid uninformative experiments in establishing "safe" doses. If one's interest is in obscuring carcinogenic effects, an experiment which is less informative because of the obscuring effect of a high spontaneous rate can be ideal—but by the Mantel-Bryan approach such uninformative experiments will be penalized by the assignment of a low "safe" dose. In a mixture of experiments, some highly informative, others with only minimal information, the up-dated Mantel-Bryan procedure will be much more influenced by the high "safe" doses of the informative experiment than by the low ones of the uninformative experiment. (However if a low "safe" dose arises in a relatively informative experiment, it will be given high weight. This could signify a situation in which there is a true difference in "safe" doses in the several experiments.) To the extent that high spontaneous rates lead to less clear indications of induced tumor rates, certain kinds of experiments would be best avoided. These include experiments with animal strains with high spontaneous rates. Also it would be better not to count tumors which occur very late in animal life (though we can be free to observe them if we wish). Such tumors are, in principle, less important; they give rise to higher spontaneous rates, hence less information about induced rates and so to reduced "safe" doses; they could lead to misinterpreting a life-prolonging effect as a tumor-inducing effect.

An added point of interest I wish to make is the improper high "safe" dose estimates which could result when data at excessively high dose levels are included. I deliberately permitted these to be shown routinely as they occurred in the foregoing analyses so that I might point them out. If tumor

rates go down at high doses because of early lethal toxicity, these reduced rates should not be given full faith and credit. Apparently the investigators in the dieldrin study did make some allowance for early toxicity by excluding from animals considered at risk those dying early—but their adjustment did not seem to have been fully adequate. Note that in dieldrin experiment 2.2 there was only a single non-zero dose level. Suppose that in such an experiment we knew only the final outcome and had no clue as to whether an observed low tumor rate were due to competing lethal toxicity or whether it resulted from the test agent being only weakly carcinogenic. Any "safe" dose we might calculate would then be necessarily suspect. The remedy here is that our experiment should involve a series of dose levels in order to permit differentiating between true and only apparent low tumor rates.

Let me note that the feature of the up-dated Mantel-Bryan procedure which allows combining the data of several experiments also permits making up-dated estimates of "safe" doses as the results of new experiments are added to the old.

Table 1. Influence of varying the slope, the assurance level, and the risk level on the "safety" analysis of the data from Tomatis et al., liver tumor data only, dietary DDT.

DDT DOSE ppm or RISK LEVEL	DATA FOR ALL MICE						DATA FOR 70 WEEK SURVIVORS					
	tumors within 70 weeks only			all liver tumors			tumors within 99 weeks only			all liver tumors		
	both sexes combined	males only	females only	both sexes combined	males only	females only	both sexes combined	males only	females only	both sexes combined	males only	females only
	1A upper limits on intercept parameter, slope = 1.0, assurance level = 99%											
2	-1.719	-1.059	-1.965	-1.449	-0.400	-1.790	-1.689	-0.995	-1.874	-1.407	-0.225	-1.696
10	-2.473	-1.470	-2.663	-2.000	-0.914	-2.136	-2.381	-1.295	-2.586	-1.889	-0.596	-2.043
50	-2.990	-2.235	-3.127	-2.455	-1.673	-2.562	-2.941	-2.045	-3.105	-2.316	-1.314	-2.438
250	-2.587	-2.131	-2.734	-2.286	-1.894	-2.328	-2.387	-1.766	-2.491	-1.972	-1.143	-2.102
	"safe" doses, ppt DDT, corresponding to minimum, underlined, upper limit											
10^{-8}	2390	420	3270	700	190	890	2130	270	3110	500	50	670
10^{-7}	6180	1090	8470	1800	490	2310	5520	700	8050	1310	130	1730
10^{-6}	17,300	3030	23,700	5030	1380	6440	15,400	1960	22,500	3660	360	4840
10^{-5}	53,100	9330	72,800	15,500	4260	19,800	47,400	6030	69,200	11,200	1120	14,900
	1B upper limits on intercept parameter, slope = 1.0, assurance level = 95%											
2	-1.874	-1.163	-2.143	-1.597	-0.499	-1.978	-1.855	-1.111	-2.058	-1.568	-0.338	-1.894
10	-2.606	-1.560	-2.774	-2.101	-1.007	-2.250	-2.519	-1.387	-2.743	-1.995	-0.694	-2.162
50	-3.108	-2.350	-3.265	-2.544	-1.790	-2.668	-3.080	-2.165	-3.265	-2.411	-1.437	-2.550
250	-2.636	-2.200	-2.795	-2.337	-1.986	-2.387	-2.442	-1.839	-2.657	-2.028	-1.234	-2.165
	"safe" doses, ppt DDT, corresponding to minimum, underlined upper limit											
10^{-8}	3130	550	4500	850	240	1140	2940	360	4500	630	70	870
10^{-7}	8110	1420	11,600	2210	610	2940	7600	920	11,600	1630	170	2240
10^{-6}	22,600	3950	32,500	6180	1710	8220	21,200	2580	32,500	4550	480	6270
10^{-5}	69,700	12,200	100,000	19,000	5260	25,300	65,300	7940	100,000	14,000	1490	19,300
	1C upper limits on intercept parameter, slope = 1.5, assurance level = 99%											
2	-1.870	-1.209	-2.116	-1.599	-0.550	-1.940	-1.840	-1.145	-2.025	-1.557	-0.376	-1.846
10	-2.967	-1.985	-3.200	-2.499	-1.450	-2.612	-2.854	-1.748	-3.121	-2.369	-1.031	-2.516
50	-3.862	-3.222	-3.970	-3.330	-2.713	-3.427	-3.822	-3.048	-3.954	-3.175	-2.385	-3.289
250	-3.635	-3.260	-3.762	-3.348	-3.109	-3.346	-3.374	-2.811	-3.581	-2.911	-2.222	-3.041
10^{-8}	68,100	27,000	80,400	31,000	21,400	34,900	64,100	19,500	78,500	23,700	7060	28,300
10^{-7}	128,000	50,900	152,000	58,300	40,400	65,900	121,000	36,800	148,000	44,700	13,300	53,300
10^{-6}	255,000	101,000	301,000	116,000	80,200	131,000	239,000	73,000	293,000	88,700	26,400	106,000
10^{-5}	539,000	214,000	636,000	245,000	170,000	276,000	507,000	154,000	620,000	188,000	55,800	224,000
	1D upper limits on intercept parameter, slope = 1.5, assurance level = 95%											
2	-2.024	-1.313	-2.293	-1.747	-0.650	-2.129	-2.005	-1.262	-2.208	-1.719	-0.489	-2.044
10	-3.124	-2.104	-3.405	-2.608	-1.578	-2.734	-3.011	-1.863	-3.333	-2.484	-1.150	-2.644
50	-3.985	-3.348	-4.115	-3.433	-2.842	-3.553	-3.966	-3.184	-4.122	-3.287	-2.530	-3.423
250	-3.688	-3.335	-3.830	-3.407	-3.207	-3.415	-3.434	-2.894	-3.656	-2.974	-2.329	-3.115
	"safe" doses (ppt), DDT corresponding to minimum, underlined, upper limit											
10^{-8}	82,300	30,900	100,000	35,300	24,900	42,400	79,900	24,100	102,000	28,200	8820	34,700
10^{-7}	155,000	58,300	189,000	66,500	47,000	79,900	151,000	45,300	191,000	53,100	16,600	65,500
10^{-6}	308,000	116,000	376,000	132,000	93,200	158,000	299,000	90,000	380,000	105,000	33,000	130,000
10^{-5}	651,000	245,000	794,000	279,000	197,000	335,000	632,000	190,000	803,000	223,000	69,700	275,000

NOT REPRODUCIBLE

Table 2. Influence of varying the slope, the assurance level, and the risk level on the "safety" analysis of the data from Walker et al; data for all liver tumors, dietary dieldrin

DIELDRIN DOSE, ppm OR RISK LEVEL	OVERALL COMBINED DATA	COMBINED EXPERIMENTS SEPARATE SEXES		COMBINED SEXES SEPARATE EXPERIMENTS			SEPARATE EXPERIMENTS, SEPARATE SEXES					
							EXPERIMENT 1		EXPERIMENT 2.1		EXPERIMENT 2.2	
		MALE	FEMALE	EXPT 1	EXPT 2.1	EXPT 2.2	MALE	FEMALE	MALE	FEMALE	MALE	FEMALE
2A upper limits on intercept parameter, slope = 1.0, assurance level = 99%												
0.1	0.208	0.172	0.498	0.208		--	0.172	0.498	--	--	--	--
1.0	-0.453	-0.581	-0.106	-0.453		--	-0.581	-0.106				
1.25	-0.664	-0.722	-0.374	--	-0.807	--	--	--	-0.544	-0.644	--	--
2.5	-0.641	-0.668	-0.416	--	-0.646	--	--	--	-0.490	-0.528	--	--
5	-0.512	-0.455	-0.409	--	-0.421	--	--	--	-0.177	-0.457	--	--
10	-0.289	-0.172	-0.306	0.011	-0.509	-0.519	0.004	0.152	-0.285	-0.530	0.095	-0.649
20	-0.346	-0.197	-0.394	--	-0.645	--	--	--	-0.343	-0.739	--	--
"safe" doses, ppt dieldrin, corresponding to minimum, underlined, upper limit												
10^{-8}	11	13	6	7	16	8	9	3	9	13	2	11
10^{-7}	29	33	16	18	41	21	24	8	22	35	5	28
10^{-6}	81	93	46	50	110	58	67	23	62	97	14	79
10^{-5}	250	290	140	150	350	180	210	69	190	300	44	240
2B upper limits on intercept parameter, slope = 1.0, assurance level = 95%												
0.1	0.109	0.024	0.175	0.109	--	--	0.024	0.175	--	--	--	--
1.0	-0.561	-0.716	-0.209	-0.561	--	--	-0.716	-0.209				
1.25	-0.750	-0.847	-0.480	--	-0.972	--	--	--	-0.753	-0.860	--	--
2.5	-0.717	-0.768	-0.509	--	-0.743	--	--	--	-0.624	-0.664	--	--
5	-0.570	-0.513	-0.490	--	-0.495	--	--	--	-0.278	-0.562	--	--
10	-0.326	-0.222	-0.358	-0.014	-0.579	-0.617	-0.057	0.088	-0.382	-0.626	-0.061	-0.772
20	-0.382	-0.246	-0.443	--	-0.711	--	--	--	-0.434	-0.832	--	--
"safe" doses, ppt dieldrin, corresponding to minimum, underlined upper limit												
10^{-8}	14	17	8	8	23	10	13	4	14	18	3	14
10^{-7}	36	45	20	22	59	26	33	10	36	46	7	37
10^{-6}	99	124	57	61	170	73	92	29	100	130	20	100
10^{-5}	300	380	180	190	510	220	280	88	310	390	63	320
2C upper limits on intercept parameter, slope = 1.5, assurance level = 99%												
0.1	0.708	0.672	0.998	0.708	--	--	0.672	0.998	--	--	--	--
1.0	-0.519	-0.622	-0.141	-0.519	--	--	-0.622	-0.141				
1.25	-0.741	-0.771	-0.464	--	-0.856	--	--	--	-0.593	-0.692	--	--
2.5	-0.754	-0.757	-0.542	--	-0.777	--	--	--	-0.619	-0.654	--	--
5	-0.666	-0.575	-0.589	--	-0.622	--	--	--	-0.368	-0.665	--	--
10	-0.622	-0.458	-0.675	-0.228	-0.764	-1.019	-0.219	-0.073	-0.521	-0.798	-0.405	-1.149
20	-0.707	-0.503	-0.797	--	-0.992	--	--	--	-0.641	-1.135	--	--
"safe" doses, ppt dieldrin corresponding to minimum, underlined, upper limit												
10^{-8}	380	590	620	400	830	870	470	220	490	1020	340	1060
10^{-7}	1090	1120	1160	760	1570	1610	890	420	920	1920	640	2000
10^{-6}	2160	2210	2300	1500	3110	3240	1760	840	1820	3820	1260	3960
10^{-5}	4360	4660	4880	3180	6580	6850	3730	1780	3840	8070	2670	8370
2D upper limits on intercept parameter slope = 1.5, assurance level = 95%												
0.1	0.609	0.524	0.875	0.609	--	--	0.524	0.875	--	--	--	--
1.0	-0.615	-0.763	-0.264	-0.615	--	--	-0.763	-0.264				
1.25	-0.831	-0.900	-0.579	--	-1.021	--	--	--	-0.802	-0.908	--	--
2.5	-0.828	-0.860	-0.641	--	-0.872	--	--	--	-0.754	-0.781	--	--
5	-0.727	-0.656	-0.676	--	-0.698	--	--	--	-0.471	-0.722	--	--
10	-0.661	-0.512	-0.730	-0.281	-0.836	-1.117	-0.290	-0.152	-0.620	-0.898	-0.563	-1.272
20	-0.746	-0.557	-0.851		-1.064	--	--	--	-0.736	-1.229	--	--
"safe" doses, ppt dieldrin corresponding to minimum, underlined, upper limit												
10^{-8}	650	720	670	470	930	1010	580	270	620	1200	430	[illegible]
10^{-7}	2220	1360	1260	840	1750	1900	1100	510	1170	2250	810	[illegible]
10^{-6}	7430	2700	2500	1760	3470	3770	2190	1020	2320	6470	1610	[illegible]
10^{-5}	5140	5710	5300	3700	7140	7960	4610	2150	4910	9460	3400	[illegible]

...cy analysis of the data from Walker et al.; ..., dietary dieldrin.

or RISK LEVEL	...ED DATA	...D EXPERIMENTS SEPARATE SEXES		COMBINED SEXES SEPARATE EXPERIMENTS			SEPARATE EXPERIMENTS, SEPARATE SEXES				
		MALE	FEMALE	EXPT 1	EXPT 2.1	EXPT 2.2	EXPERIMENT 1 MALE	EXPERIMENT 1 FEMALE	EXPERIMENT 2.1 MALE	EXPERIMENT 2.1 FEMALE	EXPERIMENT 2.1 MALE
		3A upper limits on intercept parameter, slope = 1.0, assurance level = 99%									
0.1	-0.486	-0.554	-0.208	-0.486	-1.290	—	-0.554	-0.208	-0.860	-1.461	—
1.0	-1.130	-1.176	-0.905	-1.130	-1.614	—	-1.176	-0.905	-1.321	-1.610	—
1.25	-1.286	-1.227	-1.098	—	-1.617	—	—	—	-1.485	-1.495	—
2.5	-1.498	-1.397	-1.324	—	-1.702	—	—	—	-1.571	-1.597	—
5	-1.552	-1.502	-1.370	-0.884	-1.687	-1.549	-0.849	-0.507	-1.443	-1.733	-1.350
10	-1.215	-1.161	-1.174	—		—	—	—			—
20	-1.243	-1.160	-1.234								
	"safe" doses, ppt dieldrin, corresponding to minimum, underlined, upper limit										
10^{-8}	87	78	57	33	120	87	37	20	91	130	55
10^{-7}	230	200	150	85	320	220	95	51	240	340	140
10^{-6}	630	560	410	240	890	620	260	140	660	960	400
10^{-5}	1940	1730	1270	730	2740	1920	820	440	2020	2940	1220
	3B upper limits on intercept parameter, slope = 1.0, assurance level = 95%										
0.1	-0.595	-0.754	-0.344	-0.595	-1.463	-0.754	-0.344	-1.062	-1.802	—	—
1.0	-1.215	-1.312	-1.006	-1.215	-1.744	-1.312	-1.006	-1.479	-1.812	—	—
1.25	-1.387	-1.345	-1.207	—	-1.710	—	—	-1.611	-1.624	—	—
2.5	-1.595	-1.514	-1.477	—	-1.787	—	—	-1.690	-1.714	—	—
5	-1.632	-1.607	-1.486	-0.924	-1.760	-1.637	-0.904	-1.541	-1.838	-1.478	-1.607
10	-1.248	-1.209	-1.220	—		—	—			—	—
20	-1.277	-1.207	-1.282				-0.863				
	"safe" doses, ppt dieldrin, corresponding to minimum, underlined, upper limit										
10^{-8}	100	99	75	40	150	110	50	25	120	170	73
10^{-7}	270	260	190	140	390	270	130	64	310	440	190
10^{-6}	760	720	540	290	1080	770	360	180	860	1220	530
10^{-5}	2330	2200	1660	890	3330	2360	1120	550	2650	3740	1630
	4A upper limits on intercept parameter, slope = 1.5, assurance level = 99%										
0.1	0.014	-0.054	0.292	0.014	—	—	-0.054	0.292	—	—	—
1.0	-1.251	-1.169	-1.014	-1.251	-1.139	—	-1.169	-1.014	—	—	—
1.25	-1.404	-1.238	-1.319	—	-1.252	—	—	—	-0.909	-1.510	—
2.5	-1.641	-1.475	-1.558	—	-1.857	—	—	—	-1.454	-1.754	—
5	-1.778	-1.684	-1.648	-1.267	-2.002	-2.049	-1.211	-1.194	-1.716	-1.741	—
10	1.641	1.556	1.624		-2.006				-1.850	-1.911	—
20	1.687	1.569	1.704						1.808	-2.148	-1.850
	"safe" doses, ppt dieldrin, corresponding to minimum, underlined, upper limit										
10^{-8}	2780	2400	2480	1270	4460	4220	1170	1140	1100	4910	3110
10^{-7}	5240	4540	4680	2390	8410	7950	2200	2140	5850	9250	5860
10^{-6}	10,400	8990	9280	4740	16,700	15,800	4360	4240	11,600	18,300	11,600
10^{-5}	22,000	19,000	19,600	10,000	35,300	33,300	9230	8970	24,500	38,800	24,600
	4B upper limits on intercept parameter, slope = 1.5, assurance level = 95%										
0.1	-0.095	-0.254	0.156	-0.095	—	—	-0.254	0.156	—	—	—
1.0	-1.360	-1.309	-1.178	-1.360	—	—	-1.309	-1.178	—	—	—
1.25	-1.504	-1.359	-1.465	—	-1.511	—	—	—	-1.110	-1.850	—
2.5	-1.741	-1.597	-1.696	—	-1.882	—	—	—	-1.613	-1.958	—
5	-1.862	-1.798	-1.759	—	-1.952	—	—	—	-1.843	-1.872	—
10	-1.677	-1.606	-1.674	-1.311	-2.089	-2.137	-1.273	-1.260	-1.970	-2.031	—
20	-1.722	-1.618	-1.754	—	-2.163	—	—	—	-1.910	-2.256	-1.978
	"safe" doses, ppt dieldrin, corresponding to minimum, underlined, upper limit										
10^{-8}	3160	2870	2700	1460	5020	4820	1350	1260	3740	5790	3780
10^{-7}	5960	5400	5090	2760	9460	9100	2550	2370	7040	10,900	7120
10^{-6}	11,800	10,700	10,100	5470	18,800	18,000	5060	4690	14,000	21,700	14,100
10^{-5}	25,000	22,700	21,400	11,600	39,700	38,100	10,700	9930	29,500	43,800	29,900

	EXPERIMENT 2.1 FEMALE
0.1	4610
1.0	8690
1.25	17,200
2.5	36,400