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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

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SUBJECT: Interim Risk Assessment for Gardona Based on Hazleton Project No. 776-118

SUMMARY

The data in the mouse study (ref 2) and the analysis given below indicate that Gardona causes elevated liver tumors in female mice. This result is associated with a potency factor of $Q^*_1 = 2.3 \times 10^{-3}$. Determination of the weight of the biological evidence (ref 1) will be made by the Toxicology Branch Cancer Review Committee.

The maximum associated dietary risk based on the TMRC (see the appendix) is between 10^{-4} and 10^{-5} when rounded (see ref 4). Data are unavailable for worker risk (ref 5).

BACKGROUND

Gardona (also named Rabon, SD-8447, Tetra-chlorvinphos) is a registered chemical. The Shell Oil sponsored feeding study (ref 2), reviewed below, was motivated by the positive findings of a

National Cancer Institute Bioassay, NCI-CG-TR-33 (ref 3) dated 1978. The NCI-GSRI study demonstrated a significant dose related trend of thyroid adenomas in female rats, of hepatocellular carcinomas in male mice, and of neoplastic liver nodules in female mice at doses of 8000 and 16000 ppm.

A full characterization of the risk is not possible at this time as worker exposure data are unavailable (ref 5). There is no toxicological review available for this study.

DESCRIPTION OF STUDY

The study under review was done by Hazleton Laboratories America, Inc. for Shell Oil Company. Test chemicals were new Rabon (labelled Gardona Technical) and old Rabon (labelled SD-8447). The 102 week feeding study started March 14, 1977, and terminated March 19, 1979. The $B_6C_3F_1$ mice were put on test at age 8 weeks, after a 17 (for female)/18 (for male) day acclimatization period.

The Hazleton/Shell study included 8 dose groups: a control, six new Rabon test dosages of 17.5, 64, 320, 1600, 8000, and 16000 ppm and one dose, 16000 ppm of the original formulation. Mice were randomly assigned (from a supply of 811 males and 810 females) as follows: 160 for controls and 80 per test dose for each sex.

QUALITATIVE FINDINGS

Most findings in the Shell study were unremarkable. We summarize them below.

Lower growth weights were noted for most males (groups 3,5-8) and for all female treatment groups when compared to controls. At the same time there appears to be an increase in food consumption in those same groups. Shell claims a statistically higher survival rate for groups 6, 7, and 8 where compared to controls. However, this higher survival rate (see Table 1-a) for the females occur only in groups 7 and 8 (i.e., the 8000 and 16000 ppm dosages). Further the survival differences, ranging from 10 to 20%, at 79 to 103 weeks, are not large enough to invalidate the tumor data. Also noted are increasing relative organ weights (for example, liver and kidney) in some of the high dose groups. No diseases or other complications were observed.

The study notes an increase in hepatocellular carcinomas in high dose males and females, and kidney tumors in high dose males when compared to controls. Our trend analysis is consistent with Hazleton's.

TABLE 1-a - GARDONA TUMOR DATA AND TREND ANALYSIS

Group #	1	2	3	4	5	6	7	8
Dose (ppm)	0	17.5	64	320	1600	8000	16000-New	16000-Old
Female Liver Tumors (TBA/TOT)[1]	0/100	0/50	0/50	0/50	4/49	7/47	7/50	6/50
# Survivors at 103 Wks	71	37	40	31	36	47	46	44
Male Kidney Tumors	1/100	0/50	0/50	0/50	2/50	1/50	11/50	2/50
# Survivors at 103 Wks	80	38	43	52	55	55	48	46

TREND ANALYSIS[3]

Significant Levels

	UNADJUSTED		ADJUSTED (EQ WT)[2]		ADJUSTED (EARLY DEATHS)	
	Trend	Departure	Trend	Departure	Trend	Departure
Fem (liver)	<.0001	<.0001	<.0001	.1376	<.0001	.6224
Male (kidney)	<.0001	<.0001	<.0001	.1076	<.0001	.0910

1 (TBA/TOT) = (Tumor Bearing Animals/Total), female liver tumors include all mice with liver and/or kidney tumors

2 EqWt = Equal Weight

3 This analysis only includes the new Rabon

Table 1-b Kidney and Liver, and Survival Trends

TBA = Tumor Bearing Animals

S/TOT = Survivors/Total Animals

FEMALES/DOSE (ppm)

	0		17.5		64		320		1600		8000		16000	
Time (wks)	TBA	S/TOT	TBA	S/TOT	TBA	S/TOT	TBA	S/TOT	TBA	S/TOT	TBA/	S/TOT	TBA	S/TOT
0-26	0	159/160	0	78/80	0	79/80	0	80/80	0	79/80	0	78/80	0	78/80
Kill #1	0	0/20	0	0/10	0	0/10	0/	0/10	0	0/10	0	0/10	0	0/10
27- 53	0	139/139	0	68/68	0	69/69	0	70/70	0	69/69	0	68/68	0	68/68
Kill #2	0	0/20	0	0/10	0	0/10	0	0/10	0	0/10	0	0/10	0	0/10
54-78	0	113/119	0	57/58	0	57/59	0	59/60	0	57/59	0	57/58	0	58/58
Kill #3	0	0/20	0	0/10		0/10	0	0/10	0	0/10	0	0/10	0	0/10
79-103	0	81/93	0	37/47	0	43/47	0	42/49	0	44/47	0	45/47	0	48/48
Term Kill	0	0/81	0	0/37	0	0/45	0	0/42	4	0/44	7	0/45	7	0/48
MALES														
0-26	0	155/160	0	79/80	0	80/80	0	78/80	0	76/80	0	80/80	0	80/80
Kill #1	0	0/20	0	0/10	0	0/10	0	0/10	0	0/10	0	0/10	0	0/10
27-53	0	134/135	0	68/69	0	69/70	0	63/68	0	65/66	0	70/70	0	69/70
Kill #2	0	0/20	0	0/10	0	0/10	0	0/10	0	0/10	0	0/10	0	0/10
54-78	1	108/114	0	58/58	0	58/59	0	48/53	1	53/55	0	59/60	3	58/59
Kill #3	0	0/20	0	0/10	0	0/10	0	0/10	0	0/10	0	0/10	0	0/10
79-103	8	71/88	3	37/48	4	40/48	0	31/38	3	36/43	0	47/49	2	46/48
Term Kill	18	0/71	11	0/37	10	0/40	9	0/31	10	0/36	20	0/47	22	0/46

[redacted]

Table 1-b was constructed in order to more finely observe tumors and survival over time. From there we observe (see the S/Tot columns) that survival appears to be fairly insensitive to dose, sex or time period. All female liver and kidney tumors appear only at the terminal kill. Male kidney and liver tumors begin appearing in the 54-78 week period in the controls and in two treatment groups, as can be seen by observing the TBA columns. Note that elevated tumor rates are demonstrated at 1600, 8000, 16000 ppm for females and only at 8000 and 16000 ppm for males. However, there is a definite tumor-dose trend relationship. This is shown in the lower half of Table 1-a where the trend is shown to be significant at less than .0001 under both unadjusted and adjusted conditions[2]. A significant (<.0001) departure from trend is observed in the unadjusted data, but that disappears under the adjusted data conditions. We note that the trend relationship is strong enough to justify a dose-response analysis. This is carried out in the next section.

QUANTITATIVE RISK ASSESSMENT

1 Preliminary Remarks

An attempt may have been made to show that Gardona is "benign" at low doses. A control and six treatment groups were used. Note (in Table 1) that there are no tumors for either sex in the lowest three groups while tumors do occur in the three higher dose groups. It is possible (personal communication from Dr. Henry Spencer) that these differences in responses may be due to animal-system overload which would cause the chemical to go down an alternate metabolic pathway. Further, the difference in cancer sites (liver vs kidney) may be due to male mouse inability to metabolize Gardona. Unfortunately, to prove conjectures of this type using standard feeding studies (like the Shell report) would require many thousands of animals.

An indication of this situation is shown in Figures 1 and 2. There, for various sample sizes (n=150,500, 1000, 2000, 8000, 32000), we have plotted the probability that no animal in a sample (group) has a tumor versus the individual risk (probability) that one animal develops a tumor. For example, (see Fig 1) for n=150 animals and a risk of 10^{-4} we have a high probability (P= .985) that all 150 animals will be tumor free. However, even when the individual risk is as high as 10^{-2}, there is still a .22 probability that all test animals will still be tumor free.

1 The unadjusted analysis considers only the proportion of tumor bearing animals in each group analyzed. Adjusted (Eq wt) analyses also considers time to death with tumor, assigning equal weight to all tumor bearing animals. Adjusted (early deaths) analyses gives proportionally more weight to tumors detected early in the study.

P (n Animals have no tumors) vs Risk Level

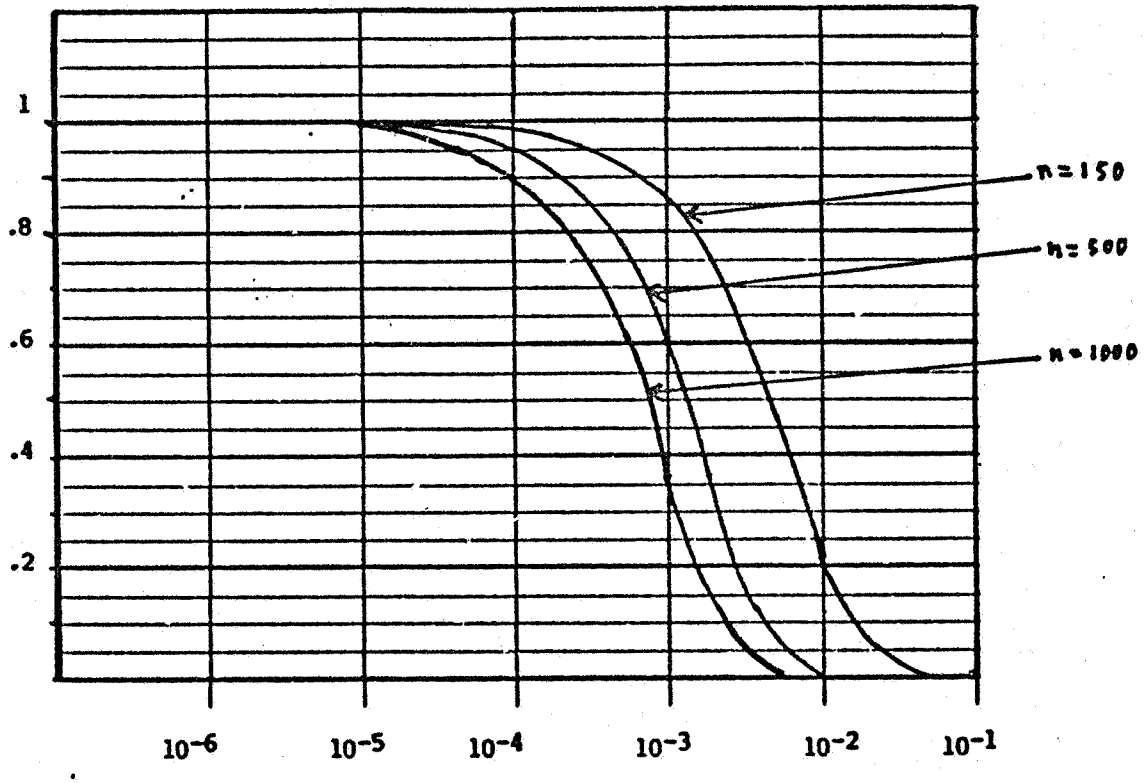

Fig 1

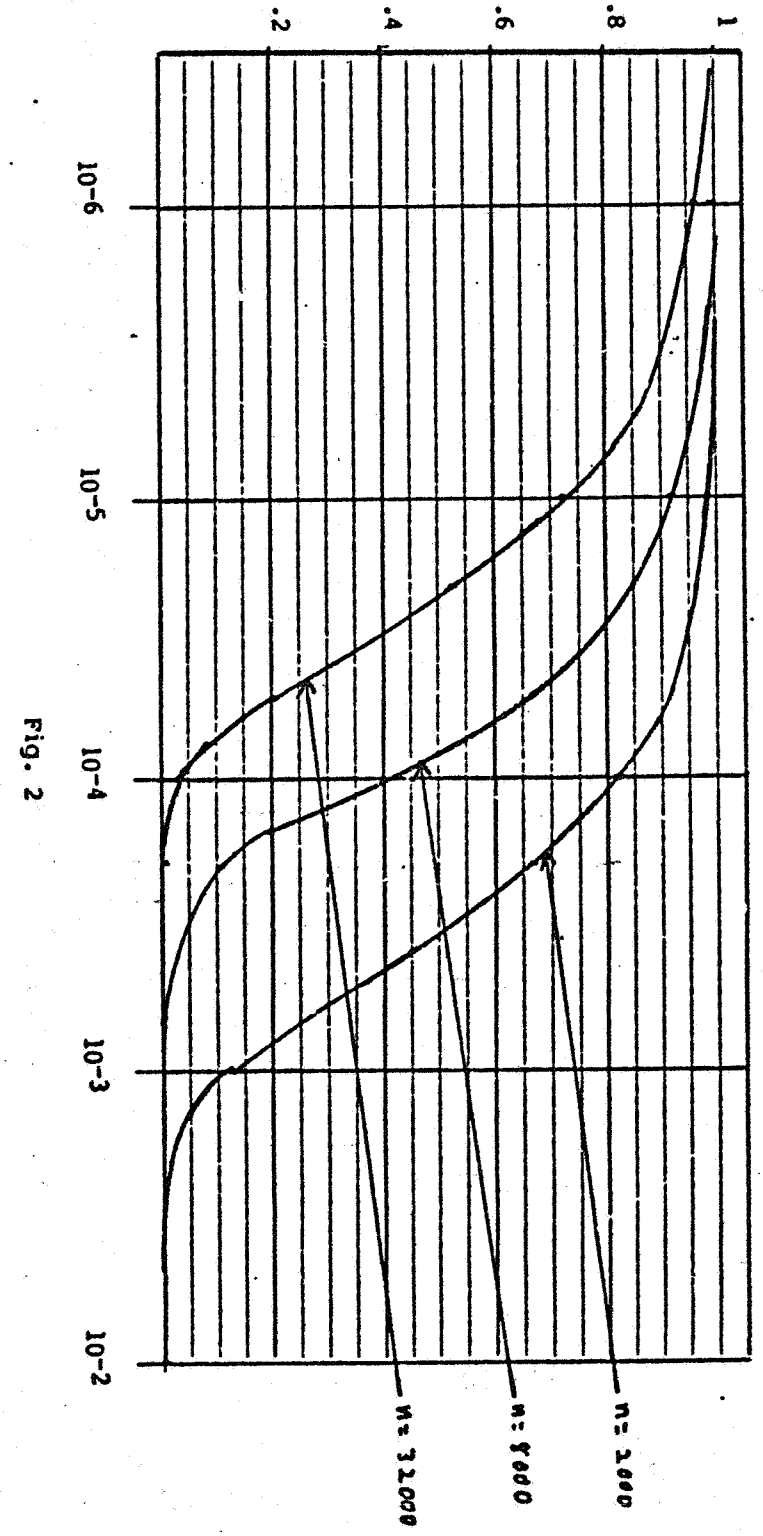
P (n animals are tumor free) vs Risk Level
1
.8
.6
.4
.2
10-2
10-3
10-4
10-5
10-6
n= 2000
n= 8000
n= 32000

Fig. 2

Experimenters wish to protect themselves from situations of that type (i.e., having experimental results that could have been generated by a low risk, e.g. 10^{-4}, but which simultaneously could have been generated by a much higher risk, say 10^{-2} in the example given).

One solution to this problem is to increase the sample size. For example, it requires 32000 animals (see Fig 2) to be tested and to be tumor free before we can assert that there is only a .05 probability that the test results were generated by risks greater than 10^{-4}. Hence, this solution, (i.e., increasing n) is at the very least economically infeasible.

In the absence of adequate metabolic or other study data a threshold or a highly non-linear tumor-dose response is not convincingly demonstrated. In view of this we proceed below with the multihit model dose extrapolation.

2 Model Fitting

In view of the preceding discussion, the data in Table 1-a were fitted with the multihit model using the human equivalent in mg/kg/day estimated by Dynamac (ref 6). There are four basic analyses:

i Female liver/kidney data (New Rabon, 7 groups)

ii Male kidney data (New Rabon, 7 groups)

iii Female liver data (Old Rabon, 2 groups)

iv Male kidney data (Old Rabon, 2 groups)

The new Rabon analyses (i & ii) include dose groups 1-7 and the old Rabon analyses (iii & iv) refer to groups 1 and 8. The results are given in Table 2.

Table 2 - Chi Sq, Q^*_1, and Maximum Likelihood Estimate of Q_1 for runs i-iv

Run	Chi Sq (df)	Q_1^* for (mg/kg/day)	MLE of Q_1
i	8.25 (6)	2.3×10^{-3}	1.6×10^{-3}
ii	5.03 (4)	1.2×10^{-3}	3.3×20^{-4}
iii	<.1 (1)	1.5×10^{-3}	8.2×10^{-4}
iv	<.1 (1)	6.9×10^{-4}	2.1×10^{-4}

Note the following in Table 2. The Chi Square fit is reasonable for i and ii considering that there are 7 treatment groups while the "perfect" fits for iii and iv are almost meaningless due to the fact that there are only two groups. The Q_1*s (i.e., the .95 upper confidence bound found on Q_1) are grouped fairly closely together and are also not too far from the maximum likelihood estimates. All this implies that the data are of reasonable quality and the model choice is reasonable.

In choosing the most appropriate data for qualitative risk assessment the old Rabon findings are rejected because the new compound formulation is the one that people will be at risk. Of the remainder analysis i is preferred as it included animals with liver and/or kidney tumors. The potency factor for these data are $Q_1^* = 2.3 \times 10^{-3}$.

CHARACTERIZATION OF RISK

No worker exposure data are available (ref 5). The latest published dietary tolerances (see appendix) give rise to the risks given in Table 3.

Using the latest published TMRC (Sept. 14, 1979) of 1.5238 mg/day/(1.5 kg diet) and a $Q_1^* = 2.3 \times 10^{-3}$ gives rise to

$$\text{Maximum Dietary Risk} = \frac{\text{TMRC}}{60} \cdot Q_1^*$$

$$= 5.8 \times 10^{-5}$$

This gives 10^{-5} to 10^{-4} when rounded (as per ref 4).

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Table 3 - Upper .95 Confident Limits on Risks for Selected Crops

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Crops	Tolerance	mg/kg/day	Upper .95 Bound on Risk
Apple	10	.0063	$6.3.10^{-6}$
Corn	10	.0063	$6.3.10^{-6}$
Tomatoes	5	.00359	$3.6.10^{-6}$
Cattle	1.5	.00088	$8.8.10^{-7}$
Hogs	1.5	.0004	4.10^{-7}
Dairy Products	.5	.00358	$3.6.10^{-6}$
Eggs	.1	.00007	$7.1.10^{-8}$
Peaches	.1	.000022	2.10^{-8}
TMRC		.00254	$2.5.10^{-5}$

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References

1. EPA Draft, Revised Interim Guidelines for the Health Assessment of Suspected Carcinogens, Aug. 20, 1984

2. Hazleton Laboratories America, Project No.: 776-118 "103-Week Chronic Feeding Study in Mice, SD-8447 and Original SD-8447", June 20, 1984

3. National Cancer Institute, NCI-CG-TR-33, Bioassay of Tetrachlofvinphos for Possible Carcinogenicity, 1978

4. Memo from Bert Litt to Statistics Team. Subject: Procedures for Expressing Estimates of Public Health Risks, Nov. 30, 1984

5. Memo from Reinert to Spencer, Subject: Exposure Assessment for Rabon, May 22, 1984

6. See original Dynamac Output on Gardona/Krewski dated July 26, 1984.