MAR 4 1986

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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Acetochlor, Review of Dynamac's Draft for the Risk Assessment of Acetochlor.

FROM: Herbert Lacayo, Statistician Herbert Lacayo / Mar 4, 1986
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Attached is a Dynamac draft for the risk assessment of Acetochlor. The data were fit by a variety of models and estimates for dose corresponding to risks to humans of 10^{-4} and 10^{-6} were made. No dietary or applicator risks were calculated. This cover memo contains a summary of the risks in terms of animal and human Q_1^* when pooling tumors.

FIG. 1

POOLED TUMORS COUNT

Dose (ppm)		0	500	1500	5000
MICE -	Males [1]	23/60	22/54	31/60	32/56
	Females [2]	5/58	15/59	14/59	21/57
RAT -	Males [3]	8/70	8/70	15/68	19/68
	Females [4]	4/69	3/70	4/69	13/64

1 Liver and/or lung tumors, $P < .05$ (0 vs. 5,000) + trend
2 Liver, lung, and/or uterine tumors, $P < .05$ (0 vs. 500)+trend
3 Liver, testicular and/or thyroid tumors, $P < .05$ (0 vs. 5,000) + trend
4 Liver, thyroid, and/or uterine tumors, $P < .05$ trend only.

1

005580

Tumors were pooled (see Fig. 1 above) in accordance with the Agency's risk assessment guidelines. Next using the dose estimates for the Multistage model given in Tables 7-13 of the Dynamac report, it is possible to estimate Q_1^* (mg/kg/day)$^{-1}$ for humans and then to further estimate (using the surface area correction the corresponding Q_1^* for mice and rats. This is done in Fig. 2 below. Fig 3 gives the corresponding data for the time to tumor model given in the Risk81 program for various time.

FIG. 2 [Q_1^* in (mg/kg/day)$^{-1}$]

Mouse		Humans	
Males	Females	Males	Females
Q_1^*	Q_1^*	Q_1^*	Q_1^*
2.29×10^{-3}	1.39×10^{-3}	3.3×10^{-2}	2×10^{-2}

Rats		Humans	
Males	Females	Males	Females
Q_1^*	Q_1^*	Q_1^*	Q_1^*
2.5×10^{-4}	1.25×10^{-4}	5×10^{-3}	2.5×10^{-3}

FIG. 3 [Q_1^* in (mg/kg/day)$^{-1}$ for Various Times]

Human				Mouse			
MALES		FEMALES		MALES		FEMALES	
Total Days	Q_1^*	Total Days	Q_1^*	Total Days	Q_1^*	Total Days	Q_1^*
383	2.75×10^{-4}	383	4.1×10^{-4}	389	1.9×10^{-5}	383	2.8×10^{-5}
636	5.9×10^{-3}		N.A.	636	4.1×10^{-4}		N.A.
684	1.2×10^{-2}	674	1.2×10^{-2}	684	8.3×10^{-4}	674	8.3×10^{-4}
697	2.98×10^{-2}	698	1.5×10^{-2}	697	2.1×10^{-3}	898	1×10^{-3}

Human				Rats			
	Q_1^*		Q_1^*		Q_1^*		Q_1^*
770	5×10^{-4}	690	2.4×10^{-3}	770	2.5×10^{-5}	690	1.2×10^{-4}
812	6.8×10^{-3}	712	4.5×10^{-3}	817	3.4×10^{-4}	721	2.3×10^{-4}

The time to tumor model (partial results given in Fig. 3) was run by Dynamac after the risk assessment was written and hence are not reflected in that draft. There appears to be only a slight difference in results between the multistage and the time to tumor models.

In summary, we estimate a worst case potency to of Q_1^* $(mg/kg/day)^{-1}$ to be 10^{-2} for humans. Similarly the worst case Q_1^*s for mice and rats are 10^{-3} and 10^{-4} respectively.

#3

Note Changes on Pg 1, 4, 11

DRAFT

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EPA: 68-02-4225
DYNAMAC No. 1-18A,B
December 2, 1985

This is an information paper, its chief [illegible] should be considered.

SPECIAL REPORT

Risk Assessment of Acetochlor

STUDY IDENTIFICATION:

1. Ahmed, F. E. and Seely, J. C. MON-097: Chronic toxicity and oncogenicity study in the rat. (Unpublished study No. PR-80-006, prepared by Pharmacopathics Research Laboratories, Inc., Laurel, MD, for Monsanto Company, St. Louis, MO; dated May 20, 1983.) Accession Nos. 071962-071965.

2. Ahmed, F. E., Tegeris, A. S., Seely, J. C. MON-097: 24-month oncogenicity study in the mouse. (Unpublished study No. PR-80-007 prepared by Pharmacopathics Research Laboratories, INc., Laurel, MD, for Monsanto Agricultural Products Company, St., Louis, MO; dated May 4, 1983.) Accession Nos. 071966-071968.

APPROVED BY:

I. Cecil Felkner, Ph.D.
Program Manager
Dynamac Corporation

Signature: _____

Date: _____

EPA/ Received

4

1. CHEMICAL: Acetochlor:2-chloro-N-(ethoxymethyl)-6'-ethyl-ortho-aceto-toluidine.

2. TEST MATERIAL: MON-077, described as a maroon liquid, 95.5 percent pure.

3. STUDY/ACTION TYPE: A chronic feeding toxicity and oncogenicity study in the rat and an oncogenicity study in mice for use in risk assessment.

4. STUDY IDENTIFICATION:

1. Ahmed, F. E. and Seely, J. C. MON-097: Chronic toxicity and oncogenicity study in the rat. (Unpublished study No. PR-80-006, prepared by Pharmacopathics Research Laboratories, Inc., Laurel, MD, for Monsanto Company, St. Louis, MO; dated May 20, 1983.) Accession Nos. 071962-071965.

2. Ahmed, F. E., Tegeris, A. S., Seely, J. C. MON-097: 24-month oncogenicity study in the mouse. (Unpublished study No. PR-80-007 prepared by Pharmacopathics Research Laboratories, INc., Laurel, MD, for Monsanto Agricultural Products Company, St., Louis, MO; dated May 4, 1983.) Accession Nos. 071966-071968.

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5

ACETOCHLOR

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Pages 6 through 7 are not included.

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Survival analyses were conducted using the computer program by Thomas, et al (1977, Version 9/20/84). Tables 3 and 4 show statistical findings for these analyses.

TABLE 3. P Values by Statistical Test for Differences in Survival Among Dose Groups for Mice Fed Acetochlor for 23 Months

	Unadjusted Data	Adjusted Data	
		Cox's Test	~~Kruskal-Wallis~~ Breslow-Gehan Test
Males			
Overall Comparison	0.1403	<0.0001	<0.0001
Pairwise Comparisons			
Control vs. 500 ppm group	0.9439	0.0212	0.0574
Control vs. 1500 ppm group	0.2009	0.3883	<0.0001
Control vs. 5000 ppm group	0.0668	<0.0001	<0.0001
Females			
Overall Comparison	0.0051	<0.0001	<0.001
Pairwise Comparisons			
Control vs. 500 ppm group	0.0308	0.2929	0.1595
Control vs. 1500 ppm group	0.0504	0.0967	0.0438
Control vs. 5000 ppm group	0.0007	<0.0001	<0.0001

TABLE 4. P Values by Statistical Test for Differences in Survival Among Dose Groups for Rats Fed Acetochlor for 24/27 Months

	Unadjusted Data	Adjusted Data	
		Cox's Test	Kruskal-Wallis Test
Males			
Overall Comparison	0.0253	0.0211	0.1839
Pairwise Comparisons			
Control vs. 500 ppm group	1.0000	0.8224	0.8564
Control vs. 1500 ppm group	0.1494	0.4695	0.4701
Control vs. 5000 ppm group	0.0263	0.0325	0.0330
Females			
Overall Comparison	0.0032	<0.0000	0.0006
Pairwise Comparisons			
Control vs. 500 ppm group	0.9845	0.9773	0.9367
Control vs. 1500 ppm group	1.0000	0.8773	0.6271
Control vs. 5000 ppm group	0.0253	0.0014	0.0054

III. LOW-DOSE EXTRAPOLATION

Various low-dose extrapolation models were fit to the dose-response incidence data presented in Tables 5-6 after appropriate conversions of the experimental dose concentrations in mg/kg/day for the test animals, then applying a species-to-species conversion factor to extrapolate each species to humans. These values are then converted to human equivalent doses based on work by Mantel and Schneiderman (1975), and are given in the following equations:

$$\text{Human Equivalent Dose (mg/kg/day)} = \text{Animal Dose (mg/kg/day)} \div \left(\frac{60{,}000}{30}\right)^{1/3} \quad \text{(mice)}$$

$$\text{Human Equivalent Dose (mg/kg/day)} = \text{Animal Dose (mg/kg/day)} \div \left(\frac{60{,}000}{350}\right)^{1/3} \quad \text{(rats)}$$

where 30 and 350 are the average weights in grams of mice and rats, respectively, and 60,000 is the average human weight in grams. Table 5 presents the human equivalent doses used in this assessment.

TABLE 5. Human Equivalent Doses in mg/kg/day by Species for Animals Fed Acetochlor for Approximately 2 Years

	Administered Dose (ppm)			
	0	500	1500	5000
Rats	0	4.5	13.5	45.0
Mice	0	5.2	15.6	52.0

As no environmental doses were available, doses and associated lower 95% confidence bounds were estimated for levels of extra risk of 1×10^{-4} and 1×10^{-6} for the probit, logit, Weibull and Gamma multi-hit models.

Estimates were calculated using a software program called ANALYSIX developed under contract to the US EPA Office of Toxic Substances. This program unifies the output of the GLOBAL83 multistage model of Howe and Crump and the RISK81 models of Krewski and Kovar. Estimates for each species were calculated for each sex group. These data are presented in Tables 6-13.

TABLE 1. Incidence of Tumors in Mice Fed Diets Containing MON-097 for 23 Months

Tumor	Males (ppm)				Females (ppm)			
	0	500	1500	5000	0	500	1500	5000
Hepatocellular adenoma and/or carcinoma	14/60	11/54	19/60	29/56	3/58	0/59	0/59	8/57
Hepatocellular adenoma and/or carcinoma and/or lung adenoma and/or carcinoma	23/60	22/54	31/60	32/56	5/58	11/58	11/58	16/57
Hepatocellular adenoma and/or carcinoma and/or lung adenoma and/or carcinoma and/or uterine histiocytic sarcoma	-	-	-	-	5/58	15/59	14/59	21/57

TABLE 2. Incidence of Tumors in Rats Fed Diets Containing MON-097 for 24/27 Months

Tumor	Males (ppm)				Females (ppm)			
	0	500	1500	5000	0	500	1500	5000
Hepatocellular adenoma and/or carcinoma	6/70	4/70	8/68	14/68	1/69	3/70	3/69	7/64
Hepatocellular adenoma and/or carcinoma and/or uterine adenocarcinoma	-	-	-	-	2/69	3/70	4/69	10/64
Hepatocellular adenoma and/or carcinoma and/or testicular interstitial cell tumor	8/70	8/70	12/68	17/68	-	-	-	-
Hepatocellular adenoma and/or carcinoma and/or uterine adenocarcinoma and/or thyroid follicular cell adenoma	-	-	-	-	4/69	3/70	4/69	13/64
Hepatocellular adenoma and/or carcinoma and/or testicular interstitial cell tumor and/or thyroid follicular cell adenoma	8/70	8/70	15/68	19/68	-	-	-	-

TABLE 6. Estimated Doses (mg/kg/day) Associated with Specific Levels of Extra Risk for Various Models for Liver Tumors in Male and Female Mice Fed Acetochlor for 23 Months

	Extra Risk			
	10^{-4}		10^{-6}	
Model	MLE[a]	Lower 95% CB[b]	MLE[a]	Lower 95% CB[b]
	MALES			
Independent Probit	3×10^{-3}	5×10^{-5}	2×10^{-5}	9×10^{-7}
Independent Logit	2×10^{-5}	3×10^{-8}	2×10^{-8}	6×10^{-13}
Independent Weibull	2×10^{-6}	5×10^{-10}	2×10^{-10}	9×10^{-16}
Independent Multihit	2×10^{-6}	5×10^{-9}	2×10^{-10}	9×10^{-15}
Multistage	5×10^{-3}	4×10^{-3}	5×10^{-5}	4×10^{-5}
	FEMALES			
Independent Probit	1×10^{0}	1×10^{-1}	1×10^{-1}	9×10^{-3}
Independent Logit	4×10^{1}	0	3×10^{1}	0
Independent Weibull	4×10^{1}	0	3×10^{1}	0
Independent Multihit	2×10^{1}	1×10^{-3}	2×10^{1}	6×10^{-6}
Multistage	5×10^{0}	4×10^{-2}	5×10^{0}	4×10^{-4}

[a]Maximum likelihood estimate of dose.

[b]Lower 95% confidence bound on dose.

TABLE 7. Estimated Doses (mg/kg/day) Associated with Specific Levels of Extra Risk for Various Models for Liver and/or Lung Tumors in Male and Female Mice Fed Acetochlor for 23 Months

	Extra Risk			
	10^{-4}		10^{-6}	
Model	MLE[a]	Lower 95% CB[b]	MLE[a]	Lower 95% CB[b]
	MALES			
Independent Probit	1×10^{-8}	3×10^{-17}	4×10^{-11}	3×10^{-22}
Independent Logit	2×10^{-13}	4×10^{-27}	1×10^{-20}	6×10^{-41}
Independent Weibull	2×10^{-18}	5×10^{-37}	3×10^{-28}	2×10^{-56}
Independent Multihit	3×10^{-14}	2×10^{-22}	3×10^{-22}	7×10^{-35}
Multistage	3×10^{-3}	4×10^{-3}	3×10^{-5}	3×10^{-5}
	FEMALES			
Independent Probit	1×10^{-8}	7×10^{-21}	7×10^{-12}	2×10^{-28}
Independent Logit	1×10^{-13}	2×10^{-32}	8×10^{-22}	2×10^{-51}
Independent Weibull	5×10^{-15}	1×10^{-35}	3×10^{-24}	7×10^{-56}
Independent Multihit	8×10^{-13}	1×10^{-26}	8×10^{-21}	1×10^{-41}
Multistage	1×10^{-2}	7×10^{-3}	1×10^{-3}	7×10^{-5}

[a]Maximum likelihood estimate of dose.

[b]Lower 95% confidence bound on dose.

TABLE 8. Estimated Doses (mg/kg/day) Associated with Specific Levels of Extra Risk for Various Models for Liver, Lung, and/or Uterine Tumors in Female Mice Fed Acetochlor for 23 Months

	Extra Risk			
	10^{-4}		10^{-6}	
Model	MLE[a]	Lower 95% CB[b]	MLE[a]	Lower 95% CB[b]
Independent Probit	8×10^{-9}	4×10^{-20}	7×10^{-12}	7×10^{-27}
Independent Logit	4×10^{-14}	1×10^{-31}	3×10^{-22}	2×10^{-49}
Independent Weibull	4×10^{-16}	1×10^{-35}	2×10^{-25}	3×10^{-56}
Independent Multihit	3×10^{-13}	3×10^{-25}	3×10^{-21}	5×10^{-40}
Multistage	7×10^{-3}	5×10^{-3}	7×10^{-5}	5×10^{-5}

[a]Maximum likelihood estimate of dose.

[b]Lower 95% confidence bound on dose.

TABLE 9. Estimated Doses (mg/kg/day) Associated with Specific Levels of Extra Risk for Various Models for Liver Tumors in Male and Female Rats Fed Acetochlor for 23 Months

	Extra Risk			
	10^{-4}		10^{-6}	
Model	MLE[a]	Lower 95% CB[b]	MLE[a]	Lower 95% CB[b]
	MALES			
Independent Probit	2×10^{-2}	1×10^{-4}	7×10^{-4}	6×10^{-7}
Independent Logit	3×10^{-4}	1×10^{-7}	2×10^{-7}	6×10^{-13}
Independent Weibull	2×10^{-4}	4×10^{-8}	5×10^{-8}	7×10^{-14}
Independent Multihit	4×10^{-5}	2×10^{-9}	4×10^{-9}	4×10^{-16}
Multistage	4×10^{-2}	3×10^{-2}	4×10^{-4}	3×10^{-4}
	FEMALES			
Independent Probit	2×10^{-3}	3×10^{-8}	2×10^{-5}	2×10^{-12}
Independent Logit	5×10^{-5}	1×10^{-11}	3×10^{-9}	1×10^{-20}
Independent Weibull	3×10^{-5}	5×10^{-12}	2×10^{-9}	4×10^{-21}
Independent Multihit	2×10^{-4}	2×10^{-10}	1×10^{-8}	2×10^{-18}
Multistage	8×10^{-2}	5×10^{-2}	8×10^{-4}	5×10^{-4}

[a]Maximum likelihood estimate of dose.

[b]Lower 95% confidence bound on dose.

TABLE 10. Estimated Doses (mg/kg/day) Associated with Specific Levels of Extra Risk for Various Models for Liver, and/or Uterine Tumors in Female Rats Fed Acetochlor for 23 Months

	Extra Risk			
	10^{-4}		10^{-6}	
Model	MLE[a]	Lower 95% CB[b]	MLE[a]	Lower 95% CB[b]
Independent Probit	3×10^{-2}	2×10^{-4}	2×10^{-3}	8×10^{-7}
Independent Logit	2×10^{-3}	1×10^{-6}	2×10^{-6}	8×10^{-12}
Independent Weibull	1×10^{-3}	6×10^{-7}	1×10^{-6}	3×10^{-12}
Independent Multihit	2×10^{-4}	5×10^{-9}	4×10^{-8}	8×10^{-16}
Multistage	6×10^{-2}	4×10^{-2}	6×10^{-4}	4×10^{-4}

[a]Maximum likelihood estimate of dose.

[b]Lower 95% confidence bound on dose.

TABLE 11. Estimated Doses (mg/kg/day) Associated with Specific Levels of Extra Risk for Various Models for Liver, and/or Testicular Tumors in Male Rats Fed Acetochlor for 23 Months

	Extra Risk			
	10^{-4}		10^{-6}	
Model	MLE[a]	Lower 95% CB[b]	MLE[a]	Lower 95% CB[b]
Independent Probit	2×10^{-4}	1×10^{-8}	2×10^{-6}	3×10^{-12}
Independent Logit	2×10^{-7}	6×10^{-14}	3×10^{-12}	8×10^{-23}
Independent Weibull	4×10^{-8}	2×10^{-15}	2×10^{-13}	4×10^{-25}
Independent Multihit	9×10^{-8}	5×10^{-25}	2×10^{-19}	5×10^{-41}
Multistage	3×10^{-2}	2×10^{-2}	3×10^{-4}	2×10^{-4}

[a]Maximum likelihood estimate of dose.

[b]Lower 95% confidence bound on dose.

TABLE 12. Estimated Doses (mg/kg/day) Associated with Specific Levels of Extra Risk for Various Models for Liver, Thyroid, and/or Uterine Tumors in Female Rats Fed Acetochlor for 23 Months

	Extra Risk			
	10^{-4}		10^{-6}	
Model	MLE[a]	Lower 95% CB[b]	MLE[a]	Lower 95% CB[b]
Independent Probit	1×10^{-1}	4×10^{-3}	1×10^{-2}	7×10^{-5}
Independent Logit	1×10^{-2}	7×10^{-5}	4×10^{-5}	1×10^{-8}
Independent Weibull	8×10^{-3}	4×10^{-5}	2×10^{-5}	5×10^{-9}
Independent Multihit	5×10^{-2}	1×10^{-3}	5×10^{-4}	1×10^{-6}
Multistage	5×10^{-2}	4×10^{-2}	5×10^{-4}	4×10^{-4}

[a]Maximum likelihood estimate of dose.

[b]Lower 95% confidence bound on dose.

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TABLE 13. Estimated Doses (mg/kg/day) Associated with Specific Levels of Extra Risk for Various Models for Liver, Testicular, and/or Thyroid Tumors in Male Rats Fed Acetochlor for 23 Months

	Extra Risk			
	10^{-4}		10^{-6}	
Model	MLE[a]	Lower 95% CB[b]	MLE[a]	Lower 95% CB[b]
Independent Probit	6×10^{-4}	3×10^{-7}	1×10^{-5}	3×10^{-10}
Independent Logit	1×10^{-6}	5×10^{-12}	4×10^{-11}	1×10^{-16}
Independent Weibull	1×10^{-7}	2×10^{-13}	1×10^{-12}	4×10^{-22}
Independent Multihit	9×10^{-12}	6×10^{-24}	2×10^{-19}	6×10^{-39}
Multistage	2×10^{-2}	2×10^{-2}	2×10^{-4}	2×10^{-4}

[a]Maximum likelihood estimate of dose.

[b]Lower 95% confidence bound on dose.