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

005580

OFFICE OF  
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

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

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Toxicology Branch/HED (TS-769)

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Acting Section Head, Section V  
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THRU: Bertram Litt, Leader *Bertram Litt*  
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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 <sup>1</sup> | 23/60 | 22/54 | 31/60 | 32/56 |
| Females <sup>2</sup>      | 5/58  | 15/59 | 14/59 | 21/57 |
| RAT - Males <sup>3</sup>  | 8/70  | 8/70  | 15/68 | 19/68 |
| Females <sup>4</sup>      | 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.

*1/20*

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)<sup>-1</sup> 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)<sup>-1</sup>]

| Mouse                 |                       | Humans               |                    |
|-----------------------|-----------------------|----------------------|--------------------|
| Males                 | Females               | Males                | Females            |
| $Q_1^*$               | $Q_1^*$               | $Q_1^*$              | $Q_1^*$            |
| $2.29 \times 10^{-3}$ | $1.39 \times 10^{-3}$ | $3.3 \times 10^{-2}$ | $2 \times 10^{-2}$ |

  

| Rats                 |                       | Humans             |                      |
|----------------------|-----------------------|--------------------|----------------------|
| Males                | Females               | Males              | Females              |
| $Q_1^*$              | $Q_1^*$               | $Q_1^*$            | $Q_1^*$              |
| $2.5 \times 10^{-4}$ | $1.25 \times 10^{-4}$ | $5 \times 10^{-3}$ | $2.5 \times 10^{-3}$ |

FIG. 3 [ $Q_1^*$  in (mg/kg/day)<sup>-1</sup> 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        | $2.75 \times 10^{-4}$ | 383        | $4.1 \times 10^{-4}$ | 389        | $1.9 \times 10^{-5}$ | 383        | $2.8 \times 10^{-5}$ |
| 636        | $5.9 \times 10^{-3}$  | N.A.       |                      | 636        | $4.1 \times 10^{-4}$ | N.A.       |                      |
| 684        | $1.2 \times 10^{-2}$  | 674        | $1.2 \times 10^{-2}$ | 634        | $8.3 \times 10^{-4}$ | 674        | $8.3 \times 10^{-4}$ |
| 697        | $2.98 \times 10^{-2}$ | 698        | $1.5 \times 10^{-2}$ | 697        | $2.1 \times 10^{-3}$ | 898        | $1 \times 10^{-3}$   |

  

| Human   |                      | Rats    |                      |
|---------|----------------------|---------|----------------------|
| $Q_1^*$ | $Q_1^*$              | $Q_1^*$ | $Q_1^*$              |
| 770     | $5 \times 10^{-4}$   | 690     | $2.4 \times 10^{-3}$ |
| 812     | $6.8 \times 10^{-3}$ | 712     | $4.5 \times 10^{-3}$ |

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)<sup>-1</sup> to be  $10^{-2}$  for humans. Similarly the worst case  $Q_1^*$ s for mice and rats are  $10^{-3}$  and  $10^{-4}$  respectively.

NOTE Changes on

Py (M) 7/1/85  
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DRAFT

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

This is an informational report, its  
chief purpose is to provide information  
to the public and to the scientific community  
concerning the results of the research and  
development work conducted by the Agency  
under the authority of the Administrator  
under the provisions of the Act.

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: \_\_\_\_\_

12/10/85  
received  
12-10-85

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.

5. REVIEWED BY:

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Date: \_\_\_\_\_

Bertram Litt  
EPA Reviewer

Signature: \_\_\_\_\_

Date: \_\_\_\_\_

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ACETOCHLOR

TOX R# 005580

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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    | <del>Kruskal-Wallis Test</del><br>Breslow-Gehan |
| <u>Males</u>               |                 |               |                                                 |
| 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                                         |
| <u>Females</u>             |                 |               |                                                 |
| 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 |
| <u>Males</u>               |                 |               |                     |
| 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              |
| <u>Females</u>             |                 |               |                     |
| 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:

$$\text{Human Equivalent Dose} = \text{Animal Dose} \div \frac{60,000}{30} \quad \begin{matrix} 1/3 \\ \text{(mice)} \end{matrix}$$

(mg/kg/day)                      (mg/kg/day)

$$\text{Human Equivalent Dose} = \text{Animal Dose} \div \frac{60,000}{350} \quad \begin{matrix} 1/3 \\ \text{(rats)} \end{matrix}$$

(mg/kg/day)                      (mg/kg/day)

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  $1 \times 10^{-4}$  and  $1 \times 10^{-6}$  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.

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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 |

14 11 19 29 3 0 0 8  
 23 22 31 32 5 11 11 16  
 - - - - 5 15 14 21

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 | 10/68 | 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 | 3 <sup>0</sup><br>- | -    | -    | -     |

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

| Model                | Extra Risk           |                           |                       |                           |
|----------------------|----------------------|---------------------------|-----------------------|---------------------------|
|                      | 10 <sup>-4</sup>     |                           | 10 <sup>-6</sup>      |                           |
|                      | MLE <sup>a</sup>     | Lower 95% CB <sup>b</sup> | MLE <sup>a</sup>      | Lower 95% CB <sup>b</sup> |
| MALES                |                      |                           |                       |                           |
| Independent Probit   | 3 x 10 <sup>-3</sup> | 5 x 10 <sup>-5</sup>      | 2 x 10 <sup>-5</sup>  | 9 x 10 <sup>-7</sup>      |
| Independent Logit    | 2 x 10 <sup>-5</sup> | 3 x 10 <sup>-8</sup>      | 2 x 10 <sup>-8</sup>  | 6 x 10 <sup>-13</sup>     |
| Independent Weibull  | 2 x 10 <sup>-6</sup> | 5 x 10 <sup>-10</sup>     | 2 x 10 <sup>-10</sup> | 9 x 10 <sup>-16</sup>     |
| Independent Multihit | 2 x 10 <sup>-6</sup> | 5 x 10 <sup>-9</sup>      | 2 x 10 <sup>-10</sup> | 9 x 10 <sup>-15</sup>     |
| Multistage           | 5 x 10 <sup>-3</sup> | 4 x 10 <sup>-3</sup>      | 5 x 10 <sup>-5</sup>  | 4 x 10 <sup>-5</sup>      |
| FEMALES              |                      |                           |                       |                           |
| Independent Probit   | 1 x 10 <sup>0</sup>  | 1 x 10 <sup>-1</sup>      | 2 x 10 <sup>-1</sup>  | 9 x 10 <sup>-3</sup>      |
| Independent Logit    | 4 x 10 <sup>1</sup>  | 0                         | 3 x 10 <sup>1</sup>   | 0                         |
| Independent Weibull  | 4 x 10 <sup>1</sup>  | 0                         | 3 x 10 <sup>1</sup>   | 0                         |
| Independent Multihit | 2 x 10 <sup>1</sup>  | 1 x 10 <sup>-3</sup>      | 2 x 10 <sup>1</sup>   | 6 x 10 <sup>-6</sup>      |
| Multistage           | 5 x 10 <sup>0</sup>  | 4 x 10 <sup>-2</sup>      | 5 x 10 <sup>0</sup>   | 4 x 10 <sup>-4</sup>      |

<sup>a</sup>Maximum likelihood estimate of dose.

<sup>b</sup>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

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

<sup>a</sup>Maximum likelihood estimate of dose.

<sup>b</sup>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

| Model                | Extra Risk            |                           |                       |                           |
|----------------------|-----------------------|---------------------------|-----------------------|---------------------------|
|                      | 10 <sup>-4</sup>      |                           | 10 <sup>-6</sup>      |                           |
|                      | MLE <sup>a</sup>      | Lower 95% CB <sup>b</sup> | MLE <sup>a</sup>      | Lower 95% CB <sup>b</sup> |
| Independent Probit   | 8 x 10 <sup>-9</sup>  | 4 x 10 <sup>-20</sup>     | 7 x 10 <sup>-12</sup> | 7 x 10 <sup>-27</sup>     |
| Independent Logit    | 4 x 10 <sup>-14</sup> | 1 x 10 <sup>-31</sup>     | 3 x 10 <sup>-22</sup> | 2 x 10 <sup>-49</sup>     |
| Independent Weibull  | 4 x 10 <sup>-16</sup> | 1 x 10 <sup>-35</sup>     | 2 x 10 <sup>-25</sup> | 3 x 10 <sup>-56</sup>     |
| Independent Multihit | 3 x 10 <sup>-13</sup> | 3 x 10 <sup>-25</sup>     | 3 x 10 <sup>-21</sup> | 5 x 10 <sup>-40</sup>     |
| Multistage           | 7 x 10 <sup>-3</sup>  | 5 x 10 <sup>-3</sup>      | 7 x 10 <sup>-5</sup>  | 5 x 10 <sup>-5</sup>      |

<sup>a</sup>Maximum likelihood estimate of dose.

<sup>b</sup>Lower 95% confidence bound on dose.

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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

| Model                | Extra Risk           |                           |                      |                           |
|----------------------|----------------------|---------------------------|----------------------|---------------------------|
|                      | 10 <sup>-4</sup>     |                           | 10 <sup>-6</sup>     |                           |
|                      | MLE <sup>a</sup>     | Lower 95% CB <sup>b</sup> | MLE <sup>a</sup>     | Lower 95% CB <sup>b</sup> |
| MALES                |                      |                           |                      |                           |
| Independent Probit   | 2 x 10 <sup>-2</sup> | 1 x 10 <sup>-4</sup>      | 7 x 10 <sup>-4</sup> | 6 x 10 <sup>-7</sup>      |
| Independent Logit    | 3 x 10 <sup>-4</sup> | 1 x 10 <sup>-7</sup>      | 2 x 10 <sup>-7</sup> | 6 x 10 <sup>-13</sup>     |
| Independent Weibull  | 2 x 10 <sup>-4</sup> | 4 x 10 <sup>-8</sup>      | 5 x 10 <sup>-8</sup> | 7 x 10 <sup>-14</sup>     |
| Independent Multihit | 4 x 10 <sup>-5</sup> | 2 x 10 <sup>-9</sup>      | 4 x 10 <sup>-9</sup> | 4 x 10 <sup>-16</sup>     |
| Multistage           | 4 x 10 <sup>-2</sup> | 3 x 10 <sup>-2</sup>      | 4 x 10 <sup>-4</sup> | 3 x 10 <sup>-4</sup>      |
| FEMALES              |                      |                           |                      |                           |
| Independent Probit   | 2 x 10 <sup>-3</sup> | 3 x 10 <sup>-8</sup>      | 2 x 10 <sup>-5</sup> | 2 x 10 <sup>-12</sup>     |
| Independent Logit    | 5 x 10 <sup>-5</sup> | 1 x 10 <sup>-11</sup>     | 3 x 10 <sup>-9</sup> | 1 x 10 <sup>-20</sup>     |
| Independent Weibull  | 3 x 10 <sup>-5</sup> | 5 x 10 <sup>-12</sup>     | 2 x 10 <sup>-9</sup> | 4 x 10 <sup>-21</sup>     |
| Independent Multihit | 2 x 10 <sup>-4</sup> | 2 x 10 <sup>-10</sup>     | 1 x 10 <sup>-8</sup> | 2 x 10 <sup>-18</sup>     |
| Multistage           | 8 x 10 <sup>-2</sup> | 5 x 10 <sup>-2</sup>      | 8 x 10 <sup>-4</sup> | 5 x 10 <sup>-4</sup>      |

<sup>a</sup>Maximum likelihood estimate of dose.

<sup>b</sup>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

| Model                | Extra Risk         |                           |                    |                           |
|----------------------|--------------------|---------------------------|--------------------|---------------------------|
|                      | $10^{-4}$          |                           | $10^{-6}$          |                           |
|                      | MLE <sup>a</sup>   | Lower 95% CB <sup>b</sup> | MLE <sup>a</sup>   | Lower 95% CB <sup>b</sup> |
| Independent Probit   | $3 \times 10^{-2}$ | $2 \times 10^{-4}$        | $2 \times 10^{-3}$ | $8 \times 10^{-7}$        |
| Independent Logit    | $2 \times 10^{-3}$ | $1 \times 10^{-6}$        | $2 \times 10^{-6}$ | $8 \times 10^{-12}$       |
| Independent Weibull  | $1 \times 10^{-3}$ | $6 \times 10^{-7}$        | $1 \times 10^{-6}$ | $3 \times 10^{-12}$       |
| Independent Multihit | $2 \times 10^{-4}$ | $5 \times 10^{-9}$        | $4 \times 10^{-8}$ | $8 \times 10^{-16}$       |
| Multistage           | $6 \times 10^{-2}$ | $4 \times 10^{-2}$        | $6 \times 10^{-4}$ | $4 \times 10^{-4}$        |

<sup>a</sup>Maximum likelihood estimate of dose.

<sup>b</sup>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

| Model                | Extra Risk         |                           |                     |                           |
|----------------------|--------------------|---------------------------|---------------------|---------------------------|
|                      | $10^{-4}$          |                           | $10^{-6}$           |                           |
|                      | MLE <sup>a</sup>   | Lower 95% CB <sup>b</sup> | MLE <sup>a</sup>    | Lower 95% CB <sup>b</sup> |
| Independent Probit   | $2 \times 10^{-4}$ | $1 \times 10^{-8}$        | $2 \times 10^{-6}$  | $3 \times 10^{-12}$       |
| Independent Logit    | $2 \times 10^{-7}$ | $6 \times 10^{-14}$       | $3 \times 10^{-12}$ | $8 \times 10^{-23}$       |
| Independent Weibull  | $4 \times 10^{-8}$ | $2 \times 10^{-15}$       | $2 \times 10^{-13}$ | $4 \times 10^{-25}$       |
| Independent Multihit | $9 \times 10^{-8}$ | $5 \times 10^{-25}$       | $2 \times 10^{-19}$ | $5 \times 10^{-41}$       |
| Multistage           | $3 \times 10^{-2}$ | $2 \times 10^{-2}$        | $3 \times 10^{-4}$  | $2 \times 10^{-4}$        |

<sup>a</sup>Maximum likelihood estimate of dose.

<sup>b</sup>Lower 95% confidence bound on dose.

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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

| Model                | Extra Risk           |                           |                      |                           |
|----------------------|----------------------|---------------------------|----------------------|---------------------------|
|                      | 10 <sup>-4</sup>     |                           | 10 <sup>-6</sup>     |                           |
|                      | MLE <sup>a</sup>     | Lower 95% CB <sup>b</sup> | MLE <sup>a</sup>     | Lower 95% CB <sup>b</sup> |
| Independent Probit   | 1 x 10 <sup>-1</sup> | 4 x 10 <sup>-3</sup>      | 1 x 10 <sup>-2</sup> | 7 x 10 <sup>-5</sup>      |
| Independent Logit    | 1 x 10 <sup>-2</sup> | 7 x 10 <sup>-5</sup>      | 4 x 10 <sup>-5</sup> | 1 x 10 <sup>-8</sup>      |
| Independent Weibull  | 8 x 10 <sup>-3</sup> | 4 x 10 <sup>-5</sup>      | 2 x 10 <sup>-5</sup> | 5 x 10 <sup>-9</sup>      |
| Independent Multihit | 5 x 10 <sup>-2</sup> | 1 x 10 <sup>-3</sup>      | 5 x 10 <sup>-4</sup> | 1 x 10 <sup>-6</sup>      |
| Multistage           | 5 x 10 <sup>-2</sup> | 4 x 10 <sup>-2</sup>      | 5 x 10 <sup>-4</sup> | 4 x 10 <sup>-4</sup>      |

<sup>a</sup>Maximum likelihood estimate of dose.

<sup>b</sup>Lower 95% confidence bound on dose.

(1 x 10<sup>-3</sup>) I-6

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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

| Model                | Extra Risk          |                           |                     |                           |
|----------------------|---------------------|---------------------------|---------------------|---------------------------|
|                      | $10^{-4}$           |                           | $10^{-6}$           |                           |
|                      | MLE <sup>a</sup>    | Lower 95% CB <sup>b</sup> | MLE <sup>a</sup>    | Lower 95% CB <sup>b</sup> |
| Independent Probit   | $6 \times 10^{-4}$  | $3 \times 10^{-7}$        | $1 \times 10^{-5}$  | $3 \times 10^{-10}$       |
| Independent Logit    | $1 \times 10^{-6}$  | $5 \times 10^{-12}$       | $4 \times 10^{-11}$ | $1 \times 10^{-15}$       |
| Independent Weibull  | $1 \times 10^{-7}$  | $2 \times 10^{-13}$       | $1 \times 10^{-12}$ | $4 \times 10^{-22}$       |
| Independent Multihit | $9 \times 10^{-12}$ | $6 \times 10^{-24}$       | $2 \times 10^{-19}$ | $6 \times 10^{-39}$       |
| Multistage           | $2 \times 10^{-2}$  | $2 \times 10^{-2}$        | $2 \times 10^{-4}$  | $2 \times 10^{-4}$        |

<sup>a</sup>Maximum likelihood estimate of dose.

<sup>b</sup>Lower 95% confidence bound on dose.