Data Package of the Peer Consultation Meeting on the Chloroacetanilide Degradates

May 11th – 12th, 2009

Northern Kentucky University, METS Center

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Peer Consultation on Chloroacetanilide Degradates– Charge to the Panel and Preliminary Data Evaluation

Dear Panel Member,

We look forward to assisting the panel to derive RfDs for selected environmental degradates of the crop protection chemicals, acetochlor and alachlor. A charge to the panel is included in the technical data package that accompanies this letter.

To facilitate the work of the panel, scientists from Toxicology Excellence for Risk Assessment (*TERA*) have compiled the data for the parent chemicals (acetochlor and alachlor) and their tertiary-ethanesulfonic acid (ESA) and tertiary-oxanilic acid (OXA) degradates. This data package includes issue descriptions and tables of selected studies that have been developed to provide ready access to key findings that will inform the selection of the critical effects, the point of departure alternatives, and uncertainty factor selection. A more thorough summary description of key studies and supporting dose-response modeling is provided in the Appendix to this package and full study reports will be available to the panel.

TERA's role in organizing and facilitating this peer workshop included organizing the available data to allow the panel to conserve their time and focus on the key information. We attempted to develop data tables and issue summaries that outline the key decision points and highlight critical considerations. In some cases, data analysis (including benchmark dose modeling) was done. Our intent was to ensure that the information likely to be needed by the panel would be readily available, which required us to make judgments about the potential impact of each study. Our goal was not to promote a preferred data-basis for the RfDs, rather we intended to present an array of those data that might be viewed as most important for RfD development. *TERA* staff are happy to provide additional background data or data analyses that panel members feel would be helpful in their deliberations.

Sincerely,

Bernard Gadagbui, PhD, DABT and Andrew Maier, PhD., CIH, DABT

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1.0 Charge to External Reviewers for the Toxicological Review of Acetanilide Degradates

May 11-12, 2009

1. Are you aware of any additional relevant data that should have been included in this assessment? If so, please provide a copy of reference(s). Please provide comments on how the new data contribute to the completeness of the assessment.

2. Are there sufficient data for each of the four acetanilide degradates to develop individual reference doses (RfDs)? If the database for the individual degradates is inadequate, is the anticipated toxicity of the parent chemicals sufficiently similar to use in deriving the RfDs for the degradates? If data for the parent molecules is used as the basis for the RfDs, are there additional potency or dosimetric adjustment approaches based on mode of action or toxicokinetic understanding that should be made to better represent the expected toxicity of the degradates? If data for the degradates are judged inadequate, what would be the appropriate RfD based on data for the parents?

3. What are the potential critical effects for the acetanilide degradates?
    - Are the observed effects on body weight treatment-related and toxicologically significant? Are the effects on body weight fully explained by food or water palatability or is there evidence for a contribution of general systemic toxicity?
    - Acetochlor and alachlor affect the thyroid through a mode of action hypothesized to be secondary to induction of hepatic uridine diphosphate glucuronosyl transferase activity (UDPGT). Some changes in thyroid hormones were observed in 28-day studies for acetochlor ESA and OXA. Do the available data provide a consistent pattern of effects that suggest that there are treatment-related, toxicologically-significant thyroid effects for the degradates? If so, are thyroid effects or changes in thyroid hormone levels alone appropriate endpoints for deriving a RfD? Were adequate studies conducted to address this endpoint?
    - Reproductive and developmental toxicity studies have been completed for acetochlor and alachlor and developmental toxicity studies have been completed for acetochlor OXA and alachlor ESA. Do the available data suggest that reproductive or developmental toxicity are critical endpoints for deriving the RfD? Are there adequate data to arrive at conclusions regarding reproduction endpoints for the degradates using studies for the parent chemicals, and for the developmental endpoints using the developmental toxicity studies for acetochlor OXA, alachlor ESA and/or parent compounds? If not, what additional studies might be necessary?
    - Small, but statistically significant clinical pathology changes were observed in several toxicology studies with the degradates. Were the observed changes treatment-related and toxicologically significant? For example, a number of statistically significant changes in hematology and clinical chemistry parameters were reported in a 91-day drinking water study with alachlor ESA but were not observed, even at higher dose levels, in a subsequent 90-day rat feeding study with alachlor ESA. Are the observed hematology and clinical chemistry changes in the drinking water study likely to be treatment-related, toxicologically-significant adverse effects that could serve as the

basis for the RfD for alachlor ESA? Are data for these endpoints from studies with the parent chemicals or other degradates useful to help inform this decision? Are the differences among the studies likely to be a result of differential absorption between drinking water and dietary administration, changes in drinking water consumption, or were there other factors responsible? What impact, if any, does this have on setting groundwater or drinking water standards?

- Is there evidence for other treatment-related, toxicologically-significant effects that might serve as the basis for deriving RfDs for the degradates?

4. For each of the potential critical effects, what is the appropriate point of departure for each degradate? What are the appropriate NOAELs and LOAELs for the potential critical effects? Was BMD modeling done appropriately and the correct model selected for each endpoint?

5. For derivation of the RfD value for each degradate what uncertainty factors (UF) should be applied?
    - UF_A: No adequate human effects information for developing an RfD was identified. Since animal studies will serve as the basis for the RfD, are there adequate data related to interspecies differences in toxicokinetics or toxicodynamics to develop a chemical-specific adjustment factor for this area of uncertainty? If not, what UF should be used?
    - UF_H: Are there adequate data related to human variability in toxicokinetics or toxicodynamics to develop a chemical-specific adjustment factor for this area of uncertainty? If not, what UF should be used?
    - UF_L: Are the most appropriate point of departure estimates based on NOAELs, LOAELs, or BMDL values? If a NOAEL or BMDL was selected as the point of departure, should a factor of 1 be used for this area of uncertainty? If a LOAEL is selected as the point of departure, are there data to support use of a UF value other than 10?
    - UF_S: The available database for the acetanilide degradates is limited to studies of subchronic or shorter duration. Do data on the relationship between subchronic and chronic effects for the parent molecules inform the selection of a UF for extrapolation from a study of less than chronic duration? Does comparison of effects from the 28-day and 90-day studies for the degradates inform the selection of UFs? Are there mode of action data that inform this decision? The lowest NOAELs for the parent chemicals are from dog studies, not rat studies. Is an additional uncertainty factor needed to account for extrapolation from a one-year dog study with the parents, since it does not encompass more than 10% of a beagle's lifespan? What is the panel's opinion regarding the adequacy of the 1-year dog study (which is no longer required by the USEPA) for developing chronic RfDs?
    - UF_D: The parent chemicals have robust databases. The available studies for the acetanilide degradates are more limited. Do the existing studies for the parent chemicals or for other degradates serve to fill key data gaps? For example, can data be bridged from another chemical (e.g., alachlor ESA teratology to acetochlor ESA, and acetochlor OXA teratology to alachlor OXA)? In some cases, effects for the parent chemicals were observed in species other than rats, or the effects in other species were observed at lower doses than observed in rats, while for degradates only

studies in rats are available. Given the observations for the parent chemicals that the dog is more sensitive than the rat for some endpoints, is the absence of toxicity studies in dogs a key data gap for the degradates? Based on the body of literature for the parents and degradates, what are the remaining data gaps for each degradate? What is the appropriate UF for the remaining database insufficiencies? What studies are needed to reduce this area of uncertainty?

- Are there data to indicate that children represent a sensitive subgroup that would not be adequately addressed by two of the above UFs, that for human variability (UF_H) and database completeness (UF_D)? If so, is an additional factor needed and what value should be used for this factor?

6. For each acetanilide degradate, what is the appropriate RfD after considering the candidate point(s) of departure and UFs? What is the confidence in each RfD?

7. Is there sufficient evidence of a common mode of action or common toxic effect to justify a cumulative risk assessment or RfD for more than one parent and/or degradate? If so, what approach would be suggested?

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2.0 Background Data

2.1 Data available

A complete database exists for the parent compound. In contrast, a complete database is not available for any of the degradates. There are no human health studies available for the degradates and all the studies identified were conducted in only one animal species, the rat. The database for acetochlor ESA consists of an acute oral toxicity study and 28-day and 90-day dietary toxicity studies. For acetochlor OXA, an acute oral toxicity study, 28-day and 90-day dietary toxicity studies, and a developmental toxicity study are available. An acute oral toxicity study, two oral subchronic (91-day drinking water and 90-day dietary) studies and developmental toxicity studies (a range-finding study and a main study) were available for alachlor ESA. Alachlor OXA has an acute oral toxicity and 28- and 90-day dietary toxicity studies available. No chronic or reproductive toxicity studies are available for any of the degradates and no developmental studies are available for acetochlor ESA or alachlor OXA.

2.2 Key Data Summaries

Summaries of the key studies available for the degradates are provided in Tables 1 and 2. Detailed descriptions of these studies are provided in Appendix A. The raw data will be available during the Workshop for panel review. Table 3 presents summaries of significant dose-related effects or trends observed in the available studies.

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3.0 Key Issues Summary for Potential Point of Departure Endpoints

Candidate critical studies were reviewed to identify the set of endpoints that would most likely be the critical effect(s) and serve as the basis for the point of departure. This critical review identified several endpoints, which appeared to be affected by treatment with the degradates. The data for such endpoints have been extracted from the study reports and presented in Tables 3-1 through 3-9. For these endpoints a description of key issues related to judging whether the observed effects represent treatment-related adverse effects for RfD derivation is provided in the summaries in this section of the review package. Changes in body weight and food consumption over time for selected exposure durations for the degradates are presented after the Data Tables.

3.1. Decreased Body Weight

Summary of the Key Findings

Subchronic and chronic studies with the parent compounds, acetochlor and alachlor, have shown that body weight change is a key effect for these compounds.

Acetochlor: A 4-week dietary study with acetochlor reported a significant decrease in body weight gain at 1200 ppm (132 mg/kg-day) and 300 ppm (33 mg/kg-day) for males and at 2400 ppm (279 mg/k-day) for females. The decrease observed in males at 300 ppm was much lower than for the next two higher doses (600 and 1200 ppm); hence, not likely to be toxicologically significant. The reported NOAELs for decreases in body weight gain were 68 and 139 mg/kg-day for males and females, respectively (Broadmeadow, 1985; as cited in the EU Draft Assessment Report (DAR), 2005). In a 13-week dietary study, acetochlor produced a depression of weight gain of 14% in male and 23% in female rats at 2000 ppm (161 mg/kg-day for males and 192 mg/kg-day for females; average for both sexes, 176.5 mg/kg-day) (Broadmeadow, 1986). The NOAEL in this study was 16.1 mg/kg-day for males and 18.8 mg/kg-day for females, with the average for both sexes of 17.5 mg/kg-day. The dose causing the decrease in body weight gain was also associated with lowered food consumption and decreased food utilization. In a combined oncogenicity and toxicity study in rats, acetochlor administered in the diet caused 12 and 33% reduction in weight gain for males and females, respectively, at the high dose level of 1750 ppm (66.9 mg/kg-day for males and 92.1 mg/kg-day for females, with the average for both sexes of 79.5 mg/kg-day) (Broadmeadow, 1989). There was no statistically significant effect on body weight at 6.37 mg/kg-day for males and 8.53 mg/kg-day for females, with the average for both sexes of 7.45 mg/kg-day. When rats were chronically administered acetochlor in the diet, males exhibited a statistically significant decrease (ranging from 5 to 15% during the second year of study) in body weights at 47.5 mg/kg-day (HDT) while only slight

reduction (less than 7%) in body weights were observed for females at 60 mg/kg-day (Naylor and Ribelin, 1986; as cited in EU DAR, 2005). The NOAEL in this study was 9.4 mg/kg-day for males. Other short-term or subchronic studies in rats have reported body weight changes following acetochlor administration in the diet (Pharmacopathics Research Laboratories, Inc., 1986; Hotz and Wilson, 1996).

Alachlor: In a 90-day, toxicity study (Wolf, 1966), alachlor caused decreased body weights and body weight gains, decreased food consumption and efficiency in both sexes of rats at a dose of 146 mg/kg-day, with a NOAEL of 15 mg/kg-day. However, U.S. EPA (1998) classified this study as unacceptable since it is an invalidated IBT (Industrial Biotest, 1968) study. In a chronic dietary study, alachlor produced reduced body weights in males of 12% and 20%, relative to controls, at 42 and 126 mg/kg-day, respectively, while in females, the differences of up to 16% were noted (Daly, 1981). The NOAEL for body weight effects in this study was 14 mg/kg-day. Similarly to acetochlor, other short-term or subchronic studies in rats have reported body weight changes following alachlor administration in the diet. Body weight losses and/or reduced body weight gains have also been reported in developmental toxicity studies in which alachlor or acetochlor was administered by oral gavage (Rodwell and McMeekin, 1980; Brooker et al., 1989). These results establish body weight changes as a sensitive endpoint of exposure to the parent compounds. The observation of effects on food utilization as well as in gavage dosing studies, suggests that the effects observed in the chronic dietary studies are not solely due to decreased food palatability.

Acetochlor ESA: Like the parent chemical, subchronic dosing with acetochlor ESA also appears to affect body weight in rats. In rats administered the test material for 28 days in the diet, acetochlor ESA at doses up to 12,000 ppm (1579 and 1607 mg/kg-day for males and females, respectively) did not cause significant changes in body weight, body weight gain or food consumption (Lees, 2000a) (Table 3-1; Figures 2a-d present body weight and food consumption versus time). However, dietary exposure of acetochlor ESA for 90 days caused a 10% decrease in body weight that was not statistically significant, but there were statistically-significant reductions in food utilization (11% lower than controls) and food consumption (9% lower than controls) in males at 12,000 ppm (919 mg/kg-day) (Lees, 2000b) (Table 3-2; for changes in body and food consumption over time, see Figures 3a-d). Body weight and food consumption were only reduced by approximately 3%, while a statistically-significant decrease in food utilization of 8% in females was observed at the same high-dose level of 12,000 ppm (1073 mg/kg-day). These results suggest that males were more sensitive than females for body weight effects. In the 90-day study, cumulative body weight gains were not provided. However, based on the body weight data provided for Weeks 1 and 14, a rough estimate of 17% and 7% reductions in body weight gain can be estimated for the high dose males and females, respectively. The NOAEL for reductions in body weight gain and food utilization in this study was 225 mg/kg-day in males.

Acetochlor OXA: Acetochlor OXA produced a significant decrease (12%) in body weight in male rats and a 4% body weight decrease in females in a 28-day dietary study at 12,000 ppm (1468 mg/kg-day for males and 1507 mg/kg-day for females) (Williams, 2000a) (Table 3-3; for changes in body weight and food consumption, see Figures 4a-d) . A corresponding decrease of 18% for males and 8% for females in cumulative body weight gain can be estimated from the data, while food consumption was slightly reduced throughout the study for males, but not in females. Males appeared to be more sensitive to acetochlor OXA than females. The NOAEL for body weight changes in this study was 769 mg/kg-day for males. Williams (2000b) also reported significantly reduced body weights (when data are combined for the main and satellite groups), adjusted for initial bodyweight differences, in both sexes of rats at 12,000 ppm (955 and 1083 mg/kg-day for males and females, respectively) in a 90-dietary study (Table 3-4; for changes in body weight and food consumption, see Figures 5a-d). The reductions in bodyweight were maximally 7% for males and 5% for females by the end of the study. Adjusted body weights were also slightly decreased in males only at 3000 ppm (230 mg/kg-day), but the differences in the body weights attained statistical significance for 7 out of 13 weeks (when the data for the main and satellite phases were combined). Accompanying the body weight changes at 12,000 ppm was a decrease in food utilization of 11% in males and 8% in females. Changes in body weight gains were not reported, but based on data provided for Weeks 1 and 14, the apparent decrease in body weight gain was about 13% for males and 7% for females. The authors reported a NOAEL of 230 mg/kg-day (males) for body weight changes.

Alachlor ESA: A preliminary range-finding study in which rats were administered alachlor ESA in drinking water for 28 days reported a NOAEL of 656/749 mg/kg-day (M/F), with a LOAEL of 2217/2379 mg/kg-day (M/F), based on significant decreases in body weight, food consumption, and significant changes in water intake (Siglin, 1993) (Table 3-5; author did not present figures for body weight and food consumption versus time). A 90-day dietary study (Kirkpatrick, 2002) and a 91-day drinking water study (Siglin, 1993; Heydens et al., 1996) were available for alachlor ESA. No test article-related effects on body weight or body weights gains were observed in the dietary study at doses up to 12,000 ppm (788 and 926 mg/kg-day for males and females, respectively) (Table 3-7; for changes in body weight and food consumption with time, see figures 7a-d). The test material only caused transient effects in the 91-day drinking water study as indicated by significant decreases in body weight, weight gain, food consumption and water intake for both sexes of rats at 10,000 ppm (896 and 1108 mg/kg-day for male and females, respectively) during the first week of the study (Siglin, 1983; Heydens et al., 1996) (Table 3-6; authors did not present figures for body weight and food consumption versus time, but changes in body weight versus time based on the Siglin (1993) data are presented in Figures 7a & b). These decreases were accompanied by clinical signs, and clinical chemistry and hematology changes. Increases in both water intake and body weight gain were noted during the second week of the study, and the authors attributed the early adverse effects to initially decreased palatability of the drinking water solutions. At day 91, male body weights were no

longer statistically significant relative to controls. However, cumulative body weight gains remained decreased compared to controls at the high dose (10% in males and 14% in females) at the end of the study. The NOAEL in this study was 2000 ppm (157 mg/kg-day for males and 207 mg/kg-day for females), with a LOAEL of 10,000 ppm (896 mg/kg-day for males and 1108 mg/kg-day for females), based on decreases in body weights and food consumption in males and females and clinical signs in males. While the highest dose tested (788 and 926 mg/kg-day for males and females, respectively) in the dietary study did not affect body weights, body weight changes were observed in the drinking water study, with a NOAEL of 157 mg/kg-day for males and 207 mg/kg-day for females.

Alachlor OXA: No dose-related effects on body weight or body weight gain were observed in a 28-day dietary study with alachlor OXA at concentrations up to 20,000 ppm (1539 and 1595 mg/kg-day for males and females, respectively), although food consumption was significantly reduced at all doses tested without a dose-response relationship (Stout and Thake, 2000). Similarly, alachlor OXA did not cause significant body weight or weight gain changes in the rat in a 90-day dietary study (Lemen et al., 2000) at doses up to 835 and 1008 mg/kg-day for males and female rats, respectively (Table 3-9; authors did not present figures for body weight and food consumption versus time, but changes in body weight versus time are presented in Figures 8a & b).

Key Points for Consideration

Consistency of findings and strength in observed dose-response relationships. Decreased body weights or metrics related to body weight occurred following subchronic and chronic studies for both acetochlor and alachlor and subchronic studies for most of their sulfonic and oxanilic acids degradates. In most cases a dose-response trend was evident, even though in some cases the observed changes were not statistically significant. The data from key studies are shown in Table 3-1 to 3-9. For the degradates, the decrease in absolute body weight versus controls was of borderline biological significance – less than 10% in most cases. However, the studies were of less than chronic duration, and the use of a 10% benchmark response as a cut point for toxicological significance, as is often done for chronic studies, might be too stringent. Moreover, body weight gain decreases exceeded 10% in many cases.

Coherence with Biology Understanding. No data were identified that provided conclusive evidence for a specific underlying mode of action for the observed body weight changes. However, several underlying causes are plausible and some combination of effects is also possible. Such causes include: decreased body weight due to decreased food consumption (secondary to decreased palatability or general illness caused by systemic toxicity) and decreased nutrition or food utilization (decreased food absorption secondary to GI tract effects). Of these or other potential hypotheses, only the cause secondary to decreased palatability would typically

be considered as inappropriate as the critical effect basis for RfD development. Thus, key data that inform the likelihood of this cause of the observed body changes are noted:

- Body weight decreases were not limited to dietary studies; effects on body weight were also observed in the drinking water study for alachlor ESA.
- In general, body weight decreases were paralleled by decreases in food consumption. However, this was not always the case. For example, for the 90-day study with acetochlor OXA, adjusted body weight was decreased at the high doses for males and females, while food consumption decreased but the change was not statistically significant. For alachlor ESA, a significant decrease in female body weight was observed without a corresponding change in food consumption.
- In several studies, food utilization was significantly decreased in a dose-dependent manner. In some cases, body weight changes were not statistically significantly decreased but showed a dose-dependent decrease.
- No pair-feeding studies were available to assess growth after controlling directly for food consumption differences.
- In some cases, decreases in body weight were sustained or of greater magnitude at the longer durations, whereas decreased food consumption due to reduced palatability might be expected to occur early in the dosing period. Moreover, there was an apparent difference in response of male and female rats in some studies, which might not be expected if palatability were the underlying cause of the body weight body weight decreases.

3.2. Thyroid Effects

Proposed Mode of Action for Thyroid Effects for Acetochlor and Alachor

The U.S. EPA (2004, 1998) and the European Union (2005) have concluded that the parent chemicals, acetochlor and alachlor, cause a slight increase in thyroid follicular tumors in rats, but at doses at or above the Maximum Tolerated Dose (MTD) and through a mode of action that is generally considered to be of minimal relevance to humans. The parent compounds are known to disrupt thyroid-pituitary homeostasis (at levels at or near the MTD) secondary to clearance of thyroid hormones by increased hepatic uridine diphosphate glucuronosyl transferase (UDPGT). The effect is caused indirectly through the pituitary-thyroid axis by increasing the excretion of thyroxine (T4) by enhanced glucuronidation and subsequent biliary excretion (Heydens et al., 1996). The increased excretion reduces plasma T4 levels and a feedback mechanism leads to increased synthesis of thyroid stimulating hormone (TSH) by the pituitary. Increased levels of TSH are thought to be responsible for the chronic stimulation of the thyroid follicular cell epithelium and may result in follicular cell hypertrophy, hyperplasia, and ultimately neoplasia.

Increases in liver and thyroid weights accompany such a mechanism, as consistently observed during high levels of alachlor administration (Wilson et al., 1996).

Summary of Key Data for Parent Chemicals

Acetochlor: Hotz and Wilson (1996) evaluated liver weights, thyroid weights, serum concentrations of TSH, T4 and T3 and hepatic T4-UDPGT activity in male rats exposed to acetochlor in the dietary concentrations up to 5000 ppm (270.3 and 280.9 mg/kg-day for two separate experiments) for 14 to 90 days. Liver weight increases were observed from 28 to 90 days at 1750 ppm (91.9-100.6 mg/kg-day) and from 14 to 90 days at 5000 ppm (270.3-280.9 mg/kg-day). Thyroid weights were increased at 14 days in animals fed 1750 ppm (91.9-100.6 mg/kg-day) and at 14 and 28 days in animals fed 5000 ppm (270.3-280.9 mg/kg-day), while relative thyroid weight were significantly different from controls at 14 and 28 days at 1750 ppm (91.9-100.6 mg/kg-day) and at 14 and 90 days at 5000 ppm (270.3-280.9 mg/kg-day). Total hepatic T4-UDPGT and circulating levels of serum TSH were significantly increased in dose- and duration-dependent manner. The authors concluded that the results of these studies provide evidence that an indirect, hormonally-mediated process may be responsible for the acetochlor-induced thyroid follicular cell tumors. The LOAEL of 100.6 mg/kg-day in one experiment was the lowest dose tested, while in the second experiment, the NOAEL was 10.4 mg/kg-day, with a LOAEL of 91.9 mg/kg-day for liver and thyroid effects.

Alachlor: Liver weights, thyroid weights, hepatic UDPGT activity, and circulating levels of TSH were also significantly increased in animals administered alachlor at a dose of 126 mg/kg-day via the diet for up to 120 days (Hotz et al., 1993). These increases were seen as early as 7 to 14 days after administration and persisted throughout the observation period. Circulating levels of T4 in alachlor treated animals were significantly decreased compared to control animals at 7 days, but had returned to control levels at 28 days. Alachlor had a significant effect on circulating levels of T3 at all time points except 28 days.

Summary of Key Data for Degradates

The potential of the degradates to elicit thyroid effects have been evaluated and presented in Tables 3-1 3-2, 3-3, 3-4, 3-7, and 3-9.

Acetochlor ESA: In a 28-day study with acetochlor ESA (Lees, 2000a), thyroid weights were unaffected. There were dose-related increases in free T3 levels (2-28%, relative to controls) and TSH levels (15 – 61%) in males but these increases did not reach statistical significance at any dose level up to 12,000 ppm (1579/1607 mg/kg-day for males and females, respectively) (Table

3-1). Plasma levels of free T4 levels did not change in a dose-dependent manner, although T4-UDPGT activity was statistically significantly increased in both males and females at the high dose. No dose-related changes in liver or thyroid weights or histopathology were observed in the 90-day dietary study at doses up to 919/1073 mg/kg-day (M/F) (Lees, 2000b). Thyroid hormones were not evaluated in this study.

Acetochlor OXA: In a 28-dietary study in rats (Williams, 2000a) (Table 3-3), no liver weight changes were observed at concentrations up to 12,000 ppm (1468 and 1507 mg/kg-day for males and females, respectively). A slight but statistically significant ($p<0.05$) increase was noted in absolute thyroid weights in males at 767 and 1468 mg/kg-day (and in "adjusted" thyroid weights – covariate with terminal body weight – at all dose levels) but there was no clear dose-response relationship and thyroid-to-body weight ratios were not affected. In addition, the thyroid weights from the treated males in this study were lower than those of the control animals in the concurrent 28-day rat study with acetochlor ESA (average control thyroid weights in the OXA study was about half that in the ESA study, 0.010 ± 0.002 g vs. 0.019 ± 0.006 g). Furthermore, no thyroid weight changes were noted in females and there were no correlative histopathology findings. Therefore, the differences in male thyroid weights were not considered to be treatment related. Total and free plasma T3 levels decreased (24-35%) in males, but not in females, at the high dose. TSH levels were reduced at the high dose (37-54%), but without statistical significance, in either sex. However, the direction of this change (decrease) in TSH levels is not consistent with increased thyroid growth stimulation. A statistically significant decrease (37-41%) in hepatic T4-UDPGT activity was observed in females and an increase of 3-18% in males without statistical significance, at the high dose. The direction of this change (decrease) in the females is also not consistent with increased thyroid growth stimulation. These results suggest possible slight or equivocal changes in some thyroid hormone parameters at the high dose, but without any correlative treatment-related effects on thyroid weights or histopathology, the toxicological significance of these changes is not clear. In a 90-day dietary study (Williams, 2000b), liver weight was decreased by 9% in the high-dose males (12,000 ppm; 955 and 1083 mg/kg-day for males and females, respectively), with no significant change in females, and no liver histopathology. There were no consistent dose-related or significant changes in thyroid weight or effects on thyroid histopathology in either sex at any dose level. Thyroid hormones were not evaluated in this study. Based on the results, the highest doses tested of 1468/1507 mg/kg-day (M/F) in the 28-day dietary study and 955/1083 mg/kg-day (M/F) in the 90-day dietary study were regarded as the dose levels, the NOAEL, at which no effects on thyroid were observed.

Alachlor ESA: No 28-day or short-term studies were available that evaluated thyroid parameters (weight or hormones) for alachlor ESA. Two subchronic studies were available for alachlor ESA; the 91-day drinking water study (Siglin, 1993; Heydens et al., 1996) (Table 3-6) and the 90-dietary study (Kirkpatrick, 2002) (Table 3-7). Neither of these subchronic studies indicates

that the test article was associated with any significant changes in liver or thyroid/parathyroid weights or histopathology, while thyroid hormones levels were not measured. The highest doses tested in these 90-day studies were 896/1108 mg/kg-day (M/F, drinking water) (Siglin, 1993; Heydens et al., 1996) and 788/926 mg/kg-day (M/F, dietary) (Kirkpatrick, 2000).

Alachlor OXA: A 28-day study for alachlor OXA is available, but thyroid effects were not evaluated. A 90-day dietary study (Lemen et al., 2000) (Table 3-9) reported a slight increase (9%) in absolute thyroid weight in males at the high dose of 835/1008 mg/kg-day (M/F), but a decrease of 16% in absolute thyroid weight in females at the high dose of 1073 mg/kg-day. There were no changes in absolute liver weight, although a slight but significant reduction (7%) in relative liver was observed in females only at the high dose. There were no changes in liver or thyroid histopathology. Thyroid hormones were not evaluated in this 90-day study.

Key Points for Consideration for the Thyroid Findings

Relative Potency of Parents for Degradates. The data appear to support the ability of both acetochlor and alachlor to induce thyroid stimulation, primarily at dose levels at or above the MTD. A mode of action hypotheses has been proposed and the data for both parent compounds are consistent with this mode of action. A key step in the proposed MOA is the induction of (UDPGT) in the liver (with a resulting increase in T4 excretion). The available data for these degradates show at most weak effects related to the thyroid. Key issues for consideration include:

- Information on thyroid hormone levels is available for 28-day studies only for acetochlor degradates. The observed patterns of changes do not appear to be consistent with the expected biology (i.e., T4 decrease, T3 decrease, TSH increase, and thyroid and liver weight increases). Does the lack of consistency with the expected pattern of changes suggest that the observed effects are not treatment-related or not toxicologically significant?
- Data for the parent molecules indicate that both acetochlor and alachlor affect thyroid parameters. Data on hormone levels are only available for acetochlor ESA and acetochlor OXA. Are these data (along with thyroid weight and histopathology data for the two alachlor degradates) sufficient to draw conclusions regarding the alachlor degradates?
- Is the underlying mechanism for the induction of UDPGT known? In many cases, such liver enzymes are inducible by their own substrates. Do the metabolism data support or refute the hypothesis that the degradates lack significant effects on thyroid hormonal activity because UDGPT lacks affinity for these polar degradates and is not induced by them? Is the absence of a robust effect for the degradates adequately explained by lower oral bioavailability than the parent molecules? Are there other MOA hypotheses that are

consistent with the apparent difference in thyroid effects between the parents and degradates?

3.3. Reproductive and Developmental Toxicity

Summary of the Data

Three two-generation reproductive toxicity studies exist for acetochlor (MRID 00131391; Willoughby, 1989; 45357503) and one for alachlor (Schroeder et al., 1981). Two of the studies for acetochlor indicated that the test article was not a reproductive toxicant. In one of these studies, a reproductive NOAEL of 5000 ppm (324.5 mg/kg-day in males, 441.5 mg/kg-day in females) was reported (MRID 00131391). In the second study, the reproductive NOAEL was 1750 ppm (123.8 mg/kg-day in males, 157.4 mg/kg-day in females). The third acetochlor reproductive toxicity study reported a LOAEL of 1750 ppm (196.4 mg/kg-day in F1 males; 215.9 mg/kg-day in F1 females), based on decreased number of implantations (MRID 45357503). The reproductive toxicity NOAEL in this study was 600 ppm (65.6 mg/kg-day in F1 males; 70.9 mg/kg-day in F1 females). The parental NOAEL for the acetochlor studies were 500 ppm (30.8 mg/kg-day in males, 46.2 mg/kg-day in females), 175 ppm (12.6 mg/kg-day in males, 15.5 mg/kg-day in females), and 200 ppm (21.2 mg/kg-day in F1 males; 22.4 mg/kg-day in F1 females), respectively. For alachlor, the NOAEL for reproductive effects was ≥30 mg/kg-day, the highest dose test. The parental/offspring systemic toxicity LOAEL was 30 mg/kg-day based on kidney effects, with a NOAEL of 10 mg/kg-day. No reproductive toxicity studies have been conducted for the acetanilide degradates.

A developmental toxicity study in rats with acetochlor (Brooker et al., 1989) reported maternal toxicity (two deaths following marked weight loss and adverse signs of reaction to treatment, a marked increase in water consumption, reduction in food intake, and a reduction in body weight gain) as well as fetal toxicity (decreased fetal weight and increased variant sternebrae) at 600 mg/kg-day, with a NOAEL of 150 mg/kg-day for maternal and fetal toxicity. Rodwell (1980) reported maternal toxicity (decreases in mean body weight gain and adjusted body weight) accompanied by a non-statistically significant decrease in fetal weight when rats were administered acetochlor at 400 mg/kg-day. The maternal NOAEL in this study was 200 mg/kg-day. Acetochlor was not teratogenic in either of the rat developmental toxicity studies and neither alachlor nor acetochlor produced developmental toxicity in rabbits, even at maternally toxic dose levels.

In a developmental toxicity study in rats (Tasker and Rodwell, 1980), alachlor produced maternal toxicity (mortality, clinical signs of toxicity and decreased weight gain) and developmental toxicity (increased resorptions and decreased litter size) at 400 mg/kg-day, without any teratogenic effects. The maternal and developmental NOAEL in this study was 150 mg/kg-day.

The available studies for the parent compounds indicate that the NOAELs for rat developmental toxicity were 150-200 mg/kg-day. These levels exceed the dose levels at which the parent compounds caused maternal body weight changes, for example.

A developmental toxicity study available for acetochlor OXA (Holson, 2000) indicated that the test material caused maternal mortality in two of 25 rats at a dose of 1000 mg/kg-day (the LOAEL), with a NOAEL for maternal toxicity as 500 mg/kg-day. No developmental toxicity was observed, indicating a developmental NOAEL of ≥ 1000 mg/kg-day.

An oral gavage developmental toxicity study available for alachlor ESA reported increased incidence of rales at 1000 mg/kg-day (Holson, 1995; Heydens et al., 1996). The authors considered the incidence to be treatment-related. However, since no other signs of toxicity (no definitive evidence, e.g., body weight effects) of maternal toxicity were observed, the authors (and EPA) did not regard this effect to be a definitive sign of a systemic toxic effect, but likely due to local effects from oral gavage of a large volume of ESA. No developmental toxicity was observed. Therefore, both the maternal and developmental NOAELs in this study were 1000 mg/kg-day (adjusted to 900 mg/kg-day based on 90% purity of the test material).

The data available indicate that the NOAEL for developmental toxicity is 5 to 6 times higher for acetochlor OXA than that for acetochlor, while the NOAEL for maternal toxicity is at least 6 times higher for alachlor ESA than that for alachlor. Overall, developmental NOAELs were at least 5 to 6 times higher for the degradates compared to the parent chemicals.

Key Points for Consideration

Reproductive Toxicity as a Key Data Gap. No reproductive toxicity studies were conducted for any of the degradates. For three reproductive studies available for acetochlor, only one reported evidence of reproductive toxicity, while the remaining two and the reproductive toxicity study for alachlor reported no effect on reproductive endpoints at doses lower than those that caused systemic toxicity. No effects on male or female reproductive organs were observed in the subchronic studies for the degradates. In the context of hazard characterization and developing testing requirements such findings are often adequate to fill the data requirement for this endpoint. Are such data sufficient to address reproductive toxicity for the acetanilide degradates for developing RfDs?

Developmental Toxicity as a Key Data Gap. The parent chemicals induce developmental effects in rats only at maternally-toxic doses and are not teratogenic. They did not induce developmental toxicity in rabbits. Rat developmental toxicity studies have been completed for two of the degradates (acetochlor OXA and alachlor ESA), with results showing no developmental toxicity at 1000 mg/kg-day (HDT). Are these data sufficient to address the absence of such studies in the other degradates and in a second species for each degradate? Are there MOA data that support developmental toxicity as a potential critical effect?

3.4. Rat Hematology and Clinical Chemistry Parameters

Summary of the Data for Parent Chemicals

Acetochlor: The EU review for acetochlor identified alterations in hematology and clinical chemistry parameters in a 28-day dietary study in rats (Vol. 3 Annex B Ch. 6 - Tox & Metabolism_March_2005.pdf) at doses of 132 mg/kg-day and above. Male rats treated with ≥132 mg/kg-day of acetochlor had decreased prothrombin time. At the next higher dose of 519 mg/kg-day, a small, but statistically significant, decreased packed cell volume (mean cell volume, MCV) was also noted in male rats. At the highest dose tested (1012 mg/kg-day in males and 1018 mg/kg-day in females) slightly decreased hemoglobin (Hb), MCV and mean cell hemoglobin (MCH) were noted in both sexes.

Similarly, in a 90-day dietary study, slight but statistically significant increases were reported for Hb levels (3%) and mean cell hemoglobin concentration (MCHC) (3%) in males and RBC counts (3%) in females at 2000 ppm (176.5 mg/kg-day, average for M&F) (Broadmeadow, 1986). There were no treatment-related alterations in clinical chemistry parameters that are of toxicological significance in this study. In a separate 91-day dietary study, Ahmed (1980) reported that acetochlor had no effect on hemoglobin levels, RBCs, hematocrit, or clinical chemistry parameters attributable to treatment at dose levels up to 6000 ppm (450/530 mg/kg-day, M/F). Although statistically significant increases in Hb were seen in females in the top dose group (530 mg/kg-day), this author also indicated that the hematology and clinical chemistry parameters in all groups were outside the testing laboratory's normal biological ranges. As such, those changes were not considered to be compound-related in the absence of an underlying histopathology.

Alachlor: Reviews available for alachlor have not identified alteration in hematology and clinical chemistry parameters in 28- and 90-day dietary studies in rats (U.S. EPA, 1998, 2007). However, the USEPA (2007) considers the RBC to be a toxicological target, based on hemosiderosis and anemia observed in dogs after one year of treatment.

Summary of Key Data for Degradates

Acetochlor ESA: In a 28-day dietary study, Lees (2000a) (Table 3-1) reported statistically significant decreases in MCV, and MCH in males and females at 6000 ppm (767/762 mg/kg-day, M/F), but the changes were only seen in males at 12,000 ppm (1579 mg/kg-day). Eosinophil counts in males were also increased at 12,000 ppm. Because all of these changes in hematology parameters were small and exhibited no evidence of a dose-related trend, the changes were not considered to be of any biological or toxicological significance. In clinical chemistry, no changes were observed that are of biological or toxicological significance.

In a 90-day dietary study, Lees (2000b) (Table 3-2) reported minimal increases in hemoglobin and RBC counts and minimal decreases in MCV in females only at 12000 ppm (1073 mg/kg-day), while clinical chemistry changes were limited to a minimal increase in total bilirubin for

males at 12000 ppm (919 mg/kg-day). These minimal changes in hematology and clinical chemistry parameters were not considered to be of toxicological significance.

Acetochlor OXA: In a 28-day range finding experiment, Williams (2000a) (Table 3-3) observed a statistically significant increase in eosinophil count and a statistically significant decrease in platelet count in males at the highest dose level of 12,000 ppm (1468 mg/kg-day). A statistically significant decrease in MCV in males was also seen in mid-dose males (6000 ppm), but in the absence of a dose-response and of any other alteration in RBC parameters this small change appears to be unrelated to treatment. With blood clinical chemistry parameters, several parameters (glucose levels, alanine aminotransferase (ALT) activity, creatinine kinase activity, albumin levels, total protein, total bilirubin, and alkaline phosphatase activity) were altered at lower dose levels, but not at the highest dose level; hence, these changes were not of toxicological significance.

In a 90-day dietary study, Williams (2000b) (Table 3-4) reported minimal but statistically significant decreases in MCV (~3%) and MCH (~3%) in males at the highest dose tested, 12,000 ppm (955 mg/kg-day). These increases lack a dose response or are minor; hence not considered toxicologically significant.

Alachlor ESA: No 28-day dietary study was available for this degradate. In a 90-day dietary study, Kirkpatrick (2002) (Table 3-7) observed no test article-related effects on hematology at dose levels up to 12000 ppm (788/926 mg/kg-day, M/F), but mean absolute and percent reticulocytes were statistically significantly increased in males receiving 6000 ppm (389 mg/kg-day) and 12,000 ppm, when compared to controls. However, the reticulocyte counts are often highly variable and there were no correlating changes in other hematology parameters (RBCs and indices), the response was not dose-related, and there were no related microscopic findings; hence, these increases were not considered to be test article-related.

In a 28-day range-finding experiment, rats received 700, 2000, 7000, or 20000 ppm alachlor ESA in drinking water (Siglin, 1993); however, hematology and clinical chemistry were not performed. In a 91-day drinking water study, alachlor ESA caused several statistically significant hematological effects. In males, these changes included decreased hemoglobin, hematocrit, and MCH at 10,000 ppm (896 mg/kg-day), and decreased RBC counts at 2000 ppm (157 mg/kg-day) and 10,000 ppm (Siglin, 1993; Heydens et al., 1996) (Table 3-6). The changes observed in these parameters were small (2-5%) and did not correlate with other hematological or histopathological changes. In addition, the authors indicated that although each measured parameter was statistically different, the respective control value exceeded the normalized historical control range for the strain and age of the male rats used in this study. The only statistically significant differences in hematology data for females were limited to an increase in leukocyte counts at 10,000 ppm, but the difference did not follow any apparent dose-response relationship and was, therefore, not considered biologically meaningful. In clinical chemistry, a dose-dependent decrease in glucose, total bilirubin, and an increase in phosphorus was reported in males at 10,000 ppm, but these did not correlate with any abnormal histopathology. In addition, albumin levels were statistically decreased in males at 2000 ppm (2.7%) and 10,000 ppm (4.0%). These changes were small and there was no real decrement over a wide range of doses. Therefore, the changes in albumin levels were not considered biologically meaningful.

Alachlor OXA: In a 28-day dietary study, Stout and Thake (2000) (Table 3-8) observed statistically significant differences in hematology that occurred only at 20,000 ppm (1539/1595 mg/kg-day, M/F). These changes in males included increased numbers of lymphocytes, basophils and large unstained cells (154%, 282%, and 174% of controls respectively). Because individual variations often occur in these parameters and because of the small number of animals used in this study as well as the absence of similar changes in females, the authors did not consider the changes to be toxicologically significant. Decreases in RBC counts (91% of controls) and increases in MCV (105% of controls) in males at 20,000 ppm and decreases in MCH (95% of controls) in females were also statistically significant but because these changes were small and occurred in the absence of any corroborative changes for any of these changes in blood cells, the increases or decreases in these parameters were considered to be of no toxicological significance. The only blood chemistry parameter that was significantly affected was creatinine (133% of controls) in females at 1000 ppm. But this change did not occur at higher dose levels and, therefore, of no toxicological relevance. In a 90-day dietary study, Lemen et al. (2000) (Table 3-9) reported only statistical differences in MCHC in females at all dose levels, but the differences were minimal and not considered treatment related. For clinical chemistry, a small, but not statistically significant increase in aspartate aminotransferase (AST) and ALT in females at the high dose level of 13,000 ppm (1008 mg/kg-day). But due to the small magnitude of change and/or the lack of dose-response, the changes were not considered biologically and toxicologically relevant.

Key Points for Consideration

The parent chemicals do not appear to significantly alter hematological and/or clinical chemistry parameters in any of the available rat subchronic studies. In short-term or subchronic dietary studies where the degradates appear to alter these parameters, the changes were very small in magnitude and occurred generally at high dose-levels and in the absence of changes in other hematology or clinical chemistry parameters, morphological or histological changes. In the subchronic drinking water study with alachlor ESA, several statistically significant hematological and clinical chemistry effects, primarily in males, were observed. Like the 90-day dietary studies, the changes observed in the drinking water study were also small in magnitude (2-5%) and were also judged to be of little or no biological or toxicological significance.

- Are these data robust to adequately evaluate and draw a conclusion regarding the potential of any of the degradates to produce hematological and/or clinical chemistry alterations that are of biological and toxicological significance?
- Are there data that suggest concern regarding this endpoint for the degredates?
- If data are not sufficient to draw any conclusion, what other toxicity studies may be recommended?

3.5. Comparative Toxicity and Toxicokinetics

A critical consideration in this data evaluation relates to the degree to which data for the parent molecules can be used to inform the derivation of risk assessment values for the degradates. If the database for the degradates is judged too limited to support risk value development directly, then data for the parent molecules might be considered as a substitute if the data support such a bridging approach. Alternatively if the data for the degradates are judged adequate to support derivation of risk values, the data for parents and the other related degradates might be used to fill data gaps or provide MOA insights that affect selection of the point of departure or uncertainty factor approaches for each degradate. This section provides information distilled from the overall database for the parent chemicals and degradates on comparative toxicity and toxicokinetics that is meant to aid in evaluating the degree to which bridging approaches can be used for this assessment.

3.5.1. Comparative Toxicity

Summary of Key Data on Comparative Toxicity

Table 4 compares the dose levels at which potential treatment-related effects were observed for the parent compounds and their degradates among studies of similar design. Such comparisons are intended to provide information on the degree to which the degradates cause a similar array of effects as those caused by the parent chemical under similar study conditions and to provide insights into relative potencies among the compounds.

Body Weight. Body weight changes have been reported in subchronic and short-term toxicity studies for both parents and degradates. In a 28-day dietary study, acetochlor caused a significant decrease in body weight gain at a dose of 132 mg/kg-day in male rats, with a NOAEL of 68 mg/kg-day (Broadmeadow, 1985). In similar 28-day dietary studies, acetochlor ESA did not produce any effects on body weight in rats at the highest dose tested of 1579/1607 mg/kg-day (males/females) (Lees, 2000a), while for acetochlor OXA, a NOAEL of 769 mg/kg-day and a LOAEL of 1468 mg/kg-day were identified for decreased body weight (Williams, 2000a). In these 28-day dietary studies, the dose producing body weight changes and the NOAELs were 11 times higher for acetochlor OXA than that of acetochlor, while the dose of acetochlor ESA that produced no effect on body weight was about 12 times higher than the NOAEL for body weight effects for acetochlor.

In a 13-week dietary study of acetochlor in rats, a significant decrease in body weight gain was reported at 161/192 mg/kg-day (M/F), with a NOAEL of 16/19 mg/kg-day (M/F) (Broadmeadow, 1986). Acetochlor ESA caused a 10% decrease in mean body weight in males at 919 mg/kg-day, with a NOAEL of 225 mg/kg-day (Lees, 2000b). Acetochlor OXA also

caused decreased body weight in male rats at 955 mg/kg-day, with a NOAEL of 230 mg/kg-day (Williams, 2000b). The dose producing body weight changes was approximately 6 times higher and the NOAELs about 14 times higher for both acetochlor degradates than for the parent compound.

For alachlor, Hotz et al. (1993) reported that this parent chemical caused no changes in terminal body weights in male rats (the only sex tested) at a dose of 126 mg/kg-day (the only dose tested). No comparable 28-day dietary studies were identified that evaluated body weight changes for alachlor ESA, but a NOAEL of 656/749 mg/kg-day (M/F) and a LOAEL of 2217/2378 mg/kg-day (M/F) were estimated for alachlor ESA based on body weight effects in rats in a 28-day drinking water study (Siglin, 1993). Alachlor OXA administered in the diet to rats did not cause any body weight changes at the highest dose tested of 1539/1595 mg/kg-day (M/F) (Stout and Thake, 2000). Based on the available data, the dose at which alachlor OXA produced no effects on body weights in the 28-day dietary study was approximately 12 times higher than that for the parent, alachlor.

Alachlor also caused a progressive decrease in body weight gain in both sexes of rat (approximately 14% at the end of the study) at 139/153 mg/kg-day (M/F) in a 90-day dietary study (Wolf, 1966). A NOAEL of 15 mg/kg-day (average for both sexes) was reported in this study. In a drinking water study, alachlor ESA caused decreased total body weight gain (10% in males and 14% in females) at 896/1108 mg/kg-day (M/F), with a NOAEL of 157/207 mg/kg-day (M/F) (Siglin, 1993; Heydens et al., 1996). However, this study was confounded by apparent water palatability problems, particularly during the early part of the study. No treatment-related effects on body weight were noted in a 90-day dietary feeding study with alachlor ESA at dose levels up to 788/926 mg/kg-day (M/F) (HDT) (Kirkpatrick, 2002). Similarly, alachlor OXA did not elicit any treatment-related body weight changes in rats in a dietary study at doses up to 835/1008 mg/kg-day (M/F). For both 90-day dietary studies, the average NOAELs (for males and females) for the degradates were approximately 857 and 922 mg/kg-day for ESA and OXA, respectively, which are about 60 times higher than the NOAEL for alachlor.

Overall, the available data demonstrate a consistent pattern of effects on body weight changes with parent chemicals affecting body weight changes at lower doses than their acetanilide degradates. While decreased food consumption was a relatively consistent finding among the chemicals, the underlying MOA for decreased body weights is unclear, and relative impacts of different mechanisms was not readily apparent from the available data. However, the degradates are clearly much less potent in repeat-dose studies in rats, with LOAELs that are at least 6 times higher than those of the parent compounds and NOAELs that range from 14 to 60 times higher for the degradates compared to the parent chemicals.

Liver Toxicity. Available short-term and subchronic dietary studies with the acetanilide degradates reported small changes in liver weights (relative or absolute weights but not both) that were of very marginal toxicological relevance and occurred only at doses much higher than those

observed for the parent chemicals. The minor changes in the liver weights were not accompanied by toxicologically relevant changes in clinical chemistry or histopathology.

In a 28-day dietary study, acetochlor caused increased liver weight at 100.6 mg/kg-day (the lowest dose tested) in one study and at 91.9 mg/kg-day, with a NOAEL of 10.4 mg/kg-day (Hotz and Wilson, 1996). In another 28-dietary study (Broadmeadow, 1985, as cited in European Union, 2005), a significant increase in relative liver weight was also reported in rats at 267/279 mg/kg-day (M/F), with a NOAEL of 132/139 mg/kg-day (M/F). In the 28-day dietary studies for the degradates, the highest doses tested for acetochlor ESA (1579/1607 mg/kg-day, M/F) (Lees, 2000a) and acetochlor OXA (1468/1507 mg/kg-day, M/F) (Williams, 2000a) produced no significant changes in liver weights. These dose levels are, therefore, regarded as the free-standing NOAELs for changes in liver weights. For the 28-day dietary studies, the doses that produced no effects on liver weights were 140 to 150 times higher for the acetochlor degradates than for the parent chemical.

In a 90-day dietary study, acetochlor caused small but significant increases in relative liver weight in rats at 161/192 mg/kg-day (M/F; average, 176.5 mg/kg-day), with a NOAEL of 16/19 mg/kg-day (M/F; average, 17.5 mg/kg-day) (Broadmeadow, 1986). The highest dose tested in the 90-day dietary study for acetochlor ESA (919/1073 mg/kg-day, M/F) caused no significant changes in liver weights. Although acetochlor OXA caused a significant decrease (9.2%) in liver weight at 12,000 ppm (955 mg/kg-day) in males, this decrease occurred without any accompanying histopathological changes in the liver and the direction of the change was not consistent with that of the parent chemical and is of unclear toxicological significance. Therefore, the highest doses tested for these degradates are regarded as free-standing NOAELs for liver effects. For these 90-day dietary studies, the doses that caused no adverse effects on liver weights were approximately 50 to 60 times higher for the acetochlor degradates than that for the parent chemical.

For alachlor, a special study conducted to evaluate its potential to cause changes in specific biochemical endpoints relevant to thyroid function indicated that alachlor at a dose of 126 mg/kg-day (the only dose tested) caused a significant increase in absolute liver weights (14% over controls) in male rats (the only sex studied) when these animals were exposed in the diet for 28 days (Hotz et al., 1993). In the 28-day dietary study available for the alachlor degradates, alachlor OXA at the highest dose tested (1539/1595 mg/kg-day, M/F) did not produce any adverse effects on liver weights (Stout and Thake, 2000). This dose is therefore regarded as the free-standing NOAEL for liver effects. The 28-day drinking water study with alachlor ESA did not report on liver weight effects (Siglin, 1993). Although no NOAEL for effects on liver weights was identified for alachlor, the dose producing no effects on liver weight in the 28-day dietary study for alachlor OXA is 12 times higher than the dose that produced such effects for the parent chemical.

In a 90-day dietary study, alachlor produced increased relative liver weights at a LOAEL of 139/153 mg/kg-day (M/F; average, 146 mg/kg-day), with a NOAEL of 15 mg/kg-day (average for M&F) (Wolf, 1966). In this study, there was an increase in hepatic UDPGT activity (when adjusted for liver weight and expressed as estimated total activity/liver weight). For the degradates, the highest dose tested in 90-day dietary studies with alachlor ESA (788/926 mg/kg-day, M/F) (Kirkpatrick 2002), and alachlor OXA (835/1008 mg/kg-day, M/F) (Lemen et al., 2000) produced no adverse effects on liver weight and are, therefore, regarded as free-standing NOAELs for changes in liver weights. In a 91-day drinking water study, alachlor ESA also did not adversely affect liver weights at the highest dose level of 896/1108 mg/kg-day, (M/F) (Siglin, 1993; Heydens et al., 1996). For the 90-day dietary studies, the doses that caused no effects on liver weights were approximately 60 times higher for the alachlor degradates than the NOAEL for changes in liver weight for the parent compound.

For alachlor ESA, the 28-day (Siglin, 1993) and the 90-day (Siglin, 1993; Heydens et al., 1996) drinking water studies did not report any effects on the liver weights of the rats. For this degradate, small changes in several clinical chemistry parameters were observed in a 90-day drinking water study, with no corresponding changes in liver weight or histopathology. Similar effects were not observed in the 90-day dietary study.

Differences in hepatic metabolism of the parent versus the degradates (which may be a key activation event in the MOA for liver effects of the parent chemicals) and differences in the nature of the observed liver changes indicate that the liver effects may not be suitable for bridging across the chemicals. However, differences in oral bioavailability, rather than underlying differences in toxic mechanism, might also be a key driver for the observed greater degree of liver effects from the parent chemicals than the degradates. If differences in bioavailability are the underlying cause of the observed differences in liver effects, then the use of data for the parents with appropriate dosimetric adjustment (for differences in liver dose) might be considered.

Thyroid Effects. The available data suggest that the degradates did not produce any statistically or toxicologically significant effects on thyroid weights or hormone levels at the highest doses tested.

For acetochlor, the lowest NOAEL reported for effects on thyroid weight was 10.4 mg/kg-day, with a LOAEL of 91.9 mg/kg-day (Hotz and Wilson, 1996) in a 28-day dietary study. In the 28-day dietary studies for the degradates, the highest doses tested for acetochlor ESA (1579/1607 mg/kg-day, M/F) (Lees, 2000a) and acetochlor OXA (1468/1507 mg/kg-day, M/F) (Williams, 2000a) produced no toxicologically relevant adverse effects on thyroid weight. Compared to the NOAEL of 10.4 mg/kg-day for changes in thyroid weight for acetochlor, the NOAELs for this endpoint for the acetochlor degradates are approximately 140 to 150 times higher than that for the parent chemical.

Hotz and Wilson (1996) also reported a NOAEL of 10.4 mg/kg-day and a LOAEL of 91.9 mg/kg-day for thyroid weight changes in a 90-day dietary study for acetochlor. The available 90-day dietary studies for the acetochlor degradates reported no treatment-related effects on thyroid weights or histopathology (hormone levels were not measured) at the highest dose levels of 919/1073 mg/kg-day (M/F) (Lees, 2000b) for acetochlor ESA and 955/1083 mg/kg-day (M/F) for acetochlor OXA (Williams, 2000b). For acetochlor degradates, the doses producing no toxicologically relevant changes in thyroid weights or histopathology were approximately 100 times higher than the NOAEL for changes in thyroid weights or histopathology for acetochlor.

For alachlor, no NOAEL was identified for changes in thyroid weights, although a LOAEL of 126 mg/kg-day was reported for this endpoint (Hotz et al., 1993) in a 28-day dietary study. No data for this endpoint was available for the alachlor degradates, and this precludes potency evaluation of it and its OXA degradate.

No NOAEL was also identified for changes in thyroid weight for alachlor in a 90-day dietary study. However, Hotz et al. (1993) reported that alachlor caused significant increases in thyroid weights at a dose of 126 mg/kg-day in a 90-day dietary study. The available 90-day dietary studies for the alachlor degradates reported no treatment-related effects on thyroid weights or histopathology at the highest doses tested of 788/926 mg/kg-day (M/F) for alachlor ESA (Kirkpatrick, 2000), and 835/1008 mg/kg-day (M/F) for alachlor OXA (Lemen et al., 2000). Although no NOAEL for effects on thyroid weights was available for alachlor, the doses of the alachlor degradates that produced no effects on thyroid weights and/or caused no histopathological lesions were approximately 7 times higher than the dose (LOAEL) of 126 mg/kg-day of alachlor that caused significant increase in thyroid weights (Hotz et al., 1993). The 90-drinking water study also observed no changes in thyroid weights at doses up to 896/1108 mg/kg-day (M/F) (Siglin, 1993; Heydens et al., 1996).

For thyroid hormone effects, the only data available for the degradates indicate that acetochlor ESA in a 28-day dietary study produced marginal changes in thyroid hormones at a dose of 1579/1607 mg/kg-day (M/F) (Lees, 2000a) that is 17 times higher than that for acetochlor (91.9 mg/kg-day; Hotz and Wilson, 1996), while the NOAEL (767/762 mg/kg-day, M/F) was at least 74 times higher for this degradate than that for acetochlor. The thyroid hormone changes observed (e.g., decrease in TSH levels and significant decrease in T4-UDPGT activity for acetochlor OXA) were not consistent with the expected pattern of changes that are caused by the parent chemicals. As a result, the use of the parent data for bridging to the degradates might not be appropriate. As noted above, however, differences in the observed effects might also reflect differences in oral bioavailability rather than underlying MOA differences, which would suggest it is appropriate to use such data for hazard characterization and bridging purposes (after dosimetric adjustments).

Developmental Toxicity. The parent chemicals have a full complement of reproductive and developmental toxicity studies. Developmental toxicity studies are available only for acetochlor

OXA and alachlor ESA. The comparable studies across the parent chemicals and degradates demonstrate that neither the parents nor the degradates cause developmental effects at lower than maternally-toxic doses, nor are either parents or degradates teratogens.

3.5.2. Conparative Metabolism

Summary of Key Data on Comparative Metabolism

The structures of the parent compounds and the degradates are presented in Figure 1.

The metabolism of the parent compounds have been extensively reviewed (U.S. EPA, 1998, 2006, 2007; European Union, 2005). All 4 degradates have been identified as major aerobic environmental (soil) metabolites that are not formed in animals, but found in trace amounts in crops likely due to uptake from the soil. Toxicokinetic studies (summarized in Table 5) available in the rat for the parent compounds demonstrate near complete absorption and bi-phasic elimination kinetics for the parent compounds. Greater than 70% of the administered acetochlor dose was eliminated by day 2, with the elimination being biphasic (rapid phase ½-life of 5.4-10.4 hours, slow phase of 128.6-284.4 hours for a 10 mg/kg dose) (Carr et al., 1983). In other studies (Hawkins et al., 1987a,b,c; Hawkins et al., 1989; Jones, 1990), 92-96% of the acetochlor dose was eliminated by day 5 (½-life of elimination 20-30 hours), primarily in the urine (about 60% by 24 hours). About 89% of alachlor was eliminated in 10 days, with the elimination also being biphasic (initial rapid phase had a ½-life of 0.2 to 10.6 hours, and a slow ½-life of 5 to 16 days for a 7 or 700 mg/kg dose (Wilson et al., 1983). Other studies with alachlor indicate that between 30 to 47% of the dose was excreted in urine and 41 to 45% excreted in feces at single oral doses of 7, 70, or 700 mg/kg (Wilson and Hall, 1986; Howe et al., 1986c; Stoltz, 1986; Howe and Chott, 1986d). Both alachlor and acetochlor are widely distributed in tissues. A whole body autoradiography (WBA) study in Sprague-Dawley, Fischer 344, and Long-Evans rats given a single gavage dose with the parent alachlor at 7 or 70 mg/kg (Hall and Wilson, 1992) showed localization of the radiolabel in the liver, lungs, heart, kidney, adrenal gland, spleen, intestinal contents, and nasal mucosa, with nasal staining most pronounced in Long-Evans rats at 24 hours. At 120 hours, liver, kidney, adrenal, heart and lungs were the major areas of radiolabel localization. For acetochlor, tissues did not retain radioactivity but test material was retained in blood (binding to RBC) and well-perfused organs (heart, spleen, kidney, lung, liver). Both acetochlor and alachlor are completely metabolized (acetochlor: 15 in urine, 4 in bile, and 5 in feces; alachlor: 14 metabolites identified in urine and 13 in feces). For acetochlor, glutathione, mercapturic acid or glucuronide conjugation of n-dealkylated acetochlor was the major route of metabolism, while sulphoxymethyl and cysteine conjugates were also identified in feces. In urine, the major acetochlor metabolite was mercapturic acid conjugate of N-deethylated acetochlor and in bile, the major metabolite was the glucuronide conjugate (Hawkins et al., 1987a,b,c; Hawkins et al., 1989; Jones, 1990). For alachlor, the eliminated metabolites were conjugates of mercapturic acid, glucuronide acid and sulphate (Wilson et al. 1983).

In contrast, toxicokinetic studies available for the degradates indicate that they are poorly absorbed following oral administration, undergo limited metabolism (they are excreted largely unchanged), and show no evidence of accumulation or localization in any tissue. For example, feces were the primary route of elimination for both degradates of acetochlor (Albin and Kraus, 2000a; 2000b). Following administration of a single dose of 300 mg/kg of the acetochlor degradates in rats, 76.7 to 80% (av. 78%) of the ESA degradate and about 56% of the OXA degradate were excreted in the feces, while 10.2 to 12.7% (11% av.) of the ESA and 34.0 to 38.6% (36% av.) of the OXA degradates were excreted in the urine of both sexes of rat. Excretion was rapid for both degradates, with 88% of the acetochlor OXA and 87% of the ESA degradate excreted within the first 24 hours with no sex differences observed. WBA studies revealed radioactivity being found primarily in the gastrointestinal tract of rat 24 hours after dosing with either the ESA or OXA degradate, consistent with the conclusion that the primary elimination route of fecal excretion reflected lack of significant absorption. After 5 days of dosing, negligible radioactivity levels were found in the body. For acetochlor ESA, 75.5 to 79.2% (~77%; representing 72.4% in feces and 3.2% in urine for males and 69.5% in feces and 9.5% in urine for females) of the administered dose was excreted unchanged. The only metabolite identified was acetochlor secondary ESA, which accounted for 3.2 to 5.2% of the administered dose and was eliminated primarily in the urine. A few other, unidentified metabolites were also found, primarily in male urine, but each represented ≤1% of the administered dose. For acetochlor OXA, 81.4% to 84.9% (~83%) of the administered dose was excreted unchanged. Two unidentified metabolites of acetochlor OXA were found, primarily in the urine, with neither of them constituting more than 5% of the administered dose.

As for the acetochlor degradates, following a single dose administration (70 mg/kg; the same dose used in alachlor metabolism/WBA studies) in rats, alachlor ESA was poorly absorbed and underwent limited metabolism. An average (for males and females combined) of 72% of the administered dose was excreted via the feces during the first 24 hours following dosing, while approximately 11.5% of the dose was eliminated in the urine during the same period. Five days after dosing, approximately 83% and 11% of the dose was excreted in the feces and urine, respectively. Greater than 90% of the radioactivity in urine samples for females and 41% for males and an average of 93% of the fecal-contained radioactivity were shown to be unmetabolized alachlor ESA (Kraus et al., 1995; Heydens et al., 2000). Three unidentified metabolites were found in urine and were also present in the fecal samples. None of these metabolites represented more than 4% of the administered dose. WBA data showed that after 24 hours of dosing, radioactivity was localized in the stomach contents, cecum, intestinal contents, urinary bladder and lining of the tongue and esophagus, while no sites of localization of radioactivity was observed 5 days after dosing. No toxicokinetics data were available for alachlor OXA. However, similarities in toxicology of the degradates predict that alachlor OXA, following a single oral administration, would also be poorly absorbed, rapidly eliminated, excreted largely unchanged, and with no evidence of accumulation or localization in any tissue.

In summary, the available toxicokinetic data suggest that 10-12% of acetochlor ESA, 34-39% of acetochlor OXA, and 2-19% of alachlor ESA are absorbed following oral dosing and that the degradates undergo only minimal metabolism. In addition, the degradates are not likely to undergo conjugation reactions due to lack of a reactive dehalogenation site as is present in the parent chemicals.

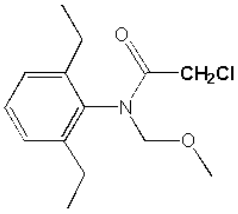
Key Points for Consideration

1. Does the array of comparative toxicity data support the use of the parent chemicals for assessing the toxicity of the degradates for effects on body weight? Effects on the liver? Effects on the thyroid? Effects on reproductive and developmental toxicity? Other effects?

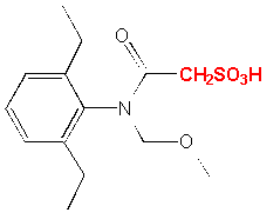
2. Do the mechanistic and toxicokinetic data support commonalities in MOA for the parents and degradates for each critical endpoint? Do these MOA findings support using the data for parents or other degradates for hazard characterization of each degradate? For dose-response assessment of each degradate?

3. Are the toxicokinetic data adequate to develop dose-response adjustments based on relative target tissue dose? To develop CSAF approaches?

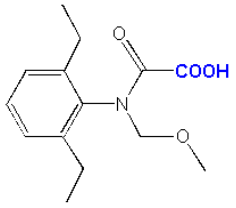
(1) Figure 1. Structures of Acetochlor and Alachlor and their Degradates



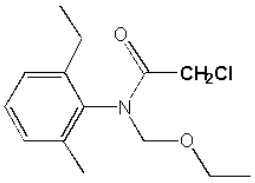
Alachlor



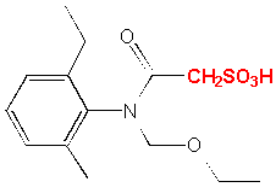
Alachlor t-ESA



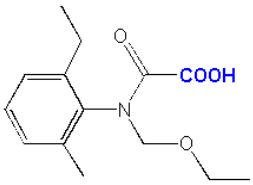
Alachlor t-OXA



Acetochlor



Acetochlor t-ESA



Acetochlor t-OXA

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4.0 Tables

Table 1. Summary of Available Toxicity Studies on Acetochlor and the Degradates, Acetochlor ESA and Acetochlor OXA*

Test	Acetochlor	Acetochlor ESA	Acetochlor OXA
Acute oral LD50	**U.S. EPA (2006)**: LD50(M&F) = 4124 (3557-4691) mg/kg (**MRID 41565104, Cummins, 1986**) LD50 2389 mg/kg (M) LD50: 1929 mg/kg (966-2489) (F) (**Branch, 1982**)	**U.S. EPA (2006)**: LD50 (M&F) > 2000 mg/kg (no mortality at limit dose) (**MRID 44632704, Lees, 1997a**)	**U.S. EPA (2006)**: LD50 (M&F) > 2000 mg/kg (**MRID 44632703, Lees, 1997b**)
4-Week feeding range finding (ESA)/thyroid mechanistic (acetochlor) (rats)	**U.S. EPA (2006)**: Males administered acetochlor in diet at 100.6 or 280.9 mg/kg-day for 14, 28 or 56 days: increased liver and thyroid weights, hepatic UDPGT activity, circulating serum TSH, T4; decreased T3, some or all time points. Males administered acetochlor at 10.4, 91.9 or 270.3 mg/kg-day for 90 or 160 days: increased liver weight (slight increase in thyroid wt) at 91.9 mg/kg-day, increased hepatic UDPGT at 270.3 mg/kg-day. (**MRID 44496208, Hotz and Wilson, 1996**) **European Union (2005)**: NOAEL = 600/1200 ppm (68/139 mg/kg-day, males/females)	**U.S. EPA (2006)**: NOAEL = 370.3/374.6 mg/kg-day [M/F] LOAEL = 766.6/762.3 mg/kg-day [M/F], based on decreased body weights and body weight gain and increased TSH and free T3 in males. At 1578.7 mg/kg-day (HDT) there was a statistically significant increase in T4-UDPGT (microsomal enzyme) (**MRID 45300503, Lees, 2000a**) ***TERA*'s Conclusion**: Body weight - 12000 ppm: a maximum reduction of body weights of approx. 6% on day 2, reaching stat. significance from day 2 to day 5 for males and from day 2 to day 4 for females 6000 ppm: maximal reduction in b. wt of approx. 3% for males and 6% for females	**U.S. EPA (2006)**: NOAEL = 372.6/367.2 mg/kg-day [M/F] LOAEL = 768.5/737.3 mg/kg-day [M/F], based on decr. TSH & T3 and incr. absolute & relative thyroid weights in males and decr. TSH & T3 in females. (**MRID 45300506, Williams, 2000a**) ***TERA*'s Conclusion**: 12000 ppm [1467.9 mg/kg-day, males, and 1506.5 mg/kg-day, females]. Sig. bodyweight reduction in male rats (12% compared with the control value). Slight (not statistically significant) reduction in b. wts for females (4% of control levels). 6000 ppm: no effects on b.

Test	Acetochlor	Acetochlor ESA	Acetochlor OXA
	LOAEL = 1200/2400 ppm (132/279 mg/kg-day, males/females), significant decrease in body weight gain and shorter prothrombin times in males at 1200 ppm. Significantly increase on relative liver, kidney and brain weights and a decrease on food consumption at 2400 ppm in males. Significantly decrease in body weight gain and increase on relative liver and kidney weights in females at 2400 ppm. Marked elevation of γ-glutamyl transpeptidase activity in all animals at 4800 ppm or above. Lower of packed cell of volume in males at 4800 and 9600 ppm and lower cell haemoglobin in all animals treated at 9600 ppm. (Broadmeadow, 1985)	on day 2, stat, sig. being attained from day 2 to day 3 for males and from day 2 to day 4 for females. Male group mean b. wts stat. sig. lower than controls on day 22 and 29. 3000 ppm: no effects on b. wts. Author indicated there were no clear treatment-related effects on b. wt present at the end of the study and the initial reductions are considered to be of no toxicological significance. TSH and free T3 levels increased in a dose-dependent manner in males, but did not reach stat. sig. at any dose level. T4-UDPGT activity increased stat. sig. in females at 12000 ppm [1607.4 mg/kg-day] and to a minimal degree in males [1578.7 mg/kg-day. Absent any clear changes in thyroid hormone parameters or any related organ weight or pathology changes, increases in TSH, free T3 and T4-UDPGT are considered toxicologically insignificant. Organ weight: increases in relative epididymides weight (non-dose dependent and without stat. sig.) and testes weights (stat. sig at 3000 ppm – 370.3 mg/kg-day – and above -, but non-dose dependent). Absent dose-dependence and associated pathology findings, the increase is considered to be of no toxicological significance. NOAEL = 12000 ppm [1578.7 mg/kg-day, males; 1607.4 mg/kg-day, females] (**Lees, 2000a, rats, diet**)	wt in either sex. 3000 ppm: Max. effects of 7% and 6% reduction in males and females, respectively. Lack of dose response makes effect at 3000 ppm toxicologically insignificant. Decrease in TSH levels in males (no dose-dependency) and females (dose-dependent), but without stat. sig. at any dose level. Dose-dependent decrease in total and free T3 levels in males, but with stat. sig. only at the highest dose level [12000 ppm; 1467.9 mg/kg-day]. T4-UDPGT activity stat. sig. increased in females at 12000 ppm in females [1506.5 mg/kg-day], but without a dose-response relationship. Absolute thyroid weights stat. sig. increased in males at 6000 ppm [768.5 mg/kg-day] and 12000 ppm [1467.9 mg/kg-day], while relative thyroid weight increased at all doses [372.6 mg/kg-day and above], but there was no dose-response relationship. In addition, there were no treatment-related microscopic findings in the thyroid gland. NOAEL = 600 ppm [769 mg/kg-day, males; 737 mg/kg-day, females]. LOAEL = 12000 ppm [1468 mg/kg-day, males; 1507 mg/kg-day, females], based stat. sig. increase in body weight in male rats. (**Williams, 2000a, rat dietary study**)

Test	Acetochlor	Acetochlor ESA	Acetochlor OXA
90-Day feeding (rats)	**U.S. EPA (2006)**: Study 1**:** NOAEL = 16.1 / 19.1 mg/kg-day [M/F] LOAEL = 161 / 191 mg/kg-day [M/F] based on hematology, small but significant increases in relative liver, kidney & brain weights. (**MRID 41565115, Broadmeadow, 1986**) Study 2: NOAEL = 40 mg/kg-day LOAEL = 100 mg/kg-day, based on body weight loss & food consumption. (**MRID 00050933, Ahmed et al., 1980**)	**U.S. EPA (2006**): NOAEL = 225.4 / 259.1 mg/kg-day [M/F] LOAEL = 919.4 / 1073.2 mg/kg-day [M/F], based on reduced body weights, body weight gains and food utilization in both sexes. Decreased cell proliferation in nasal passages was seen at the LOAEL, but not statistically significantly diff. with controls because of variability. (**MRID 45313801, Lees, 2000b**) ***TERA*'s Conclusion:** Reduced b. wts, and reduced food utilization in males and females and reduced food consumption in males at 12000 ppm [919.4 mg/kg-day, males and 1073.2 mg/kg-day, females]. Minimal reduction in b. wt. and food consumption at 3000 ppm in males [225.4 mg/kg-day] but the changes were considered not to be toxicologically sig. Minimal changes in clinical pathology parameters at 12000 ppm, but changes considered only equivocal evidence of toxicity. Decreased cell proliferation in nasal epithelium in males and females, but considerable inter-animal variability rendered changes stat. insignificant compared with controls. NOAEL = 3000 ppm [225.4 mg/kg-day, males; 259.1 mg/kg-day, females] LOAEL = 12000 ppm [919.4 mg/kg-day,	**U.S. EPA (2006)**: NOAEL = 230.2 / 268.0 mg/kg-day [M/F] LOAEL = 955.2/1082.7 mg/kg-day [M/F], based on reduced body weights, body weight gains and food utilization in both sexes. Thyroid weight increases were not seen in this study. T4-UDPGT activity was slightly, but not significantly, increased in high-dose males and was statistically significantly decreased in high-dose females (**MRID 45313805, Williams, 2000b**) ***TERA*'s Conclusion**: slight b. wt decrease in males at 3000 ppm [230.2 mg/kg-day] and stat. sig. b. wt decreases in both sexes at 12000 ppm [955.2 mg/kg-day, males and 1082.7 mg/kg-day, females]. Food utilization was slightly (7-9%0 but stat. sig. reduced in both sexes at 12000 ppm, with only a slight decrease for male rats only at 3000 ppm. There were no thyroid weight increases. **T4-UDPGT activity was not evaluated in this study.** NOAEL = 230.2 mg/kg-day, males and 268.0 mg/kg-day, females. LOAEL = 955.2 mg/kg-day, males and 1082.7 mg/kg-day, females, based on stat. sig. reduced body weights and food utilization in both sexes.

Test	Acetochlor	Acetochlor ESA	Acetochlor OXA
		males; 1073.2 mg/kg-day, females] (**Lees, 2000b; rats, diet**)	(**Williams, 2000b, rat dietary study**)
Developmental toxicity	**U.S. EPA (2006)**: Study 1 (rats): NOAEL (maternal & developmental) = 150 mg/kg-day, LOAEL (mat & dev) = 600 mg/kg-day; Maternal: based on clinical signs & decr. b. wt. gain. Developmental: based on incr. resorptions & decr. fetal body weights. (**MRID 41592005, Brooker et al., 1989**) Study 2 (rats): NOAEL (maternal & developmental) =200 mg/kg-day, LOAEL (mat & dev) = 400 mg/kg-day; Maternal: based on clinical signs & decr. b. wt. gain. Developmental: based on decr. fetal body weights (**MRID 00050929, Rodwell and McMeekin, 1980**)	**U.S. EPA (2006)**: **No data for Acetochlor ESA.** Data are for Alachlor ESA. Rats: NOAEL (maternal & developmental): greater than or equal to 900 mg/kg-day (HDT) LOAEL (maternal & developmental): greater than 900 mg/kg-day (**MRID 43908101, Holson, 1995**) ***TERA*'s Conclusion**: No data available for Acetochlor ESA.	**U.S. EPA (2006)**: Rats: NOAEL (maternal) = 500 mg/kg-day, LOAEL (maternal) = 1000 mg/kg-day, based on maternal mortality. NOAEL (developmental) ≥ 1000 mg/kg-day (limit dose). LOAEL (developmental) >1000 mg/kg-day (**MRID 45313807, Holdon, 2000**) ***TERA*'s Conclusion**: Maternal mortality in 2 of 25 dams at 1000 mg/kg-day. No other treatment-related effects in dams (mortality) and no developmental toxicity. NOAEL (maternal toxicity) = 500 mg/kg-day LOAEL (maternal toxicity) = 1000 mg/kg-day NOAEL (developmental toxicity) ≥1000 mg/kg-day. (Dose levels tested: 0, 250, 500, and 1000 mg/kg-day.) (**Holson, 2000, rats, oral gavage**)

*Summaries from U.S.EPA (2006) and *TERA*'s conclusions.

Table 2. Summary of Available Toxicity Studies on Alachlor and the Degradates, Alachlor ESA and Alachlor OXA*

Test	Alachlor	Alachlor ESA	Alachlor OXA
Acute oral LD50	**U.S. EPA (2007)**: LD50 = 930 mg/kg Tox. Category III (**MRID 00139383, Heenehan et al., 1979**)	**U.S. EPA (2007)**: LD50 > 6000 mg/kg Tox. Category IV (**MRID 42701501, 1993**)	**U.S. EPA (2007)**: LD50 > 5000 mg/kg Tox. Category IV
4-Week feeding range finding (ESA)/thyroid mechanistic (alachlor) (rats)	**U.S. EPA (2007)**: LOAEL = 126 mg/kg-day (only dose tested), based on increased liver weights, increased activity of UDPGT, and increased thyroid weights , statistically significant increase in TSH levels, decreased T4 levels, and thyroid follicular hypertrophy/hyperplasia. (**Hotz et al. 1993**)	**U.S. EPA (2007):** NOAEL = 7000 ppm (656 mg/kg-day, males and 749 mg/kg-day, females) LOAEL = 20000 ppm (2217 mg/kg-day, males and 2378 mg/kg-day, females), based on mortality, clinical signs of toxicity, significant decreases in body weight, food consumption, and water intake. (**Siglin, 1993**)	**U.S. EPA (2007)**: NOAEL = 10,000 ppm (754.26 mg/kg-day, males and 829.68 mg/kg-day, females). LOAEL = 20,000 ppm (1539.32 mg/kg-day, males and 1595.26 mg/kg-day, females), based on hyperplasia of mucous cells, eosinophilic cytoplasmic inclusions of gastric epithelial cells in both sexes. (Doses tested 0, 1000, 10,000, and 20,000 ppm). ***TERA*'s Conclusion**: Hyperplasia of mucous cells and eosinophilic inclusions in the cytoplasm of epithelial cells in the stomachs of male and females. Incidence: 1/5, 0/5, and 4/5 in males at 1000, 10000, and 20000 ppm, respectively; 0/5, 1/5 and 3/5 in females at 1000, 10000, and 20000

Test	Alachlor	Alachlor ESA	Alachlor OXA
			ppm, respectively. NOAEL = 10,000 ppm [754.26 mg/kg-day, males and 829.68 mg/kg-day, females]. LOAEL: 20,000 ppm [1539.32 mg/kg-day, males; 1595.26 mg/kg-day, females] for gastric changes. (**Stout and Thake, 2000, rats, diet**)
90-Day feeding (rats)	**U.S. EPA (2007)**: Acceptable 90-day study not submitted. NOAEL in invalid 90-day rat study was 15 mg/kg-day in diet, based on decreased body weights, increased spleen, liver and kidney weights, and decreased gonad weights at LOAEL of 146 mg/kg-day. (**MRID 00023658**, **Wolf, 1966**)	**U.S. EPA (2007)**: NOAEL = 157 mg/kg-day, males and 207 mg/kg-day, females, in **drinking water**, based on clinical signs and in males, decreased body weight gain at 896 mg/kg-day, males and 1108 mg/kg-day, females. F344 rats. (**MRID 42863701; Siglin, 1993**) ***TERA*'s Conclusion**: Study 1 (**drinking water**): At 10,000 ppm: stat. sig. decrease in mean body weight, body weight gain, food consumption and water intake in males and females, accompanied by clinical signs (including few and/or small feces, urine staining, rough coat, dehydration, emaciation and dark material around the eyes, and death of one male rat on day 13), clinical chemistry (stat. sig. and dose-dependent decrease in glucose, increase in total bilirubin, and increased phosphorus in	**U.S. EPA (2007)**: NOAEL = 13,000 ppm (HDT, 834.6 mg/kg-day, males, and 1008.3 mg/kg-day, females). LOAEL not determined. (Doses tested 0, 400, 130, 4000, and 13,000 ppm). ***TERA*'s Conclusion**: No treatment-related effects on survival, clinical signs of toxicity, body weight changes, food consumption, ophthalmic function, motor activity, functional observational battery, clinical pathology (hematology, serum chemistry or clotting parameters), or gross and microscopic pathology. Gastric changes were not evaluated in this study. NOAEL = 834.6 mg/kg-day, males and

Test	Alachlor	Alachlor ESA	Alachlor OXA
		males; statistically significant decrease in albumin level ~4.0% in males. At 2000 ppm: stat. sig. decrease in albumin level, ~2.7%. The clinical chemistry changes at 2000 ppm and above occurred in the absence of gross pathology, organ weight changes, or microscopic lesions. Statistically significant decrease in erythrocyte counts in the 2000 and 10,000 ppm males; decrease in hemoglobin and hematocrit in the 10,000 ppm males; and increase in mean corpuscular hemoglobin (MCH) in the 10,000 ppm males. The hematology parameter changes did not correlate with other hematological or histopathological changes. **NOAEL** = 2000 ppm [157 mg/kg-day for males and 207 mg/kg-day for females]. **LOAEL** = 10,000 ppm [896 mg/kg-day for males and 1108 mg/kg-day for females], based on decreases in body weights and food consumption in males and females and clinical signs in males. (**Siglin 1993; Heydens et al., 1996; F344 rats, drinking water**) <u>Study 2</u> (**Dietary**): No test article-related clinical findings, no effects on body weights, food consumption, clinical pathology parameters (hematology and serum chemistry) and organ weights,	1008.3 mg/kg-day, females. Doses tested: 0, 400, 1300, 4000 or 13,000 ppm [0, 24.9, 83.5, 261.1, and 834.6 mg/kg-day, males; 0, 29.1, 95.4, 290.9, and 1008.3 mg/kg-day, females] (**Lemen et al., 2000; rats, diet**)

Test	Alachlor	Alachlor ESA	Alachlor OXA
		functional observational battery or motor activity. No treatment-related ophthalmic findings or macroscopic or microscopic changes. NOEL: 12000 ppm [788 mg/kg-day, males and 926 mg/kg-day, females] (HDT). Doses tested: 0, 3000, 6000 and 12000 ppm [0, 195, 389, and 788 mg/kg-day, males, 0, 222, 454, and 926 mg/kg-day, females]. (**Kirkpatrick, 2003; rat, diet**)	
Chronic	**U.S. EPS (2007)**: NOAEL = 2.5 mg/kg-day, based on eye effects, hepatotoxicity at 15 mg/kg-day. **Long-Evans rats.** (**MRID 00139021, Stout and Thake, 1984**). There were two other chronic rat studies. One (**MRID 00091050**) reported a NOAEL < 14 mg/kg-day and LOAEL ≤14 mg/kg-day, based on ocular lesions (uveal degeneration syndrome) and hepatic toxicity. The other (**MRID 00141060**) reported a LOAEL of 126 mg/kg-day for ocular effects (uveal degeneration syndrome).	n/a	n/a
Developmental toxicity	**U.S. EPA (2007)**: Maternal and Developmental NOAELs = 150 mg/kg-day, based on increased mortality (maternal) and increased postimplantation loss, decreased	**U.S. EPA (2007)**: Maternal and Developmental NOAELs ≥900 mg/kg-day (HDT).	n/a

Test	Alachlor	Alachlor ESA	Alachlor OXA
	live fetuses and decreased fetal weight (developmental) at 400 mg/kg-day. (**MRID 00043645, 1980**)	(**MRID 43908101, 1995**) ***TERA*'s Conclusion**: Increased incidence of rales at 1000 mg/kg-day (900 mg/kg-day, adjusted for 90% purity) during the daily examinations at the time of dosing and one hour following dosing. Although considered to be treatment-related, the rales were considered likely to be a result of local effect due to intubation of large amounts of the test article and not a systemic adverse effect. Furthermore, absence of other signs of toxicity (e.g., maternal body weight effects) renders this effect to not be definitive signs of a toxic effect. No maternal or developmental toxicity at any dose level. NOAEL = 900 mg/kg-day Developmental NOAEL ≥900 mg/kg-day (**Holson, 1995; Heydens et al., 1996; gastric intubation, rats**)	

*Studies reviewed by TERA are included.
n/a: not available.

Table 3-1. Treatment-related Effects Observed in a 28-day Toxicity Study with Acetochlor ESA

Acetochlor ESA – 28-day study (Lees, 2000a; rats, diet)						
Effect			**Doses**			
			0 ppm	**3000 ppm M/F 370.3 / 374.6 mg/kg-day**	**6000 ppm M/F 766.6 / 762.3 mg/kg-day**	**12000 ppm M/F 1578.7 /1607.4 mg/kg-day**
Body weight (g) [#]	Male N=5	D 7	192.2 ± 8.7	190.2 ± 12.5 (-1.0%)	189.4 ± 13.2 (-1.5%)	188.4 ± 11.4 (-2.0%)
		D 29	337.2 ± 26.0	328.6 ± 21.0 (-2.6%)	304.6 ± 25.7 (-9.7%)	330.0 ±41.3 (-2.1%)
	Female N=5	D 7	153.6 ± 6.9	154.4 ± 11.3 (0.5%)	155.2 ± 10.5 (1.0%)	151.6 ± 9.1 (-1.3%)
		D 29	223.0 ± 14.9	220.0 ± 26.2 (-1.3%)	218.8 ± 18.9 (-1.9%)	217.8 ± 18.6 (-2.3%)
Adjusted Body Weight (g) [#]	Male N=5	D 7	191.5	191.0 (-0.26%)	189.0 (-1.3%)	188.6 (-1.5%)
		D 29	335.7	330.4 (-1.6%)	303.8* (-9.5%)	330.5 (-1.5%)
	Female N=5	D 7	154.5	154.3 (-0.1%)	155.4 (0.6%)	150.6 (-2.5%)
		D 29	224.8	219.9 (-2.2%)	219.2 (-2.5%)	215.8 (-4.0%)
Food Consumption (g/rat/day) [##]	Male N=5	D 7	26.0	23.8	25.4	26.2
		W 4	27.9	26.7	24.6	28.9
	Female N=5	D 7	19.8	18.8	19.0	20.8
		W 4	20.2	20.1	20.7	21.0
Liver Weight (g)	Male N=5	absolute	14.2 ± 2.4	14.5 ± 2.4 (2.1%)	12.6 ± 2.2 (-11.3%)	14.5 ± 2.2 (2.1%)
		Organ to BW Ratio	4.2 ± 0.4	4.4 ± 0.5 (4.8%)	4.1 ± 0.3 (-2.4%)	4.4 ± 0.3 (4.8%)
	Female N=5	absolute	10.0 ± 1.1	9.5 ± 1.5 (-5.0%)	8.8 ± 1.4 (-12%)	9.3 ± 1.1 (-7.0%)
		Organ to BW Ratio	4.5 ± 0.2	4.3 ± 0.3 (-4.4%)	4.0 ± 0.3 (-11.1%)	4.3 ± 0.2 (-4.4%)
Thyroid weight (g)	Male N=5	absolute	0.019 ± 0.006	0.015 ± 0.003 (-21.0%)	0.018 ± 0.002 (-5.3%)	0.018 ± 0.003 (-5.3%)
		Organ to BW	0.006 ± 0.002	0.005 ± 0.001	0.006± 0.001	0.005 ± 0.000

Acetochlor ESA – 28-day study (Lees, 2000a; rats, diet)						
Effect			**Doses**			
			0 ppm	**3000 ppm M/F 370.3 / 374.6 mg/kg-day**	**6000 ppm M/F 766.6 / 762.3 mg/kg-day**	**12000 ppm M/F 1578.7 /1607.4 mg/kg-day**
		Ratio		(-20%)	(0%)	(-20%)
	Female N=5	absolute	0.015 ± 0.002	0.016 ± 0.002 (6.7%)	0.015 ± 0.002 (0%)	0.015 ± 0.002 (0%)
		Organ to BW Ratio	0.007 ± 0.001	0.007 ± 0.001 (0%)	0.007 ± 0.001 (0%)	0.007 ± 0.001 (0%)
Plasma TSH (ng/ml)	Male N=5		9.81 ±5.53	11.23 ±4.64 (14.5%)	13.62 ± 4.54 (38.8%)	15.77 ±10.44 (60.8%)
	Female N=5		6.45 ± 2.99	4.16 ± 1.52 (-35.5%)	6.26 ± 3.49 (-2.9%)	4.02 ± 1.52 (-37.7%)
Plasma T3 (mol/l)	Male N=5	total	1.27 ± 0.05	1.38 ± 0.19 (8.66%)	1.59** ± 0.17 (25.2%)	1.32 ± 0.18 (3.9%)
		free	1.47 ± 0.37	1.50 ± 0.28 (2.0%)	1.70 ± 0.38 (15.6%)	1.88 ± 0.67 (27.9%)
	Female N=5	total	1.06 ± 0.15	1.22 ± 0.22 (15.1%)	1.04 ± 0.12 (-1.9%)	1.20 ± 0.16 (13.2%)
		free	1.37 ± .34	1.41 ± 0.16 (2.9%)	1.24 ± 0.20 -9.5%)	1.27 ± 0.19 (-7.3%)
Plasma T4 (mol/l)	Male N=5	total	68.0 ± 9.5	64.9 ± 6.0 (-4.6%)	71.6 ± 6.9 (5.29%)	78.0 ± 0.67 (14.7%)
		free	14.54 ± 3.85	13.24 ± 2.15 (-9.0%)	14.16 ± 0.83 (-2.6%)	16.51 ± 2.59 (13.5%)
	Female N=5	total	52.7 ± 9.6	52.8 ± 7.0 (0.2%)	67.3* ± 5.6 (27.7%)	44.4 ± 13.1 (-15.7%)
		free	7.95 ± 1.48	11.06* ± 1.70 (39.0%)	12.02** ± 1.66 (51.2%)	8.53 ± 1.94 (7.3%)
T4-UDPGT activity – pmol/hour/g liver***	Male N=5		181.7 ± 55.9	190.0 ± 69.6 (4.6%)	179.2 ± 46.4 (-1.4%)	245.4 ±46.2 (35%)
	Female N=5		241.0± 67.0	207.3 ± 63.4 (-14.0%)	244.0 ± 45.2 (1.2%)	373.1** ± 57.8 (54.8%)
T4-UDPGT activity – pmol/hour/ total liver***	Male N=5		2580 ± 922	2641 ± 674 (2.4%)	2233 ± 599 (-13.4%)	3519* ±600 (36.4%)
	Female N=5		2137 ± 707	1975 ± 779 (-7.6%)	2114 ± 283 (-1.1%)	3436** ± 250 (60.8%)

Acetochlor ESA – 28-day study (Lees, 2000a; rats, diet)					
Effect		**Doses**			
		0 ppm	**3000 ppm M/F 370.3 / 374.6 mg/kg-day**	**6000 ppm M/F 766.6 / 762.3 mg/kg-day**	**12000 ppm M/F 1578.7 /1607.4 mg/kg-day**
T4-UDPGT activity – pmol/hour/mg protein***	Male N=5	14.5 ± 4.6	13.6 ± 3.9 (-6.2%)	15.5 ± 5.6 (6.9%)	18.5 ± 2.9 (27.6%)
	Female N=5	19.1 ± 6.3	19.4 ± 7.5 (1.6%)	18.7 ± 4.3 (-2.1%)	33.4** ± 6.3 (74.9%)
Hemoglobin (g/dl)	Male N=5	15.0 ± 0.8	14.6 ± 0.7 (-3.3%)	14.1 ± 1.1 (-6.0%)	14.7 ± 0.9 (-2.0%)
	Female N=5	14.6 ± 0.8	14.4 ± 0.7 (-1.4%)	14.1 ± 0.7 (-3.4%)	14.9 ± 0.6 (2.1%)
Hematocrit (no units)	Male N=5	0.471 ± 0.027	0.462 ± 0.024 (-1.9%)	0.446 ± 0.040 (-5.3%)`	0.468 ± 0.036 (-0.64%)
	Female N-5	0.428 ± 0.029	0.425 ± 0.024 (-0.7%)	0.414 ± 0.023 (-3.3%)	0.442 ± 0.019 (3.3%)
Red Blood Cell Count (x10**12/l)	Male N=5	7.22 ± 0.53	7.26 ± 0.24 (0.55%)	7.26 ± 0.52 (0.55%)	7.52 ± 0.44 (4.2%)
	Female N=5	7.00 ± 0.46	7.02 ± 0.44 (0.29%)	7.10 ± 0.43 (1.4%)	7.28 ± 0.22 (4%)
Mean Cell Volume (fl)	Male N=5	65.4 ± 1.5	63.7 ± 2.6 (-2.6%)	61.4** ± 1.8 (-6.1%)	62.3* ± 1.3 (-4.7%)
	Female N=5	61.3 ± 1.1	60.6 ± 2.7 (-1.1%)	58.3 * ± 0.9 (-3.8%)	60.6 ± 2.5 (-1.1%)
Mean Cell Hemoglobin (pg)	Males N=5	20.8 ± 0.6	20.2 ± 0.8 (-2.9%)	19.4** ± 0.6 (-6.7%)	19.6** ± 0.2 (-5.8%)
	Female N=5	20.9 ± 0.7	20.5 ± 0.9 (-1.9%)	19.9* ± 0.5 (-4.8%)	20.4 ± 0.9 (-2.4%)
Mean Cell Hemoglobin Concentration (g/dl)	Male N=5	31.5 ± 0.5	31.7 ± 0.3 (0.6%)	31.6 ± 0.5 (0.32%)	31.4 ± 0.6 (-0.32%)
	Female N=5	34.1 ± 0.8	33.7± 0.7 (-1.2%)	34.2 ± 0.6 (0.29%)	33.7 ± 1.0 (-1.2%)

D – Day; W - Week; N – Number of animals per dose group; Adjusted Body Weight – Adjusted to initial body weight but initial body weights not provided; # - Body weight and Adjusted body weight data reported for Days 1 through 8 and then weekly, but table only shows values for Days 7 and 29; ## - Food consumption data provided for Days 1 through 7 and then weekly (with no statistical analysis performed) and values provided are data reported for Day 7 and Week 4; *-Statistically significant difference from the control group mean at the 5% level (Student's t-test, two sided); **-Statistically significant difference from control group mean at the 1% level (Student's t-test, two sided); ± - (standard deviation); (%) – percent change from control; BW- body weight; *** - T4-

Acetochlor ESA – 28-day study (Lees, 2000a; rats, diet)				
Effect	**Doses**			
	0 ppm	**3000 ppm M/F 370.3 / 374.6 mg/kg-day**	**6000 ppm M/F 766.6 / 762.3 mg/kg-day**	**12000 ppm M/F 1578.7 /1607.4 mg/kg-day**
UDPGT (hepatic T4-uridine diphosphate glucuronosyl transferase) activity normalized to g liver, total liver, or mg protein. [T4-UDPGT is the hepatic UDPGH-mediated clearance of the thyroid hormone thyroxine (T4)].				

(4) Table 3-2. Treatment-related Effects Observed in a 90-day Toxicity Study with Acetochlor ESA

Acetochlor ESA – 90-day study (Lees, 2000b; rats, diet)						
Effect			**Doses**			
			0 ppm	**1000 ppm M/F 75.0/85.2 mg/kg-day**	**3000 ppm M/F 225.4/ 259.1 mg/kg-day**	**12000 ppm M/F 919.4/1073.2 mg/kg-day**
Body weight (g)[#]	Male N=20	MSW 6	403.9 ± 35.6	390.0 ± 35.5 (-3.4%)	385.2 ± 44.2 (-4.6%)	367.7 ± 34.1 (-8.9%)
		MSW 14	489.9 ± 47.0	470.7 ± 44.8 (-3.9%)	473.0 ± 55.3 (-3.4%)	439.0 ± 55.8 (-10.4%)
	Female N=20	MSW 6	238.9 ± 19.4	238.9 ± 16.3 (0%)	236.4 ± 13.6 (-1.0%)	233.7 ±14.4 (-2.2%)
		MSW 14	270.6 ± 22.8	273.1 ± 21.1 (0.9%)	267.5 ±15.0 (-1.1%)	263.1 ± 17.4 (-2.8%)
Food consumption (g/rat/day)[#]	Male N=5	MSW 6	30.0 ± 0.7	28.8 ± 0.4 (-4.0%)	28.5* ± 1.3 (-5.0%)	28.0** ± 1.4 (-6.7%)
		MSW 13	25.8 ± 1.1	24.8 ± 0.5 (-3.9%)	24.8 ± 1.1 (-3.9%)	23.5** ± 0.4 (-8.9%)
	Female N=5	MSW 6	21.4 ± 1.3	20.9 ± 0.5 (-2.3%)	20.8 ± 1.6 (-2.8%)	21.2 ± 0.8 (-0.9%)
		MSW 13	18.4 ± 0.3	18.3 ± 0.6 (-0.5)	17.8 ± 0.8 (-3.3%)	17.9 ± 0.9 (-2.7%)
Adjusted Body Weight (g)[#]	Male N=20	MSW 6	401.1	389.5 (-2.9%))	384.8* (-4.1%)	371.3** (-7.4%)
		MSW 14	486.5	470.1 (-3.4%)	472.6 (-2.9%)	443.4** (-8.9%)

Acetochlor ESA – 90-day study (Lees, 2000b; rats, diet)						
Effect			Doses			
			0 ppm	**1000 ppm M/F 75.0/85.2 mg/kg-day**	**3000 ppm M/F 225.4/ 259.1 mg/kg-day**	**12000 ppm M/F 919.4/1073.2 mg/kg-day**
	Female N=20	MSW 6	239.9	236.5 (-1.4%)	237.8 (-0.9%)	233.7* (-2.6%)
		MSW 14	271.5	270.7 (-0.3%)	268.9 (-1.0%)	263.1 (-3.1%)
Food utilization (g growth /100g food)	Male N=5	MS	10.97 ± 0.28	10.68 ± 0.51 (-2.6%)	10.80 ± 0.41 (-1.5%)	9.79** ± 0.68 (-10.8%)
	Female N=5	MS	5.98 ± 0.37	6.08 ± 0.70 (1.67%)	5.97 ± 0.57 (-0.17%)	5.53* ± 0.55 (-7.5%)
Thyroid weight (g)	Male N=12	absolute	0.017 ± 0.004	0.020 ± 0.005 (17.6%)	0.019 ± 0.004 (11.8%)	0.018 ± 0.005 (5.9%)
		Organ to body weight ratio	0.004 ± 0.001	0.004 ± 0.001 (0%)	0.004 ± 0.001 (0%)	0.004 ± 0.001 (0%)
	Female N=12	absolute	0.016 ± 0.003	0.017 ± 0.003 (6.25%)	0.018 ± 0.005 (12.3%)	0.017 ± 0.005 (6.25%)
		Organ to body weight ratio	0.006 ± 0.002	0.006 ± 0.001 (0%)	0.007 ± 0.001 (16.7%)	0.006 ± 0.002 (0%)
Liver weight (g)	Male N=12	absolute	15.9 ± 34.8	15.8 ± 3.3 (-0.6%)	16.4 ± 2.3 (3.1%)	15.8 ± 2.4 (-0.6%)
		Organ to body weight ratio	3.3 ± 0.2	3.3 ± 0.3 (0%)	3.5 ± 0.3 (6.1%)	3.5 ± 0.3 (6.1%)
	Female N=12	absolute	8.9 ± 0.8	9.6 ± 1.2 (7.9%)	8.8 ± 0.9 (-1.1%)	8.8 ± 0.9 (-1.1%)
		Organ to body weight ratio	3.4 ± 0.2	3.4 ± 0.3 (0%)	3.3 ± 0.2 (-2.9%)	3.3 ± 0.2 (-2.9%)
Hemoglobin (g/dl)		Male N=12	15.4 ± 0.6	15.4 ± 0.6 (0%)	15.2 ± 0.8 (-1.3%)	15.4 ± 0.7 (0%)
		Female	14.7 ± 1.0	14.8 ± 0.5	15.2 ± 0.6	15.3* ± 0.4

Acetochlor ESA – 90-day study (Lees, 2000b; rats, diet)						
Effect			Doses			
			0 ppm	**1000 ppm M/F 75.0/85.2 mg/kg-day**	**3000 ppm M/F 225.4/ 259.1 mg/kg-day**	**12000 ppm M/F 919.4/1073.2 mg/kg-day**
		N=12		(0.7%)	(3.4%)	(4.1%)
Hematocrit (no units)		Male N=12	0.449 ± 0.023	0.443 ± 0.014 (-1.3%)	0.442 ± 0.020 (-1.6%)	0.445 ± 0.019 (-0.9%)
		Female N=12	0.420 ± 0.027	0.427 ± 0.020 (1.7%)	0.432 ± 0.021 (2.9 %)	0.433 ± 0.014 (3.1%)
Red Blood Cell Count (x10**12/l)		Male N=12	8.69 ± 0.44	8.46 ± 0.32 (-2.6%)	8.48 ± 0.40 (-2.4%)	8.62 ± 0.35 (-0.8%)
		Female N=12	7.67 ± 0.48	7.75 ± 0.31 (1.0%)	7.94 ± 0.27 (3.5%)	8.13** ± 0.34 (6.0%)
Mean Cell Volume (fl)		Male N=12	51.8 ± 1.0	52.5 ± 1.9 (1.4%)	52.1 ± 1.3 (0.6%)	51.7 ± 2.1 (-0.2%)
		Female N=12	54.7 ± 1.5	55.1 ± 1.1 (0.73%)	54.4 ± 1.4 (0.55%)	53.3*0.9 (-2.6%)
Mean Cell Hemoglobin (pg)		Male N=12	17.8 ± 0.5	18.2* ± 0.6 (2.2%)	17.9 ± 0.6 (0.6%)	17.9 ± 0.9 (0.6%)
		Female N=12	19.1 ± 0.4	19.1 ± 0.4 (0%)	19.1 ± 0.5 (0%)	18.8 ± 0.4 (-1.6%)
Mean Cell Hemoglobin Concentration (g/dl)		Male N=12	34.4 ± 0.9	34.8 ± 0.5 (1.2%)	34.4 ± 0.4 (0%)	34.7 ± 0.5 (0.9%)
		Female N=12	34.9 ± 0.5	34.6 ± 0.7 (0.86%)	35.1 ± 0.9 (0.6%)	35.3 ± 0.6 (1.1%)
MS – Main + Satellite Groups; W – Week; N – Number of animals per dose group; Adjusted Body Weight – Adjusted to initial body weight but initial body weights not provided; #- Weekly body weight, adjusted body weight, and food consumption data reported, but table only shows values for weeks 6 and 14; *- Statistically significant difference from the control group mean at the 5% level (Student's t-test, two sided);**-Statistically significant difference from control group mean at the 1% level (Student's t-test, two sided); ± - (standard deviation); (%) – percent change from control.						

(5) Table 3-3. Treatment-related Effects Observed in a 28-day Toxicity Study with Acetochlor OXA

Acetochlor OXA – 28-day study (Williams, 2000a; rats, diet)						
Effect			Doses			
			0 ppm	**3000 ppm M/F 372.6 / 367.2 mg/kg-day**	**6000 ppm M/F 768.5 / 737.3 mg/kg-day**	**12000 ppm M/F 1467.9 /1506.5 mg/kg-day**
Body weight (g)[#]	Male N=5	D 7	188.0 ± 8.5	189.6 ± 12.5 (0.85%)	191.4 ± 8.6 (1.8%)	184.4 ± 6.5 (-1.9%)
		D 29	365.4 ± 27.0	345.2 ± 35.9 (-5.5%)	357.6 ± 14.5 (-2.13%)	327.6 ± 19.3 (-10.3%)
	Female N=5	D 7	152.2 ± 12.0	147.2 ± 9.7 (-3.3%)	156.2 ± 8.7 (2.6%)	148.0 ± 4.6 (-2.8%)
		D 29	222.6 ± 19.0	209.4 ± 8.3 (-5.9%)	223.4 ± 17.5 (0.36%)	214.2 ± 8.6 (-3.8%)
Adjusted Body Weight (g) [#]	Male N=5	D 7	190.3	188.8 (-0.79%)	191.6 (0.68%)	182.8 (-3.9%)
		D 29	369.9	343.5 (-7.1%)	357.6 (-3.3%)	324.4** (-12.3%)
	Female N=5	D 7	152.5	148.4* (-2.7%)	154.0 (0.98%)	148.7* (-2.5%)
		D 29	222.9	210.7 (-5.5%)	221.0 (-0.85%)	215.0 (-3.5%)
Food consumption (g/rat/day) (mean values) [##]	Male N=5	D 7	23.8	24.0 (0.84%)	25.6 (7.6%)	23.4 (-1.7%)
		W 4	31.1	29.2 (-6.1%)	30.3 (-2.6%)	28.1 (-9.6%)
	Female N=5	D 7	18.2	18.8 (3.3%)	18.0 (-1.1%)	19.8 (8.8%)
		W 4	19.6	19.0 (-3.1%)	20.5 (4.6%)	20.3 (3.6%)
Liver Weight (g)	Male N=5	absolute	16.2 ± 1.3	15.5 ± 2.5 (-4.3%)	15.5 ± 1.2 (-4.3%)	14.6 ± 1.8 (-9.9%)
		Organ to body weight ratio	4.4 ± 0.2	4.5 ± 0.4 (2.3%)	4.3 ± 0.2 (-2.3%)	4.4 ± 0.4 (0%)
	Female N=5	absolute	9.8 ± 1.4	9.5 ± 0.6 (-3.1%)	9.5 ± 0.9 (-3.1%)	9.1 ± 0.9 (-7.1%)
		Organ to body	4.4 ± 0.3	4.5 ± 0.2	4.2 ± 0.2	4.3 ± 0.3

Acetochlor OXA – 28-day study (Williams, 2000a; rats, diet)						
Effect			Doses			
			0 ppm	**3000 ppm M/F 372.6 / 367.2 mg/kg-day**	**6000 ppm M/F 768.5 / 737.3 mg/kg-day**	**12000 ppm M/F 1467.9 /1506.5 mg/kg-day**
		weight ratio		(2.3%)	(-4.5%)	(-2.3%)
Thyroid weight (g)	Male N=5	absolute	0.010 ± 0.002	0.013 ± 0.003 (30%)	0.015* ± 0.002 (50%)	0.014* ± 0.003 (40%)
		Organ to body weight ratio	0.003 ± 0.000	0.004 ± 0.001 (33.3%)	0.004 ± 0.000 (33.3%)	0.004 ± 0.001 (33.3%)
	Female N=5	absolute	0.009 ± 0.002	0.008 ± 0.002 (-11.1%)	0.008 ± 0.002 (-11.1%)	0.006 ± 0.002 (-33.3%)
		Organ to body weight ratio	0.004 ± 0.001	0.004 ± 0.001 (0%)	0.004 ± 0.001 (0%)	0.003 ± 0.001 (-25%)
Plasma TSH (ng/ml)	Male N=5		15.90 ± 10.63	15.35 ± 7.11 (-3.5%)	9.14 ± 5.25 (-42.5%)	10.00 ± 7.37 (-37%)
	Female N=5		7.63 ± 4.74	5.32 ± 3.34 (-30.3%)	3.99 ± 1.99 (-47.7%)	3.48 ± 1.49 (-54.4%)
Plasma T3 (mol/l)	MaleN=5	total	1.52 ± 0.14	1.32 ± 0.28 (-13.2%)	1.30 ± 0.14 (-14.5%)	1.15** ± 0.08 (-24.3%)
		free	2.01 ± 0.53	1.89 ± 0.42 (-6%)	1.84 ± 0.68 (-8.5%)	1.30* ± 0.08 (-35.3%)
	Female N=5	total	1.37 ± 0.23	1.37 ± 0.21 (0%)	1.21 ± 0.14 (-11.7%)	1.20 ± 0.23 (-12.4%)
		free	1.81 ± 0.30	1.58 ± 0.46 (-12.7%)	1.67 ± 0.18 (-7.7%)	1.45 ± 0.70 (-19.9%)
Plasma T4 (mol/l)	Male N=5	total	74.4 ± 14.3	63.3 ± 15.8 (-14.9%)	73.8 ± 8.1 (-0.81%)	56.5 ± 5.4 (-24.1%)
		free	20.68 ± 2.59	17.41 ± 3.89 (-15.8%)	22.66 ± 4.86 (9.3%)	16.31 ± 2.29 (-21%)
	Female N=5	total	54.4 ± 14.1	58.7 ± 13.0 (7.9%)	64.7 ± 12.0 (18.9%)	59.3 ± 23.6 (9%)
		free	15.91 ± 4.80	16.04 ± 5.31 (0.82%)	16.02 ± 3.15 (0.69%)	16.35 ± 6.68 (2.77%)
T4-UDPGT activity – pmol/hour/g liver***	Males N=5		255.1 ± 62.0	212.3 ± 54.2 (-16.78%)	252.4 ± 78.0 (-1.1%)	293.7 ± 86.1 (15.1%)
	Female N=5		404.2 ± 58.8	321.1 ± 59.9 (-20.6%)	374.5 ± 93.5 (-7.3%)	253.1** ± 59.4 (-37.4%)

Acetochlor OXA – 28-day study (Williams, 2000a; rats, diet)					
Effect		Doses			
		0 ppm	**3000 ppm M/F 372.6 / 367.2 mg/kg-day**	**6000 ppm M/F 768.5 / 737.3 mg/kg-day**	**12000 ppm M/F 1467.9 /1506.5 mg/kg-day**
T4-UDPGT activity – pmol/hour/ total liver	Male N=5	4079 ± 781	3241 ± 807 (-20.5%)	3899 ± 1173 (-4.4%)	4203 ± 1021 (3.0%)
	Female N=5	3941 ± 554	3048 ± 644 (-22.7%)	3510 ± 807 (-10.9%)	2303** ± 501 (-41.6%)
T4-UDPGT activity – pmol/hour/mg protein	Male N=5	16.5 ± 4.9	15.5 ± 5.7 (-6.1%)	17.4 ± 7.9 (5.5%)	19.5 ± 4.8 (18.2%)
	Female N=5	31.7 ± 7.0	29.2 ± 4.3 (-7.9%)	29.8 ± 8.3 (-6.0%)	26.2 ± 10.8 (-17.4%)
Hemoglobin (g/dl)	Male N=4	14.8 ± 0.3	14.7 ± 0.3 (-0.68%)	14.7 ± 0.7 (-0.68%)	14.8 ± 0.8 N=5 (0%)
	Female N=3	14.7 ± 0.2	15.1 ± 0.8 N=4 (2.7%)	14.2 ± 0.4 (-3.4%)	14.7 ± 0.3 (0%)
Hematocrit (no units)	Male N=4	0.445 ± 0.011	0.445 ± 0.011 (0%)	0.438 ± 0.021 (-1.6%)	0.448 ± 0.030 N=5 (.67%)
	Female N=3	0.421 ± 0.012	0.433 ± 0.025 N=4 (2.9%)	0.410 ± 0.013 (-5.3%)	0.419 ± 0.013 (-0.2%)
Red Blood Cell Count (x10**12/l)	Male N=4	7.18 ± 0.29	7.35 ± 0.21 (2.4%)	7.33 ± 0.32 (2.1%)	7.34 ± 0.44 N=5 (2.2%)
	Female N=5	7.20 ± 0.35	7.45 ± 0.40 N=4 (3.5%)	7.13 ± 0.38 (-1.0%)	7.30 ± 0.30 (1.4%)
Mean Cell Volume (fl)	Male N=4	62.1 ± 1.2	60.6 ± 0.6 (-2.4%)	60.0* ± 1.2 (-3.4%)	60.9 ± 1.0 N=5 (-1.9%)
	Female N=5	58.8 ± 1.3	58.2 ± 2.0 N=4 (-1.0%)	57.5 ± 1.3 (-2.2%)	57.8 ± 1.0 (-1.7%)
Mean Cell Hemoglobin (pg)	Male N=4	20.7 ± 0.4	20.1 ± 0.3 (-2.9%)	20.2 ± 0.7 (-2.4%)	20.2 ± 0.5 N=5 (-2.4%)
	Female N=5	20.5 ± 0.9	20.3 ± 0.5 N=4 (-1.0%)	19.9 ± 0.8 (-2.9%)	20.2 ± 0.5 (-1.5%)
Mean Cell Hemoglobin Concentration (g/dl)	Male N=4	33.4 ± 0.5	33.1 ± 0.1 (-0.9%)	33.6 ± 0.6 (0.6%)	33.1 ± 0.7 N=5 (-0.9%)
	Female N=5	34.9 ± 0.8	34.8 ± 0.8 N=4 (-0.29%)	34.6 ± 0.9 (-0.9%)	35.0 ± 0.4 (0.3%)
D – Day; W – Week; N – Number of animals per dose group; Adjusted Body Weight-Adjusted to initial body weight but initial body weights not provided; [#] -					

Acetochlor OXA – 28-day study (Williams, 2000a; rats, diet)				
Effect	Doses			
	0 ppm	**3000 ppm M/F 372.6 / 367.2 mg/kg-day**	**6000 ppm M/F 768.5 / 737.3 mg/kg-day**	**12000 ppm M/F 1467.9 /1506.5 mg/kg-day**
Body weight and adjusted body weight data reported for Days 1 through 8 and then weekly, but table only shows values for Days 7 and 29; [##] - Food consumption data provided for Days 1 through 7 and then weekly, but table only shows values for Day 7 and Week 4; *-Statistically significant difference from the control group mean at the 5% level (Student's t-test, two sided); **-Statistically significant difference from control group mean at the 1% level (Student's t-test, two sided); ± - (standard deviation); (%) – percent change from control; *** - T4-UDPGT (hepatic T4-uridine diphosphate glucuronosyl trransferase) activity normalized to g liver, total liver, or mg protein. [T4-UDPGT is the hepatic UDPGH-mediated clearance of the thyroid hormone thyroxine (T4)].				

(6) Table 3-4. Treatment-related Effects Observed in a 90-day Toxicity Study with Acetochlor OXA

Acetochlor OXA – 90-day study (Williams, 2000b, rat, diet)						
Effect			**Doses**			
			0 ppm	**1000 ppm M/F 77.2/ 86.5 mg/kg-day**	**3000 ppm M/F 230.2/268.0 mg/kg-day**	**12000 ppm M/F 955.2/1082.7 mg/kg-day**
Body weight (g)[#]	Male N=20	MSW 6	412.3 ± 32.4	390.5 ± 32.5 (-5.3%)	386.9 ± 28.8 (-6.2%)	388.3 ± 39.8 (-5.8%)
		MSW 14	507.8 ± 51.3	476.2 ± 37.1 (-6.22)	473.3 ± 40.6 (-6.8%)	470.9 ± 50.9 (-7.3%)
	Female N=20	MSW 6	241.9 ± 19.6	244.7 ± 18.1 (1.2%)	244.5 ± 19.9 (1.1%)	230.2 ± 20.2 (-4.8%)
		MSW 14	276.1 ± 22.3	280.6 ± 20.9 (1.6%)	278.9 ± 24.6 (1.0%)	264.0 ± 25.3 (-4.4%)
Food consumption (g/rat/day) [#]	Male N=5	MSW 6	31.3 ± 1.5	29.7 ± 1.4 (-5.1%)	29.4 ± 29.4 (-6.1%)	30.3 ± 2.4 (-3.2%)
		MSW 13	25.8 ± 0.6	25.0 ± 0.4 (-3.1%)	24.6 ± 0.8 (-4.7%)	24.7 ± 1.6 (-4.3%)
	Female N=5	MSW 6	21.7 ± 0.6	21.6 ± 1.0 (-0.5%)	22.5 ± 0.8 (3.7%)	21.5 ± 0.8 (-0.9%)
		MSW 13	18.2 ± 0.4	18.2 ± 0.4 (0%)	18.7 ± 0.8 (2.7%)	17.8 ± 1.0 (-2.2%)

Acetochlor OXA – 90-day study (Williams, 2000b, rat, diet)						
Effect			**Doses**			
			0 ppm	**1000 ppm M/F 77.2/ 86.5 mg/kg-day**	**3000 ppm M/F 230.2/268.0 mg/kg-day**	**12000 ppm M/F 955.2/1082.7 mg/kg-day**
Adjusted Body Weight (g) [#]	Male N=20	MSW 6	408.5	393.1 (-3.8%)	388.8* (-4.8%)	387.6* (-5.1%)
		MSW 14	503.8	478.9 (-4.9%)	475.3* (-5.7%)	470.1* (-6.7%)
	Female N=20	MSW 6	243.5	243.7 (0.08%)	243.6 (0.04%)	230.6** (-5.3%)
		MSW 14	277.8	279.4 (0.6%)	277.9 (0.04%)	264.4* (-5.1%)
Food utilization (g growth / 100g food)	Male	MSW 1-13	11.22 ± 0.27 N=5	10.75 ± 0.51 (-4.2%) N=4	10.68* ± 0.38 (-4.8) N=5	10.25** ± 0.27 (-8.6%) N=4
	Female	MSW 1-13	5.82 ± 0.20 N=3	6.19 ± 0.45 (6.4%) N=5	6.03 ± 0.44 (3.6%) N=4	5.39** ± 0.48 (-7.4%) N=5
Thyroid weight (g)	Male N=12	absolute	0.020 ± 0.005	0.019 ± 0.004 (-5.0%)	0.019 ± 0.003 (-5.0%)	0.020 ± 0.004 (0%)
		Organ to BW Ratio	0.004 ± 0.001	0.004 ± 0.001 (0%)	0.004 ± 0.000 (0%)	0.004 ± 0.001 (0%)
	Female N=12	absolute	0.016 ± 0.004	0.017 ± 0.003 (6.25%)	0.019 ± 0.003 (18.75%)	0.018 ± 0.005 (12.5%)
		Organ to body weight ratio	0.006 ± 0.002	0.006 ± 0.001 (0%)	0.007 ± 0.001 (16.7%)	0.007 ± 0.002 (16.7%)
Liver weight (g)	Male N=12	absolute	17.4 ±1.9	16.5 ± 1.6 (-5.2%)	16.5 ± 2.3 (-5.2%)	15.8* ± 1.7 (-9.2%)
		Organ to body weight ratio	3.4 ± 0.2	3.5 ± 0.2 (2.9%)	3.5 ± 0.2 (2.9%)	3.3 ± 0.2 (-2.9%)
	Female N=12	absolute	9.3 ± 1.1	9.5 ± 1.0 (2.2%)	9.3 ± 1.2 (0%)	9.0 ± 1.3 (-2.2%)
		Organ to body weight ratio	3.4 ± 0.3	3.4 ± 0.2 (0%)	3.4 ± 0.2 (0%)	3.4 ± 0.3 (0%)
Hemoglobin (g/dl)		Male N=12	15.4 ± 0.4	15.2 ± 0.5 (1.3%)	15.5 ± 0.3 (0.6%)	15.3 ± 0.5 (-0.6%)

Acetochlor OXA – 90-day study (Williams, 2000b, rat, diet)					
Effect		**Doses**			
		0 ppm	**1000 ppm M/F 77.2/ 86.5 mg/kg-day**	**3000 ppm M/F 230.2/268.0 mg/kg-day**	**12000 ppm M/F 955.2/1082.7 mg/kg-day**
	Female N=12	15.3 ± 0.6	15.3 ± 0.5 N=11 (0%)	15.2 ± 0.7 (-0.7%)	15.2 ± 0.6 (-0.7%)
Hematocrit (no units)	Male N=12	0.449 ± 0.016	0.448 ± 0.020 (-0.22%)	0.455 ± 0.014 (1.3 %)	0.446 ± 0.014 (-0.67%)
	Female N=12	0.437 ± 0.017	0.440 ± 0.016 N=11 (0.7%)	0.432 ± 0.023 (-1.1%)	0.437 ± 0.018 (0%)
Red Blood Cell Count (x10**12/l)	Male N=12	8.54 ± 0.30	8.55 ± 0.50 (0.12%)	8.68 ± 0.32 (1.6%)	8.75 ± 0.42 (2.5%)
	Female N=12	8.06 ± 0.26	8.09 ± 0.21 N=11 (0.4%)	8.04 ± 0.45 (-0.3%)	8.03 ± 0.35 (-0.4%)
Mean Cell Volume (fl)	Male N=12	52.6 ± 1.2	52.5 ± 1.4 (-0.2%)	52.4 ± 1.4 (-0.4%)	51.0* ± 0.5 (-3.0%)
	Female N=12	54.2 ± 1.3	54.4 ± 1.7 N=11 (0.4%)	53.7 ± 1.9 (-0.9%)	54.4 ± 2.2 (0.4%)
Mean Cell Hemoglobin (pg)	Male N=12	18.1 ± 0.4	17.9 ± 0.6 (-1.1%)	17.9 ± 0.5 (-1.1%)	17.5* ± 0.5 (-3.3%)
	Female N=12	18.9 ± 0.4	18.9 ± 0.5 N=11 (0%)	18.9 ± 0.5 (0%)	18.9 ± 0.7 (0%)
Mean Cell Hemoglobin Concentration (g/dl)	Male N=12	34.3 ± 0.6	34.1 ± 0.6 (-0.6%)	34.2 ± 0.4 (-0.3%)	34.4 ± 0.5 (0.3%)
	Female N=12	34.9 ± 0.5	34.8 ± 0.7 N=11 (-0.3%)	35.1 ± 0.6 (0.6%)	34.8 ± 0.6 (-0.3%)
MS- Main + Satellite Groups; W – Week; N – Number of animals per dose group; Adjusted Body Weight – Adjusted to initial body weight but initial body weights not provided; [#]- Weekly body weight, adjusted body weight, and food consumption data reported, but table only shows values for weeks 6 and 14; *- Statistically significant difference from the control group mean at the 5% level (Student's t-test, two sided); **-Statistically significant difference from control group mean at the 1% level (Student's t-test, two sided); ± - (standard deviation); (%) – percent change from control.					

(7) Table 3-5. Treatment-related Effects Observed in a 28-day preliminary range finding Toxicity Study with Alachlor ESA (NO FIGURES)

Alachlor ESA – 28-day range finding drinking water (Siglin 1993; F344 rats)							
Effect			**Doses**				
			0 ppm	700 ppm M/F 69/75 mg/kg-day	2000 ppm M/F 183/205 mg/kg-day	7000 ppm M/F 656/749 mg/kg-day	20000 ppm M/F 2217/2378 mg/kg-day
Body weight (g)[#]	Male N=6	D 28	254 ± 7.7	251 ± 4.6 (-1.2%)	250 ± 10.1 (-1.6%)	252 ± 14.5 (-0.8%)	230** ± 9.7 N=5 (-9.4%)
	Female N=6	D 28	158 ± 6.1	156 ± 9.1 (-1.3%)	155 ± 5.3 (-1.9%)	162 ± 6.8 (2.5%)	151 ± 10.4 (-4.4%) (N=5)
Food consumption (g/rat-day)	Male N=6	D 28	18 ± 0.3	17 ± 0.6 (-5.6%)	18 ± 0.9 (0%)	18 ± 1.2 (0%)	18 ± 0.8 (0%) (N=5)
	Female N=6	D 28	13 ± 0.3	12 ± 0.7 (-7.7%)	12 ± 0.6 (-7.7%)	13 ± 0.5 0%)	13 ± 0.5 (0%) (N=5)
Body weight gain (g)[##]	Male N=6	D 22-28	11 ± 2.2	11 ± 2.1 (0%)	11 ± 2.9 (0%)	10 ± 2.3 (-9.1%)	19** ± 3.7 (72.7%) (N=5)
	Female N=6	D 22-28	2 ± 2.4	4 ± 1.2 (100%)	2 ± 1.8 (0%)	3 ± 1.5 ((50%)	4 ± 1.8 (100%) (N=5)
Water intake (g/kg-day) [##]	Male N=6	D 22-28	85 ± 4.5	84 ± 4.5 (-1.2%)	85 ± 4.5 (0%)	87 ± 5.8 (2.4%)	121** ± 2.5 (42.4%) (N=5)
	Female N=6	D 22-28	107 ± 7.5	101 ± 5.6 (-5.6%)	100 ± 8.8 (-6.5%)	105 ± 6.8 (-1.9%)	131 ± 33.5 (22.4%) (N=5)

D – Day; N – Number of animals per dose group; [#] Body weight data provided for Days 1, 8, 15, and 28, but table shows data only for Day 28; [##] Weekly body weight gain and water intake data reported, but table shows data only for the final week (i.e., Days 22-28); *-Statistically significant difference from the control group mean at the 5% level (Student's t-test, two sided); **-Statistically significant difference from control group mean at the 1% level (Student's t-test, two sided); ± - (standard deviation); (%) – percent change from control.

(8) Table 3-6. Treatment-related Effects Observed in a 91-day Toxicity Study with Alachlor ESA (NO FIGURES)

Alachlor ESA – 91-day drinking water (Siglin 1993; Heydens et al., 1996; F344 rats)						
Effect			**Doses**			
			0 ppm	200 ppm M/F 16/ 23 mg/kg-day	2000 ppm M/F 157/ 207 mg/kg-day	10000 ppm M/F 896/1108 mg/kg-day
Body weight (g)[#]	Male N=10	D 91	333 ± 9.7	337 ± 17.2 (1.20%)	337 ± 13.3 (1.2%)	318 ± 13.9 (-4.5) (N=9)
	Female N=10	D 91	198 ± 6.7	190 ± 6.6 (-4.0%)	191 ± 8.1 (-3.5%)	188** ±7.5 (-5.1%)
Food consumption (g/rat-day)[##]	Male N=10	D 85-91	18 ± 0.7	18 ± 0.7 (0%)	18 ± 0.7 (0%)	18 ± 0.7 (0%) (N=9)
	Female N=10	D 85-91	13 ± 0.4	13 ± 0.6 (0%) N=9	13 ± 0.8 (0%) N=9	13 ± 0.9 (0%)
Body weight gain (g) [##]	Male N=10	D 85-91	3 ± 2.3	5 ± 2.7 (66.7%)	4 ± 2.6 (33.3%)	4 ± 1.7 (33.3%) (N=9)
	Female N=10	D 85-91	0 ± 2.4	1 ± 1.8	1 ± 2.3	3* ± 1.6
Water intake (g/kg-day) [##]	Male N=10	D 85	62 ± 2.0	64 ± 1.6 (3.2%)	64 ± 2.8 (3.2%)	73** ± 3.9 (17.7%) (N=9)
	Female N=10	D 85-91	93 ± 10.3	104 ± 11.2 (11.8%)	97 ± 9.6 (4.3%)	102 ± 9.9 (9.7%)
Glucose (MG/DL)	Male N=10		123.6 ± 9.37	122.2 ± 7.50 (-1.1%)	114.6 ± 9.91 (-7.3%)	110.4** ± 3.57 (-10.7%) (N=9)
	Female N=10		109.5 ± 22.59	109.2 ± 5.05 (-0.3%)	108.1 ± 19.25 (-1.3%)	103.7 ± 13.40 (-5.3%)
Total bilirubin (MG/DL)	Male N=10		0.417 ± 0.0457	0.427 ± 0.0778 (2.4%)	0.464 ± 0.0871 (11.2%)	0.517** ± 0.0558 (24.0%) (N=9)
	Female N=10		0.510 ± 0.0706	0.471 ± 0.1010 (-7.6%)	0.464 ± 0.0955 (-9.0%)	0.471 ± 0.0828 (-7.6%)
Albumin (g/dL)	Male N=10		3.634 ± 0.0789	3.657 ± 0.1165 (0.6%)	3.535* ± 0.0830 (-2.7%)	3.487* ± 0.1338 (-4.1%) (N=9)
	Female N=10		3.310 ± 0.2348	3.362 ± 0.0832 (1.6%)	3.370 ± 0.0950 (1.8%)	3.340 ± 0.0987 (0.9%)
Phosphorus (MG/DL)	Male N=10		7.595 ± 0.6779	7.912 ± 0.6327 (4.2%)	8.312 ± 0.8868 (9.4%)	8.424* ± 0.3999 (10.9%) (N=9)

Alachlor ESA – 91-day drinking water (Siglin 1993; Heydens et al., 1996; F344 rats)						
Effect			**Doses**			
			0 ppm	200 ppm M/F 16/ 23 mg/kg-day	2000 ppm M/F 157/ 207 mg/kg-day	10000 ppm M/F 896/1108 mg/kg-day
	Female N=10		7.835 ± 0.9962	7.173 ± 0.7704 (-8.5%)	7.416 ± 1.1236 (-5.3%)	7.966 ± 0.9784 (1.7%)
Liver weight (g)	Male N=10	absolute	9.65 ± 0.671	10.16 ± 0.836 (5.3%)	10.23 ± 0.874 (6.0%)	9.39 ± 0.589 (-2.7%) (N=9)
	Female N=10	absolute	5.30 ± 0.483	5.42 ± 0.589 (2.3%)	5.23 ± 0.382 (-1.3%)	5.36 ± 0.271 (1.1%)
Hemoglobin (g/dl)		Male N=10	16.45 ± 0.288	16.40 ± 0.216 (-0.3%)	15.71 ± 0.957 (-4.5%)	15.94** ± 0.391 (-3.1%) (N=9)
		Female N=10	15.71 ± 0.857	16.23 ± 0.422 (3.3%)	15.98 ± 0.349 (1.7%)	16.02 ± 0.220 (2.0%)
Hematocrit (%)		Male N=10	46.01 ± 0.754	46.41 ± 1.523 (0.9%)	45.05 ± 1.678 (-2.1%)	43.80* ± 0.96 (-4.8%) (N=9)
		Female N=10	43.78 ± 2.974	45.37 ± 1.306 (3.6%)	43.55 ± 1.211 (-0.53%)	44.14 ± 1.749 (0.82%)
Red Blood Cell Count (10*6/cmm)		Male N=10	9.520 ± 0.1033	9.60 ± 0.1633 (1.2%)	9.22** ± 0.2616 (-3.2%)	9.022* ± 0.1922 (-5.23%) (N=9)
		Female N=10	8.340 ± 0.5038	8.670 ± 0.2111 (4.0%)	8.360 ± 0.1646 (0.24%)	8.460 ± 0.2675 (1.4%)
Mean Cell Volume (fl)		Male N=10	48.34 ± 0.687	48.34 ± 1.054 (0%)	48.85 ± 0.965 (1.1%)	48.57 ± 0.714 (0.5%) (N=9)
		Female N=10	52.48 ± 0.547	52.33 ± 0.688 (-0.29%)	52.10 ± 0.616 (-0.72%)	52.15 ± 0.546 (-0.63%)
Mean Cell Hemoglobin (pg) Mean Cell Hemoglobin Concentration (g/dl)		Male N=10	17.28 ± 0.305	17.08 ± 0.326 (-1.2%)	17.02 ± 0.830 (-1.5%)	17.67** ± 0.316 (2.3%) (N=9)
		Female N=10	18.86 ± 0.455	18.72 ± 0.175 (-0.74%)	19.12 ± 0.336 (1.4%)	18.94 ± 0.378 (0.42%)
		Male N=10	35.76 ± 1.019	35.38 ± 1.181 (-1.1%)	34.91 ± 2.269 (-2.4%)	36.4 ± 0.738 (1.8%) (N=9)
		Female N=10	35.92 ± 1.187	35.76 ± 0.729 (-0.45%)	36.70 ± 1.010 (2.2%)	36.36 ± 0.999 (1.2%)
W-Week; N – Number of animals per dose group; [#] - Body weight data reported for Day 1 and at the beginning of each subsequent week, but table shows data						

Alachlor ESA – 91-day drinking water (Siglin 1993; Heydens et al., 1996; F344 rats)				
Effect	**Doses**			
	0 ppm	200 ppm M/F 16/ 23 mg/kg-day	2000 ppm M/F 157/ 207 mg/kg-day	10000 ppm M/F 896/1108 mg/kg-day
only for the final week (reported as Day 91); Weekly food consumption, body weight gain, and water intake data reported, but table shows data only for the final week (reported as Days 85-91; *-Statistically significant difference from the control group mean at the 5% level (Student's t-test, two sided); **-Statistically significant difference from control group mean at the 1% level (Student's t-test, two sided); ± - (standard deviation); (%) – percent change from control.				

(9) Table 3-7. Treatment-related Effects Observed in a 90-day Toxicity Study with Alachlor ESA

Alachlor ESA – 90-day study (Kirkpatrick, 2002; rats, diet)						
Effect			Doses			
			0 ppm	3000 ppm M/F 195 / 222 mg/kg-day	6000 ppm M/F 389 / 454 mg/kg-day	12000 ppm M/F 788 / 926 mg/kg-day
Body weight (g)[#]	Male N=15	W 6	424 ± 33.1	410 ± 49.8 (-3.3%)	427 ± 35.0 (0.7%)	408 ± 36.4 (-3.8%)
		W 13	510 ± 42.7	487 ± 68.9	510 ± 37.9	485 ± 48.0
	Female N=15	W 6	251 ± 16.8	257 ± 21.5 (2.4%)	255 ± 18.5 (1.6%)	244 ± 11.3 (-2.8%)
		W 13	278 ± 22.2	284 ± 21.6 (2.2%)	284 ± 23.3 (2.2%)	272 ± 17.2 (-2.2%)
Cumulative Body Weight Changes (g)	Male N=15		260 ± 40.2	241 ± 59.0 (-7.3%)	257 ± 32.2 (-1.2%)	236 ± 42.9 (-9.2%)
	Female N=15		87 ± 18.4	91 ± 15.8 (4.6%)	91 ± 18.6 (4.6%)	82 ± 16.4 (-5.7%)
Food Consumption (g/animal-day)[#]	Male N=15	W 6	28 ± 2.3	27 ± 3.2 (-3.6%)	27 ± 2.5 (-3.6%)	27 ± 1.8 (-3.6%)
		W 13	25 ± 2.3	23 ± 3.7 (-8.0%)	25 ± 1.7 (0%)	25 ± 1.8 (0%)
	Female N=15	W 6	19 ± 1.9	20 ± 2.6 (5.3)	20 ± 2.6 (5.3)	19 ± 1.4 (0%)
		W 13	17 ± 2.1	17 ± 1.3 (0%)	17 ± 1.7 (0%)	17 ± 1.1 (0%)
Liver Weight	Male	absolute	12.62 ± 1.342	11.89 ± 1.636	12.42 ± 1.391	11.40 ± 1.272

Alachlor ESA – 90-day study (Kirkpatrick, 2002; rats, diet)						
Effect			Doses			
			0 ppm	3000 ppm M/F 195 / 222 mg/kg-day	6000 ppm M/F 389 / 454 mg/kg-day	12000 ppm M/F 788 / 926 mg/kg-day
(g)	N=15			(-5.8%)	(-1.6%)	(-9.7%)
		Organ to body weight ratio	2.578 ± 0.1918	2.560 ± 0.1421 (-0.7%)	2.549 ± 0.1811 (-1.1%)	2.472 ± 0.1524 (-4.1%)
	Female N=15	absolute	6.91 ± 0.883	7.08 ± 0.463 (2.5%)	6.81 ± 0.486 (-1.4%)	6.66 ± 0.434 (-3.6%)
		Organ to body weight ratio	2.634 ± 0.1925	2.639 ± 0.1546 (0.2%)	2.552 ± 0.1687 (-3.1%)	2.623 ± 0.1671 (-0.4%)
Thyroid weight (g)	Male N=15	absolute	0.0259 ± 0.00403	0.0251 ± 0.00679 (-3.1%)	0.0273 ± 0.00536 (5.4%)	0.0252 ± 0.00456 (-2.7%)
		Organ to body weight ratio	0.005 ± 0.0011	0.005 ± 0.0013 (0%)	0.006 ± 0.0007 (20%)	0.006 ± 0.0012 (20%)
	Female N=15	absolute	0.0183 ± 0.00390	0.0192 ± 0.00428 (4.9%)	0.0213 ± 0.00453 (16.4%)	0.0186 ± 0.00318 (1.6%)
		Organ to body weight ratio	0.007 ± 0.0014	0.007 ± 0.0017 (0%)	0.008 ± 0.0013 (14.3%)	0.007 ± 0.0013 (0%)
Hemoglobin (g/dl)	Male N=15		15.3 ± 0.50	15.4 ± 0.70 (0.7%)	15.4 ± 0.85 (0.7%)	15.6 ± 0.69 (2.0%)
	Female N=15		14.8 ± 0.42	15.0 ± 0.86 (1.4%)	15.1 ± 0.56 (2.0%)	15.2 ± 0.83 (2.7%)
Hematocrit (%)	Male N=15		43.9 ± 1.61	44.1 ± 2.11 (0.5%)	44.1 ± 2.30 (0.5%)	44.8 ± 1.99 (2.1%)
	Female N=15		42.2 ± 1.68	42.6 ± 2.54 (0.9%)	43.1 ± 1.68 (2.1%)	43.1 ± 2.16 (2.1%)
Red Blood Cell Count (mil/uL)	Male N=15		8.58 ± 0.402	8.59 ± 0.379 (0.1%)	8.58 ± 0.479 (0%)	8.63 ± 0.392 (0.6%)
	Female N=15		7.85 ± 0.423	7.88 ± 0.377 (0.4%)	7.90 ± 0.389 (0.6%)	7.95 ± 0.406 (1.3%)
Mean Cell Volume (fl)	Male N=15		51.2 ± 1.35	51.3 ± 1.57 (0.2%)	51.4 ± 1.52 (0.4%)	51.9 ± 1.38 (1.4%)
	Female		53.8 ± 1.63	54.0 ± 1.80	54.5 ± 1.51	54.2 ± 1.49

Alachlor ESA – 90-day study (Kirkpatrick, 2002; rats, diet)					
Effect		Doses			
		0 ppm	3000 ppm M/F 195 / 222 mg/kg-day	6000 ppm M/F 389 / 454 mg/kg-day	12000 ppm M/F 788 / 926 mg/kg-day
	N=15		(0.4%)	(1.3%)	(0.7%)
Mean Cell Hemoglobin (uug)	Male N=15	17.9 ± 0.53	17.9 ± 0.52 (0%)	18.0 ± 0.52 (0.6%)	18.1 ± 0.47 (1.1%)
	Female N=15	18.9 ± 0.62	19.1 ± 0.64 (1.1%)	19.2 ± 0.63 (1.6%)	19.1 ± 0.53 (1.1%)
Mean Cell Hemoglobin Concentration (g/dl)	Male N=15	35.0 ± 0.35	34.9 ± 0.34 (-0.3%)	34.9 ± 0.36 (-0.3%)	34.8 ± 0.33 (-0.6%)
	Female N=15	35.1 ± 0.62	35.3 ± 0.36 (0.6%)	35.2 ± 0.54 (0.3%)	35.1 ± 0.49 (0%)
W – Week; N – Number of animals per dose group; Adjusted Body Weight – Adjusted to initial body weight but initial body weights not provided; [#] - Weekly body weight and food consumption data reported, but table shows data reported only for Day 29; *-Statistically significant difference from the control group mean at the 5% level (Student's t-test, two sided); **-Statistically significant difference from control group mean at the 1% level (Student's t-test, two sided); ± - (standard deviation); (%) – percent change from control; BW- body weight.					

(10) Table 3-8. Treatment-related Effects Observed in a 28-day Toxicity Study with Alachlor OXA (NO FIGURES)

Alachlor OXA – 28-day study (Stout and Thake, 2000, rat, diet)						
Effect			Doses			
			0 ppm	1000 ppm M/F 74.21/83.35 mg/kg-day	10000 ppm M/F 754.26/829.68 mg/kg-day	20000 ppm M/F 1539.32 /1595.26 mg/kg-day
Body weight (terminal) (g)[#]	Male N=5	D 29	416.8 ± 21.04	451.2* ± 17.15 (8.3%)	436.4 ± 19.40 (4.7%)	432.1 ±17.20 (3.7%)
	Female N=5	D 29	252.2 ± 31.52	240.9 ± 16.69 (-4.5%)	246.3 ± 16.86 (-2.3%)	241.3 ± 16.38 (-4.32%)
Cumulative Body Weight Changes (g)	Male N=5		185.90 ± 16.722	219.82* ± 18.283 (18.2%)	205.76 ± 14.026 (10.7%)	201.14 ± 14.165 (8.2%)
	Female N=5		78.94 ± 23.662	67.20 ± 11.349 (-14.9%)	72.14 ± 17.522 (-8.6%)	67.84 ± 15.734 (-14.1%)
Food consumption (Week 4)[#]	Male N=5	D 29	26.2 ± 1.72	30.2* ± 1.90 (15.3%)	29.5* ± 1.95 (12.6%)	30.3* ± 1.93 (15.6%)

	Female N=5	D 29	19.0 ± 3.29	18.0 ± 0.87 (-5.3%)	18.8 ± 2.55 (-1.1%)	18.2 ± 1.74 (-4.2%)
Liver Weight (g)	Male N=5	absolute	11.984 ± 0.954	13.032 ± 0.817 (8.7%)	12.385 ± 0.879 (3.3%)	13.406 ± 1.581 (11.9%)
		Organ to BW Ratio	3.121 ± 0.149	3.173 ± 0.148 (1.7%)	3.161 ± 0.155 (1.3%)	3.475* ± 0.305 (11.3%)
	Female N=5	absolute	7.601 ± 0.906	6.960 ± 0.746 (-8.4%)	7.011 ± 0.721 (-7.8%)	6.952 ± 0.668 (-8.5%)
		Organ to BW Ratio	3.328 ± 0.250	3.186 ± 0.159 (-4.3%)	3.162 ± 0.204 (-5.0%)	3.212 ± 0.213 (-3.5%)
Gastric changes - hyperplasia	Males		0/5	0/5	0/5	2/5
	Females		0/5	0/5	0/5	3/5
Gastric changes - eosinophilic inclusion	Males		1/5	0/5	0/5	4/5
	Females		0/5	0/5	0/5	3/5
Hemoglobin (g/dl)	Male N=5		16.18 ± 0.2387	15.28 ± 0.3347 (-5.6%)	15.74 ± 0.7301 (-2.7%)	15.3 ± 0.8944 (-5.4%)
	Female N=5		16.22 ± 0.8438	16.46 ± 0.8355 (1.5%)	16.34 ± 0.757 (0.74%)	16.175 ± 0.5123 N=4 (-0.28%)
Hematocrit (%)	Male N=5		49.7 ± 0.6042	46.68 ± 1.627 (-6.1%)	48.96 ± 3.1517 (-1.5%)	47.14 ± 2.6726 (-5.2%)
	Female N=5		47.62 ± 2.3414	49.08 ± 2.7725 (3.1%)	48.82 ± 1.5189 (2.5%)	48.7 ± 1.5706 N=4 (2.3%)
Red Blood Cell Count (millions per uL)	Male N=5		8.5680 ± 0.2331	7.9720 ± 0.4256 (-7.0%)	8.1620 ± 0.5412 (-4.7%)	7.7740* ± 0.5315 (-9.3%)
	Female N=5		8.1520 ± 0.3669	8.5580 ± 0.4208 (5.0%)	8.3860 ± 0.3178 (2.9%)	8.5950 ± 0.3264 N=4 (5.4%)
Mean Cell Volume (femtoliters)	Male N=5		58.04 ± 1.2482	58.62 ± 1.2696 (1.0%)	60.02 ± 2.2399 (3.4%)	60.74* ± 1.5485 (4.7%)
	Female N=5		58.48 ± 2.1464	57.36 ± 1.59 (-1.9%)	58.22 ± 0.5263 (-0.5%)	56.7 ± 1.4652 N=4 (-3.0%)
Mean Cell Hemoglobin (pg)	Male N=5		18.88 ± 0.2864	19.18 ± 0.6943 (1.6%)	19.3 ± 0.6364 (2.2%)	19.7 ± 0.3808 (4.3%)
	Female N=5		19.9 ± 0.6557	19.24 ± 0.4722 (-3.3%)	19.52 ± 0.2950 (-1.9%)	18.825* ± 0.4787 N=4 (-5.4%)
Mean Cell Hemoglobin Concentration (g/dl)	Male N=5		32.58 ± 0.4382	32.72 ± 0.5718 (0.4%)	32.16 ± 0.7301 (-1.3%)	32.4 ± 0.2915 (-0.6%)

	Female N=5	34.04 ± 0.9476	33.54 ± 0.2608 (-1.5%)	33.48 ± 0.5718 (-1.6%)	33.175 ± 0.2986 (-2.5%)
N – Number of animals per dose group; # – In-life body weights and food consumption were determined every 6-8 days, but table shows data only for Day 29; * – Statistically significant difference from the control group mean at the 5% level (Student's t-test, two sided); ** – -Statistically significant difference from control group mean at the 1% level (Student's t-test, two sided); ± - (standard deviation); (%) – percent change from control.					

(11) Table 3-9. Treatment-related Effects Observed in a 90-day Toxicity Study with Alachlor OXA (NO FIGURES)

Alachlor OXA – 90-day study (Lemen et al., 2000; rats, diet)							
Effect			Doses				
			0 ppm	400 ppm M/F 24.9/29.1 mg/kg-day	1300 ppm M/F 83.5/95.4 mg/kg-day	4000 ppm M/F 261.1/290.9 mg/kg-day	13000 ppm 834.6/1008.3 M/F mg/kg-day
Body weight (g)	Male N=10	D 43	450.9 ± 23.63	459.7 ± 49.37 (2.0%)	442.1 ± 46.07 (-2.0%)	457.4 ± 23.17 (1.4%)	432.0 ± 59.11 (-4.2%)
		D 91	550.2 ± 28.14	577.3 ± 59.98 (4.9%)	544.4 ± 66.59 (-1.1%)	563.7 ± 37.95 (2.5%)	529.9 ± 84.65 (-3.7%)
	Female N=10	D 43	276.7 ± 23.71	277.1 ± 13.50 (0.1%)	288.5 ± 22.13 (4.3%)	269.0 ± 20.65 (-2.8%)	273.5 ± 21.04 (-1.2%)
		D 91	308.8 ± 35.40	313.5 ± 20.72 (1.5%)	324.6 ± 31.94 (5.1%)	303.3 ± 22.45 (-1.8%)	306.6 ± 23.52 (-0.7%)
Cumulative Body Weight Changes (g)	Male N=10	D 1-50	247.38 ± 21.63	256.47 ± 40.41 (3.7%)	236.99 ± 39.18 (-4.2%)	250.12 ± 23.56 (1.1%)	224.81 ± 48.29 (-9.1%)
		D 1-91	325.61 ± 26.35	349.99 ± 54.95 (7.5%)	319.94 ± 54.95 (-1.7%)	337.33 ± 35.35 (-4.3%)	304.46 ± 71.48 (-6.5%)
	Female N=10	D 1-50	97.31 ± 17.88	98.08 ± 12.73 (0.8%)	108.51 ± 22.54 (11.5%)	86.48 ± 12.35 (-11.1%)	96.04 ± 22.09 (-1.3%)
		D 1-91	125.98 ± 29.95	127.23 ± 16.76 (1.0%)	140.22 ± 27.83 (11.3%)	120.50 ± 15.38 (-4.3%)	126.42 ± 23.47 (0.3%)
Food Consumption (g)	Male N=10	W 6	28.1 ± 1.81	27.0 ± 4.84 (-3.9%)	27.6 ± 2.96 (-1.8%)	29.3 ± 1.87 (4.3%)	27.1 ± 4.40 (-3.6%)
		W 13	28.5 ± 2.03	28.6 ± 2.84 (0.4%)	28.1 ± 3.28 (-1.4%)	28.6 ± 2.47 (0.4%)	26.8 ± 3.88 (6.7%)
	Female N=10	W 6	19.7 ± 2.64	19.8 ± 1.56 (0.5%)	21.0 ± 2.23 (6.7%)	19.1 ± 1.27 (-3.0%)	20.6 ± 3.03 (4.6%)

Alachlor OXA – 90-day study (Lemen et al., 2000; rats, diet)							
Effect			Doses				
			0 ppm	400 ppm M/F 24.9/29.1 mg/kg-day	1300 ppm M/F 83.5/95.4 mg/kg-day	4000 ppm M/F 261.1/290.9 mg/kg-day	13000 ppm 834.6/1008.3 M/F mg/kg-day
		W 13	19.4 ± 2.67	19.7 ± 1.66 (1.5%)	19.7 ± 1.75 (1.5%)	19.4 ± 1.44 (0%)	21.2 ± 2.89 (9.3%)
Liver Weight (g)	Male N=10	absolute	13.99 ± 1.376	15.90 ± 1.764 (13.7%)	14.426 ± 2.190 (3.1%)	14.854 ± 1.522 (6.2%)	13.278 ± 2.131 (-5.1%)
		Organ to body weight ratio	2.774 ± 0.223	2.866 ± 0.237 (3.3%)	2.930 ± 0.261 (5.6%)	2.953 ± 0.307 (6.5%)	2.836 ± 0.241 (2.2%)
	Female N=10	absolute	7.930 ± 0.823	8.316 ± 0.558 (4.9%)	8.279 ± 0.962 (4.4%)	7.737 ± 0.612 (-2.4%)	8.327 ± 0.817 (5.0%)
		Organ to body weight ratio	2.773 ± 0.261	2.865 ± 0.195 (3.3%)	2.708 ± 0.144 (-2.3%)	2.781 ± 0.164 (0.3%)	2.971* ± 0.24 (7.1%)
Thyroid weight (g)	Male N=10	absolute	0.0278 ± 0.007	0.0334 ± 0.0073 (20.1%)	0.0343 ± 0.009 (23.4%)	0.0339 ± 0.010 (21.9%)	0.0302 ± 0.0163 (8.6%)
		Organ to body weight ratio	0.006 ± 0.0013	0.006 ± 0.001 (0%)	0.007 ± 0.002 (16.7%)	0.007 ± 0.0015 (16.7%)	0.007 ± 0.004 (16.7%)
	Female N=10	absolute	0.0237 ± 0.006	0.0247 ± 0.0052 (4.2%)	0.0238 ± 0.0061 (0.4%)	0.0229 ± 0.007 (-3.4%)	0.0198 ± 0.0048 (-16.5%)
		Organ to body weight ratio	0.008 ± 0.003	0.009 ± 0.002 (12.5%)	0.008 ± 0.002 (0%)	0.008 ± 0.002 (0%)	0.007 ± 0.021 (-12.5%)
Hemoglobin (g/dl)	Male N=10		15.34 ± 0.628	14.87 ± 0.581 (-3.1%)	15.23 ± 0.720 (-0.7%)	15.23 ± 0.631 (-0.7%)	15.11 ± 0.717 (-1.5%) (N=9)
	Female N=10		15.41 ± 0.986	15.09 ± 0.626 (-2.1%)	15.10 ± 0.732 (-2.0%)	15.09 ± 0.574 (-2.1%)	14.98 ± 0.575 (-2.8%)
Hematocrit (%)	Male N=10		46.40 ± 1.9771	45.18 ± 1.729 (-2.6%)	46.31 ± 2.167 (-0.2%)	46.31 ± 2.536 (-0.2%)	45.92 ± 2.060 (-1.0%) (N=9)
	Female N=10		45.96 ± 2.621	45.21 ± 2.066 (-1.6%)	45.94 ± 2.351 (-0.4%)	46.17 ± 1.529 (0.5%)	45.58 ± 1.966 (-0.8%)
Red Blood Cell Count (millions per uL)	Male N=10		8.56 ± 0.370	8.483 ± 0.337 (-0.9%)	8.728 ± 0.274 (2.0%)	8.684 ± 0.219 (1.4%)	8.608 ± 0.423 (0.6%) (N=9)
	Female		8.372 ± 0.545	8.249 ± 0.486	8.199 ± 0.434	8.373 ± 0.298	8.067 ± 0.495

Alachlor OXA – 90-day study (Lemen et al., 2000; rats, diet)						
Effect		Doses				
		0 ppm	400 ppm M/F 24.9/29.1 mg/kg-day	1300 ppm M/F 83.5/95.4 mg/kg-day	4000 ppm M/F 261.1/290.9 mg/kg-day	13000 ppm 834.6/1008.3 M/F mg/kg-day
	N=10		(-1.5%)	(-2.1%)	(0%)	(-3.6%)
Mean Cell Volume (femtoliters)	Male N=10	54.24 ± 2.144	53.27 ± 1.301 (-1.8%)	53.05 ± 1.418 (-2.2%)	53.34 ± 2.522 (-1.7%)	53.356 ± 1.274 (-1.6%) (N=9)
	Female N=10	54.94 ± 1.209	54.85 ± 1.104 (-0.2%)	56.03 ± 1.677 (2.0%)	55.16 ± 1.523 (0.4%)	56.57 ± 1.905 (3.0%)
Mean Cell Hemoglobin (pg)	Male N=5	17.92 ± 0.590	17.51 ± 0.367 (-2.3%)	17.45 ± 0.510 (-2.6%)	17.54 ± 0.589 (-2.1%)	17.56 ± 0.445 (-2.0%) (N=9)
	Female N=5	18.42 ± 0.374	18.31 ± 0.351 (-0.6%)	18.41 ± 0.446 (-0.5%)	18.02 ± 0.457 (-2.2%)	18.61 ± 0.619 (1.0%)
Mean Cell Hemoglobin Concentration (g/dl)	Male N=5	33.03 ± 0.275	32.87 ± 0.472 (-0.5%)	32.90 ± 0.494 (-0.4%)	32.89 ± 0.649 (-0.4%)	32.89 ± 0.417 (-0.4%) (N=9)
	Female N=5	33.54 ± 0.648	33.38 ± 0.368 (-0.5%)	32.86* ± 0.530 (-2.0%)	32.69**±0.571 (-2.5%)	32.88* ± 0.343 (-2.0%)
D – Day; W – Week; # – In-life body weights were determined on Day 1 and every 6-8 days and food consumption every 6-8 days, but table shows data only for Day 43 and 91 (body weight) and Weeks 6 and 13 (food consumption); * – Statistically significant difference from the control group mean at the 5% level (Student's t-test, two sided); ** – Statistically significant difference from control group mean at the 1% level (Student's t-test, two sided); ± – (standard deviation); (%) – percent change from control;						

(12) Table 4. Comparative Toxicity of Acetochlor and Alachlor and their Degradates in Rats

Effect	**Effect Levels (mg/kg-day)***					
	Acetochlor and Degradates			**Alachlor and Degradates**		
	Acetochlor	**Acetochlor ESA**	**Acetochlor OXA**	**Alachlor**	**Alachlor ESA**	**Alachlor OXA**

Effect	Effect Levels (mg/kg-day)*					
	Acetochlor and Degradates			Alachlor and Degradates		
	Acetochlor	Acetochlor ESA	Acetochlor OXA	Alachlor	Alachlor ESA	Alachlor OXA
28-day Study						
Body weight	NOAEL: 68 (M) LOAEL: 132 (M) (Broadmeadow, 1985)	NOAEL: 1579/1607 (HDT) (M/F) (TERA) (Lees, 2000b)	NOAEL: 769 (M) LOAEL: 1468 (M) (Williams, 2000a)	NOAEL: 126 (M) (only dose tested in males) (Hotz et al., 1993)	NOAEL: 656/749 (M/F) (Drinking water) LOAEL: 2217/2379 (M/F) (Siglin, 1993)	NOAEL: 1539/1595 (HDT) (M/F) (Stout & Thake, 2000)
Hemoglobin	NOAEL: 519/539 (M/F) LOAEL: 1013/1081 (M/F) (EU, 2005)	NOAEL: 1579/1607 (M/F) (HDT) (Lees, 2000a)	NOAEL: 1568/1507 (M/F) (HDT) (Williams, 2000a)	No data	No data	NOAEL: 1539/1595 (M/F) (HDT) (Stout and Thake, 2000)
Hematocrit	No data	NOAEL: 1578/1607 (M/F) (HDT) (Lees, 2000a)	NOAEL: 568/1507 (M/F) (HDT) (Williams, 2000a)	No data	No data	NOAEL: 1539/1595 (M/F) (HDT) (Stout and Thake, 2000)
RBC	No data	NOAEL: 1579/1607 (M/F) (HDT) (Lees, 2000a)	NOAEL: 1568/1507 (M/F) (HDT) (Williams, 2000a)	No data	No data	NOAEL: 754 (M) LOAEL: 1539 (M) (Stout and Thake, 2000)
Liver	(1) LOAEL: 100.6 (LDT) (2) NOAEL: 10.4 LOAEL: 91.9	NOAEL: 1579 /1607 (M/F) (Lees, 2000a)	NOAEL: 1468/1507 (HDT) (M/F) (Williams, 2000a)	LOAEL: 126 (only dose tested (M) (Hotz et al., 1993)	No data	NOAEL: 1539/1595 (HDT) (M/F) (Stout & Thake,

Effect	Effect Levels (mg/kg-day)*					
	Acetochlor and Degradates			Alachlor and Degradates		
	Acetochlor	Acetochlor ESA	Acetochlor OXA	Alachlor	Alachlor ESA	Alachlor OXA
	(MRID 44496208; Hotz & Wilson, 1996) NOAEL: 132/139 (M/F) LOAEL: 267/279 (M/F) (Boradmeadow, 1985)					2000)
Thyroid: Weight (abs. or rel.)	(1) LOAEL: 100.6 (abs. & rel.) (m) (LDT) (2) NOAEL: 10.4 LOAEL: 91.9 (MRID 44496208; Hotz & Wilson, 1996)	NOAEL: 1579 /1607 (HDT) (M/F) (TERA) (Lees, 2000a)	NOAEL: 1468/1507 (HDT) (M/F) (Williams, 2000a)	LOAEL: 126 (only dose tested (M) (Hotz et al., 1993)	No data	NOAEL: 1539/1595 (HDT) (M/F) (Stout & Thake, 2000)
Hormones (TSH, free and/or total T3, T4)	(1) LOAEL: 100.6 (abs. & rel.) (m) (LDT) (2) NOAEL: 10.4 LOAEL: 91.9 (m) (MRID 44496208; Hotz & Wilson, 1996)	NOAEL: 1579 /1607 (M/F) (Lees, 2000a)	NOAEL: 1468/1507 (HDT) (M/F) (Williams, 2000a)	LOAEL: 126 (only dose tested) (M) (Hotz et al., 1993)		Not evaluated

Effect	Effect Levels (mg/kg-day)*					
	Acetochlor and Degradates			Alachlor and Degradates		
	Acetochlor	Acetochlor ESA	Acetochlor OXA	Alachlor	Alachlor ESA	Alachlor OXA
Gastric changes	Histopathology results not reported in review document (US EPA 2006)	No histopathological findings in the stomach (Lees 2000a)	No histopathological findings in the stomach (Williams 2000a)	No histopathological findings in the stomach (US EPA 2007)	No data	No data
90-day study						
Body weight	NOAEL: 16/19 (av. 17.5) (M/F) LOAEL: 161/192 (av. 176.5) (M/F) (MRID 41565115; Broadmeadow, 1986)	NOAEL: 225 (M) LOAEL: 919 (M) (MRID 45313801, Lees, 2000b)	NOAEL: 230 (M) LOAEL: 955 (M) (Willaims, 2000b)	NOAEL: 15 (av. M&F) LOAEL: 139/153 (av. 146) (M/F) (MRID 00023658; Wolf, 1966)	NOAEL: 157/207 (M/F) (drinking water) LOAEL: 896/1108 (M/F) (Siglin 1993; Heydens et al., 1996) NOAEL: 788/926 (M/F) (dietary) (HDT) (Kirkpatrick 2002)	NOAEL: 835/1008 (HDT) (M/F) (Lemen et al., 2000)
Hemoglobin	NOAEL: 450/530 (HDT) (M/F) (Ahmed, 1980)	NOAEL: 919/1073 (M/F) (HDT) (Lees, 2000b)	NOAEL: 955/1083 (M/F) (HDT) (Williams, 2000b)	No data	NOAEL: 896/1108 (M/F) (HDT) (drinking water) (Siglin, 1993; Heydens et al. 1996) NOAEL: 788/926	NOAEL: 835/1008 (M/F) (HDT) (Lemen et al., 2000)

Effect	Effect Levels (mg/kg-day)*					
	Acetochlor and Degradates			Alachlor and Degradates		
	Acetochlor	Acetochlor ESA	Acetochlor OXA	Alachlor	Alachlor ESA	Alachlor OXA
					(M/F) (dietary) (HDT) (Kirkpatrick 2002)	
Hematocrit	NOAEL: 450/530 (HDT) (M/F) (Ahmed, 1980)	NOAEL: 919/1073 (M/F) (HDT) (Lees, 2000b)	NOAEL: 955/1083 (M/F) (HDT) (Williams, 2000b)	No data	NOAEL: 896/1108 (M/F) (HDT) (drinking water) (Siglin, 1993; Heydens et al. 1996) NOAEL: 788/926 (M/F) (dietary) (HDT) (Kirkpatrick 2002)	NOAEL: 835/1008 (M/F) (HDT) (Lemen et al., 2000)
RBC	NOAEL: 450/530 (HDT) (M/F) (Ahmed, 1980)	NOAEL: 919/1073 (M/F) (HDT) (Lees, 2000b)	NOAEL: 955/1083 (M/F) (HDT) (Williams, 2000b)	No data	NOAEL: 896/1108 (M/F) (HDT) (drinking water) (Siglin, 1993; Heydens et al. 1996) NOAEL: 788/926 (M/F) (dietary) (HDT) (Kirkpatrick 2002)	NOAEL: 835/1008 (M/F) (HDT) (Lemen et al., 2000)
Liver	NOAEL: 16/19 (M/F) (av. 17.5) LOAEL: 161/192 (M/F; av. 176.5 mg/kg-day)	NOAEL: 919/1073 (M/F) (HDT) (Lees, 2000b)	NOAEL: 955/1083 (M/F) (HDT) (Williams, 2000b)	NOAEL: 15 (av. M/F) LOAEL: 139/153 (av. 146) (M/F)	NOAEL: 896/1108 (HDT) (M/F) (drinking water) (Siglin, 1993; Heydens et al. 1996)	NOAEL: 835/1008 (HDT) (M/F) (Lemen et al., 2000)

Effect	Effect Levels (mg/kg-day)*					
	Acetochlor and Degradates			Alachlor and Degradates		
	Acetochlor	Acetochlor ESA	Acetochlor OXA	Alachlor	Alachlor ESA	Alachlor OXA
	(MRID 41565115; Broadmeadow, 1986)			(MRID 00023658, Wolf, 1966)	NOAEL: 788/926 (M/F) (dietary) (HDT) (Kirkpatrick 2002)	
Thyroid: Weight (abs. or rel)	(1) LOAEL: 100.6 (abs. & rel.) (M) (LDT) (2) NOAEL: 10.4 LOAEL: 91.9 (m) (MRID 44496208; Hotz & Wilson, 1996)	NOAEL: 919/1073 (HDT) (M/F) (Lees, 2000b)	NOAEL: 995/1083 (HDT) (M/F) (Williams, 2000b)	LOAEL: 126 (HDT) (m) (Hotz et al., 1993)	NOAEL: 896/1108 (HDT) (M/F) (drinking water) (Siglin, 1993; Heydens et al., 1996) NOAEL: 788/926 (M/F) (dietary) (HDT) (Kirkpatrick 2002)	NOAEL:835/1008 (HDT) (M/F) (Lemen et al., 2000)
Hormone levels (TSH, free and/or total T3, T4)	NOAEL: 100.6 (M) LOAEL: 280.9 (M) (MRID 44496208; Hotz & Wilson, 1996)	Hormone levels not evaluated	Hormone levels not evaluated	Hormone levels not evaluated	Hormone levels not evaluated	Hormone levels not evaluated
Developmental						
Maternal toxicity	NOAEL: 150 LOAEL: 600	n/a	NOAEL: 500 LOAEL: 1000	NOAEL: 150 LOAEL: 400	NOAEL: 900 (HDT)	n/a

Effect	Effect Levels (mg/kg-day)*					
	Acetochlor and Degradates			Alachlor and Degradates		
	Acetochlor	Acetochlor ESA	Acetochlor OXA	Alachlor	Alachlor ESA	Alachlor OXA
	(MRID 41592005; Brooker et al., 1989)		(MRID 45313807; Holson, 2000)	(MRID 41592005; Brooker et al., 1989)	(Holson, 1995; Heydens et al., 2000)	
Developmental toxicity	NOAEL: 150 LOAEL: 600 (MRID 41592005; Brooker et al., 1989)	n/a	NOAEL: 1000 (HDT) (MRID 45313807; Holson, 2000)	NOAEL: 150 LOAEL: 400 (MRID 00043645; Rodwell and Tasker, 1980)	NOAEL: 900 (HDT) (Holson, 1995; Heydens et al., 2000)	n/a
Reproductive						
Parental/ systemic	NOAEL: 12.6/15.2 (M/F) LOAEL; 123.8/157.4 (M/F) (MRID 41565120, Willoghby, 1989)	n/a	n/a	NOAEL: 10 LOAEL: 30 (MRID 00075062; Schroder et al., 1981)	n/a	n/a
Offspring toxicity	NOAEL: 12.6/15.2 (M/F) LOAEL; 123.8/157.4 (M/F) (MRID 41565120; Willoghby, 1989)	n/a	n/a	NOAEL: 10 LOAEL: 30 (MRID 00075062; Schroder et al., 1981)	n/a	n/a

Effect	Effect Levels (mg/kg-day)*					
	Acetochlor and Degradates			Alachlor and Degradates		
	Acetochlor	Acetochlor ESA	Acetochlor OXA	Alachlor	Alachlor ESA	Alachlor OXA
Reproductive toxicity	NOAEL: 123.8/157.4 (M/F) (HDT) LOAEL: >123.8/157.4 (M/F) (MRID 41565120; Willoughby, 1989)	n/a	n/a	NOAEL: ≥30 LOAEL: ≥30 (MRID 00075062; Schroder et al., 1981)	n/a	n/a

*Lowest NOAELs reported;
n/a: study not available

Table 5. Toxicokinetic Data for Acetochlor and Alachlor and their Degradates

(13) Table 5a. Comparative Absorption

Acetochlor and Degradates			Alachlor and Degradates		
Acetochlor	**Acetochlor ESA**	**Acetochlor OXA**	**Alachlor**	**Alachlor ESA**	**Alachlor OXA**
Well-absorbed with 92-96% of dose by day 5 (MRID 41565125, -26, -27, 41592007, -08; Hawkins et al., 1987)	Quantitative estimates of percent absorption not reported but oral absorption of the test material described as relatively low due to the large amount of acetochlor ESA excreted in the feces by both sexes,	Quantitative estimates of percent absorption not reported; absorption described as incomplete due to the large amount of unmetabolized acetochlor OXA in the feces within 24 hours after dosing. U.S. EPA (2004)	Absorption at dose levels of 7 or 70 mg/kg essentially complete (MRID 42651306, 42852107, 42651308, 42852108; Wilson and Hall, 1986)	2-13% in males, 12-19% in females (Heydens et al 2000).	n/a

	the relatively low levels of radiolabel found in the urine, and the rapid rate of elimination. U.S. EPA (2004) concluded absorption was about 10-12% of the dose. (Albin and Kraus, 2000)	concluded absorption was about 34-39% of the dose. (Albin and Kraus, 2000)			

n/a: no study available

(14) Table 5b. Comparative Distribution

Acetochlor and Degradates			**Alachlor and Degradates**		
Acetochlor	**Acetochlor ESA**	**Acetochlor OXA**	**Alachlor**	**Alachlor ESA**	**Alachlor OXA**
Tissues did not retain high levels of radioactivity except for RBC, which retained about 2.5% of dose at study termination. (MRID 00130839; Carr et al., 1983) Retention in tissue/carcass negligible, primarily in blood (binding to RBC) and well-perfused organs (heart, spleen, kidney, lungs, liver).	After 24 hours: radioactivity primarily in the gastrointestinal tract; very low levels in the stomach contents, liver, and kidneys. No significant sites of tissue localization or presence of radioactivity in the systemic circulation were apparent. After 5 days: only minute levels of radioactivity detected in the intestinal	After 24 hours: Results varied between animals: radioactivity seen primarily in the gastrointestinal tract (stomach contents and lining, cecum, and intestinal contents). Lower levels of radioactivity seen in the kidney (higher in papilla), liver, skin, blood, lungs, and heart and the lining of the tongue and esophagus. After 5 days: no evidence	A whole body autoradiography (WBA) study in Sprague-Dawley, Fischer 344, and Long-Evans rats given a single gavage dose with the parent alachlor at 7 or 70 mg/kg (MRID 42852105, 1992) showed localization of the radiolabel in the liver, lungs, heart, kidney, adrenal gland, spleen, intestinal contents, and nasal mucosa, with nasal staining most pronounced	After 24 hours: radioactivity localized in the stomach contents, cecum, intestinal contents, urinary bladder and lining of the tongue and esophagus. After 5 days: no sites of localization of radioactivity observed. **(**Kraus et al., 1995)	n/a

(MRID 41565125, -26, -27, 41592007, -08; Hawkins et. al., 1987)	contents and no other sites of localization were observed. (Albin and Kraus, 2000)	of radioactivity remaining in the systemic circulation or in association with any tissue. (Albin and Kraus, 2000)	in Long-Evans rats at 24 hours. At 120 hours, liver, kidney, adrenal, heart and lungs were the major areas of radiolabel localization. (MRID 42852105, 1992)		

(15) Table 5c. Comparative Metabolism

Acetochlor and Degradates			**Alachlor and Degradates**		
Acetochlor	**Acetochlor ESA**	**Acetochlor OXA**	**Alachlor**	**Alachlor ESA**	**Alachlor OXA**
Completely metabolized (15 compounds separated in urine, 4 in bile, 5 in feces), with glutathione, mercapturic acid or glucuronide conjugation of n-dealkylated acetochlor a major route of metabolism; sulphoxymethyl and cysteine conjugates also identified in feces. In urine, major metabolite was mercapturic acid	Unchanged acetochlor ESA constituted 75.6% and 79.2% of the administered dose in males and females, respectively; representing 72.4% of the dose in the feces and 3.2% of the dose in the urine for males, and 69.6% in feces and 9.5% in the urine in females. Slightly larger amounts of unchanged acetochlor ESA excreted	Predominant radioactive component identified in excreta was unchanged acetochlor OXA, with approx. 30% of the dose in urine and 50% of the dose in feces for both genders. In total, acetochlor OXA constituted approx. 81.4% and 84.9% of the administered dose in the males and females, respectively. No	Extensively metabolized; 14 metabolites identified in urine and 13 in feces; acetochlor: 15 in urine, 4 in bile, and 5 in feces *sec*-amide hydroxymethyl sulfone metabolite predominant urinary metabolite after oral and intravenous administration, ranging from 2.1-7.4% of the dose.	>93% of 0-48 hour pooled fecal-contained radioactivity (corresponding to >72% of the administered dose) and >90% if urine-contained activity (UCA) in all females 24-hour urine samples eluted at the same retention time as an authentic alachlor ESA. In males, parent material was the major peak present in all 24-hour urine samples.	n/a

conjugate of N-deethylated acetochlor; in bile, major metabolite was the glucuronide conjugate. Major fecal metabolite not characterized. (MRID 41565125, -26, -27, 41592007, -08; Hawkins et al., 1987)	by the females compared to the males. Only one metabolite, acetochlor secondary ethane sulfonate (acetochlor sec-ESA) was found and accounted for 5.2% of the administered dose in the males and 3.2% of the dose in females. (Albin and Kraus, 2000)	metabolite exceeded 5% of the administered dose. Only one unidentified metabolite approached 5% of the dose. This metabolite was detected in excreta of males only. Males metabolized acetochlor OXA to a slightly greater extent than females. (Albin and Kraus, 2000)	*tert*-amide mercapturic acid and the disulfide appeared to be the major metabolites after single oral doses of alachlor. Increasing the dose appeared to increase the percentage of these 2 metabolites in feces. (MRID 42651306, 42852107, 42651308, 42852108; Wilson & Hall, 1986)	Three metabolites were also present, ranging from 7.4 to 27.8% of the UCA. No metabolite was measured at >4% of the administered dose. (Kraus et al., 1995)	

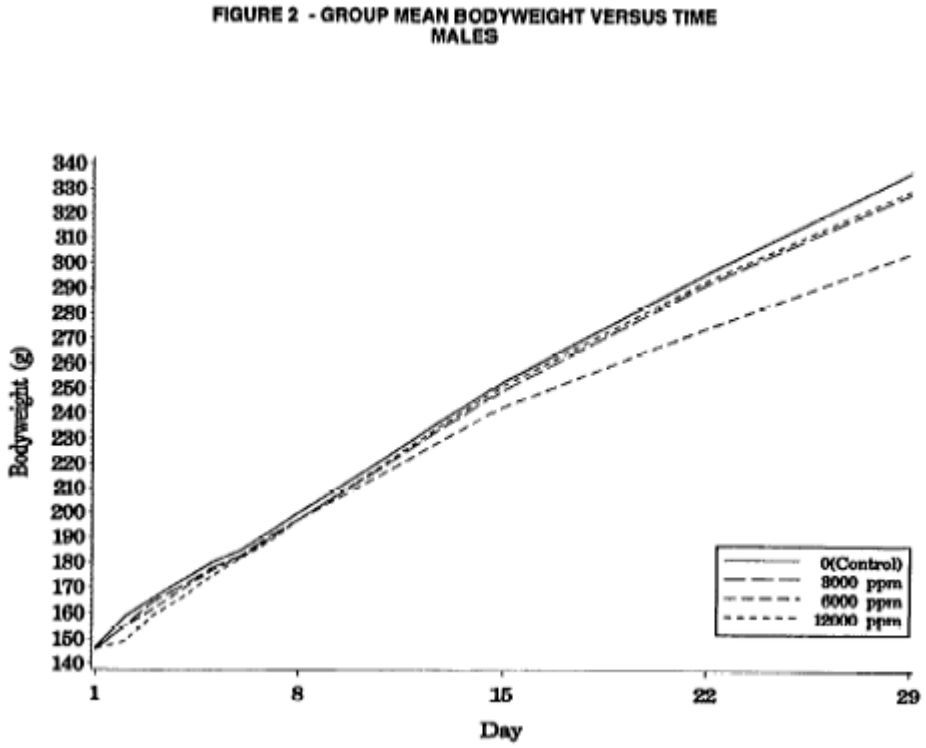
(16) Table 5d. Comparative Elimination/Excretion

Acetochlor and Degradates			**Alachlor and Degradates**		
Acetochlor	**Acetochlor ESA**	**Acetochlor OXA**	**Alachlor**	**Alachlor ESA**	**Alachlor OXA**
Rapidly eliminated (>70% of administered dose by day 2), elimination biphasic (rapid phase ½-life 5.4-10.4 hrs, slow phase 128.6-286.4 hrs for 10 mg/kg dose). (MRID 00130839; Carr et al., 1983)	Total recoveries of the administered dose for males and females averaged 90.3%. Feces accounted for 80.0% and 76.7% of the dose for males and females, respectively; urine accounted for 10.2% and 12.7% of the administered dose for males and females, respectively.	Mean total recovery of radiolabel was 93.4% of the administered dose. Feces accounted for a mean of 56.1% of the dose for both sexes; urine, 38.6% and 34.0% of the administered dose for males and females, respectively. <1% of the dose recovered in the cage wash. <2% of the dose	Mainly eliminated in urine and feces; elimination considered to be biphasic, initial phase ½-life of 0.1 to 10.6 hours followed by slow phase of 5 to 16 days); 89% of the dose was eliminated in 10 days; eliminated meta-bolites were conjugates of mercapturic acid, glucu-ronic acid, and sulfate.	An average (for males and females combined) of 72% of the administered dose excreted via the feces during the first 24 hours following dosing. Amount of dose eliminated in the 24-hour urine samples ranged from 1.5 to 18.8%. Male rats averaged 6.9% and females averaged 15.3%	n/a

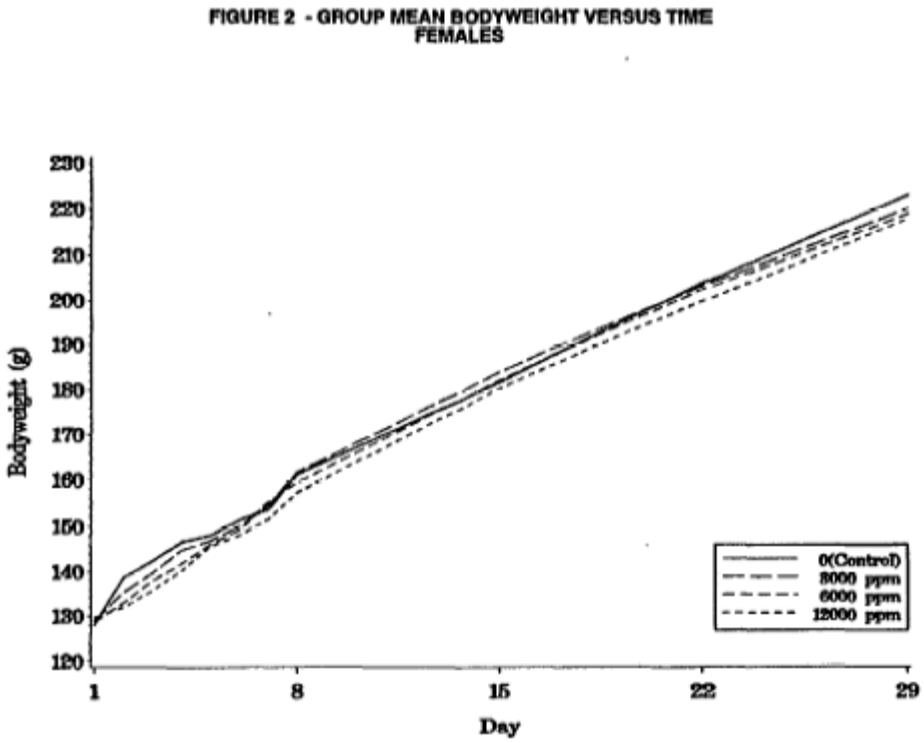
Rapidly eliminated (, ½ life of elimination 20-30 hrs), primarily excreted in urine (about 60% by 24 hrs) but significant fecal excretion observed, especially males and at high dose, with biliary excretion observed. Elimination biphasic. (MRID 41565125, -26, -27, 41592007, -08; Hawkins et al., 1987)	(Albin and Kraus, 2000)	recovered in expired air collected from each animal within 24 hours after dosing. Approx. 88% of the dose accounted for in the first 24 hours, indicating rapid excretion in both sexes. No statistically significant differences in the routes of excretion between males and females. (Albin and Kraus, 2000)	(MRID 00132045, 1983; Wilson et al., 1983) Excretion derived radioactivity approx. equivalent between urine and feces, with between 30-47% excreted in urine and 41-45% excreted in feces at single oral doses of 7, 70, or 700 mg/kg. (MRID 42651306, 42852107, 42651308, 42852108; Wilson & Hall, 1986)	off the dose in the urine 24 hours after dosing. Five days after dosing, approximately 83% and 11% of the dose were excreted in the feces and urine, respectively. (Kraus et al., 1995)	

5.0 Figures Accompanying Data Tables: Body Weight and Food Consumption versus Time

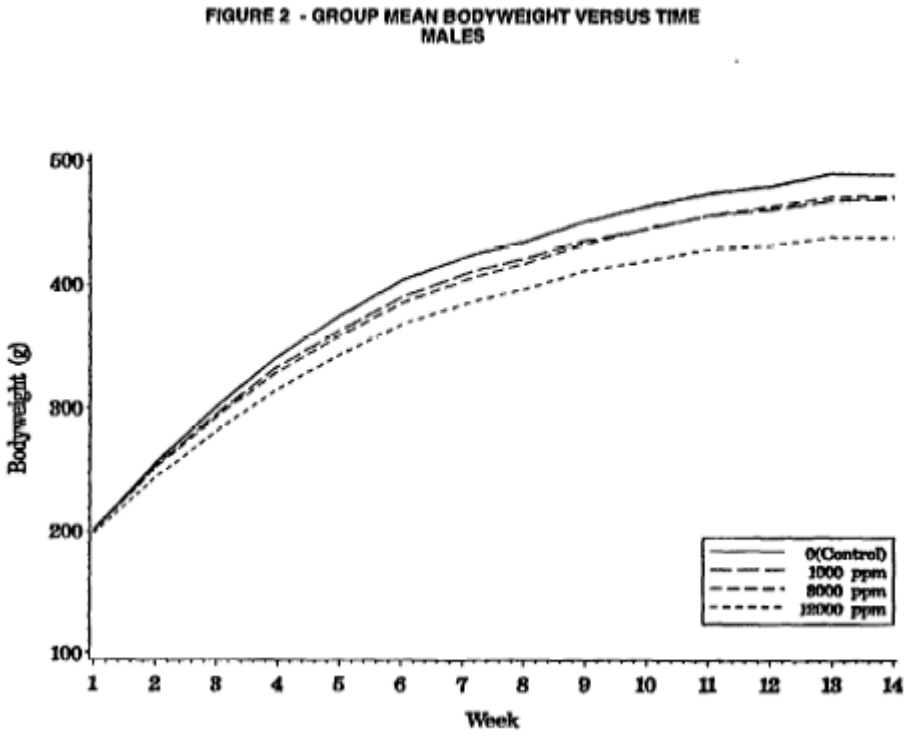
(2) Figure 2a. Body Weight versus Time (Table 3-1) (Lees 2000a – Acetochlor ESA, 28-day dietary study) - Males



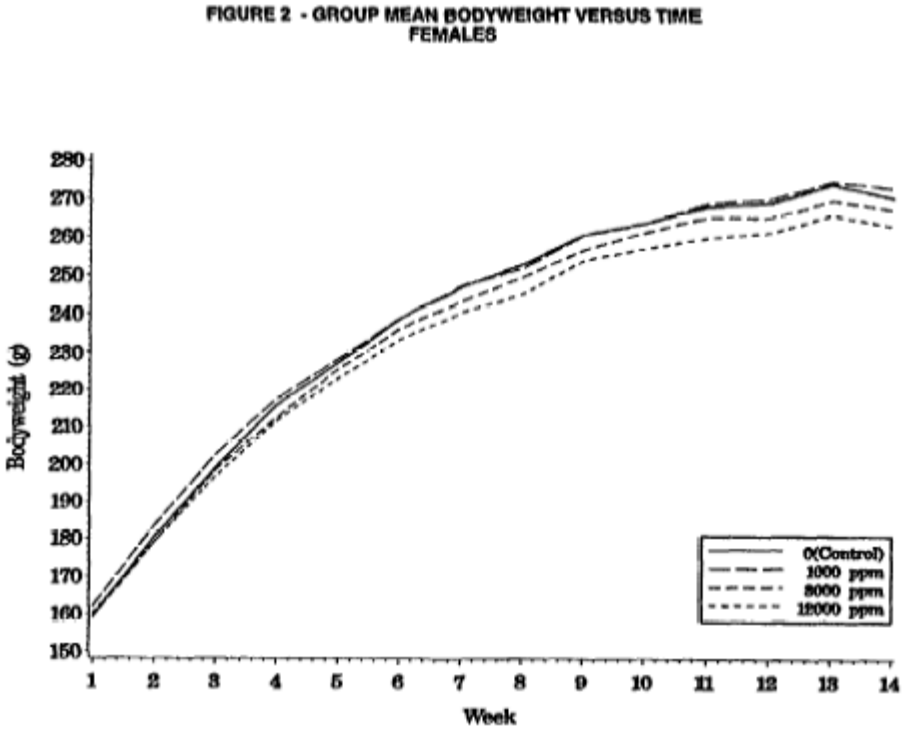
(3) Figure 2b. Body Weight versus Time (Table 3-1) (Lees 2000a – Acetochlor ESA, 28-day dietary study) - Females



(4) Figure 3a. Body Weight versus Time (Table 3-2) (Lees 2000b – Acetochlor ESA, 90-day dietary study) - Males

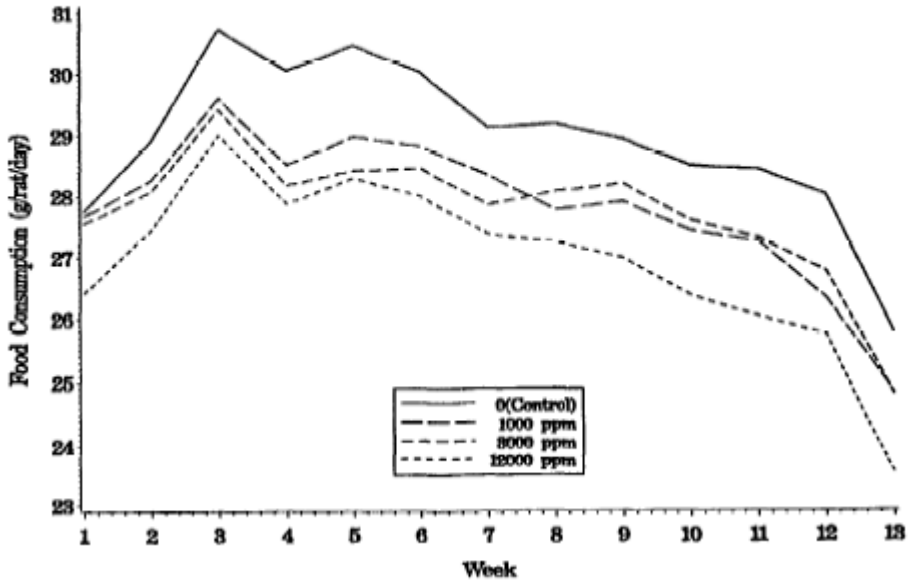


(5) Figure 3b. Body Weight versus Time (Table 3-2) (Lees 2000b – Acetochlor ESA, 90-day dietary study) - Females



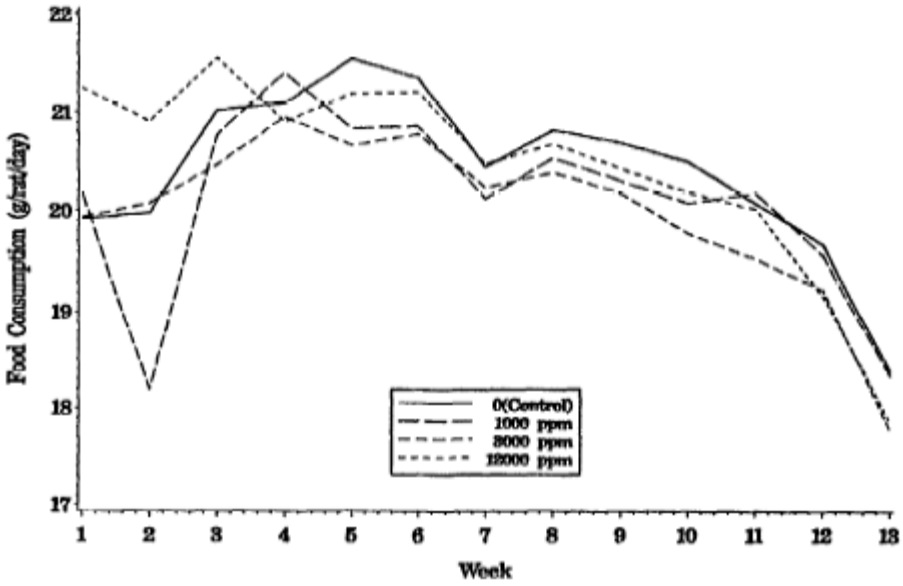
(6) Figure 3c. Food Consumption Versus Time (Table 3-2) (Lees 2000b – Acetochlor ESA, 90-day dietary study) - Males

FIGURE 4 - GROUP MEAN FOOD CONSUMPTION VERSUS TIME
MALES



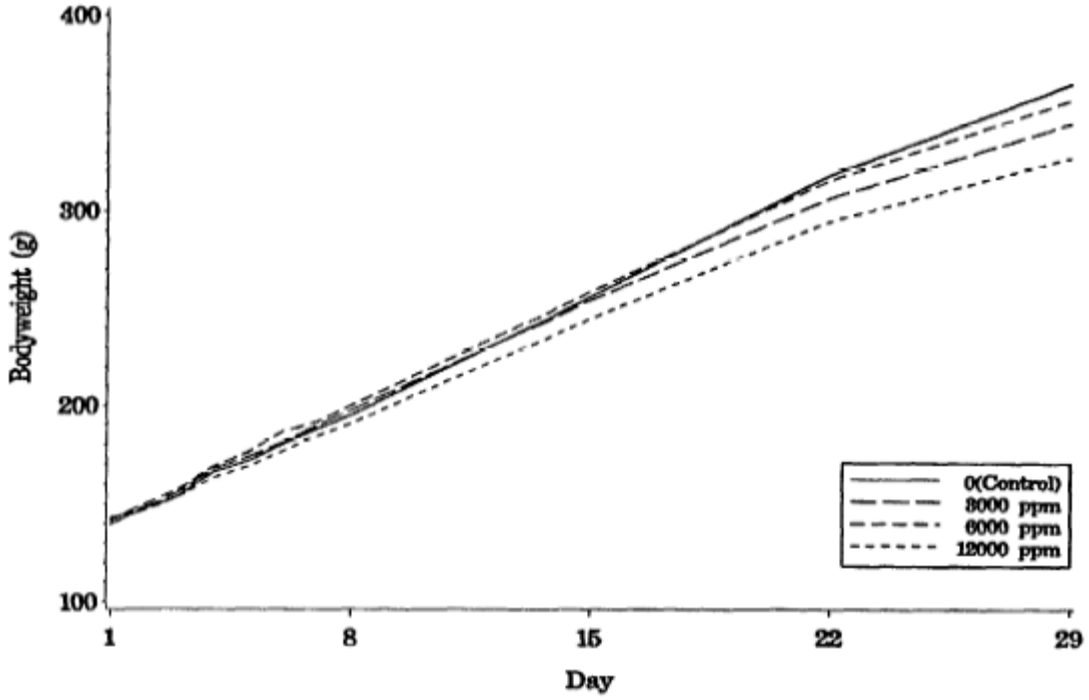
(7) Figure 3d. Food Consumption Versus Time (Table 3-2) (Lees 2000b – Acetochlor ESA, 90-day dietary study) - Females

FIGURE 4 - GROUP MEAN FOOD CONSUMPTION VERSUS TIME
FEMALES

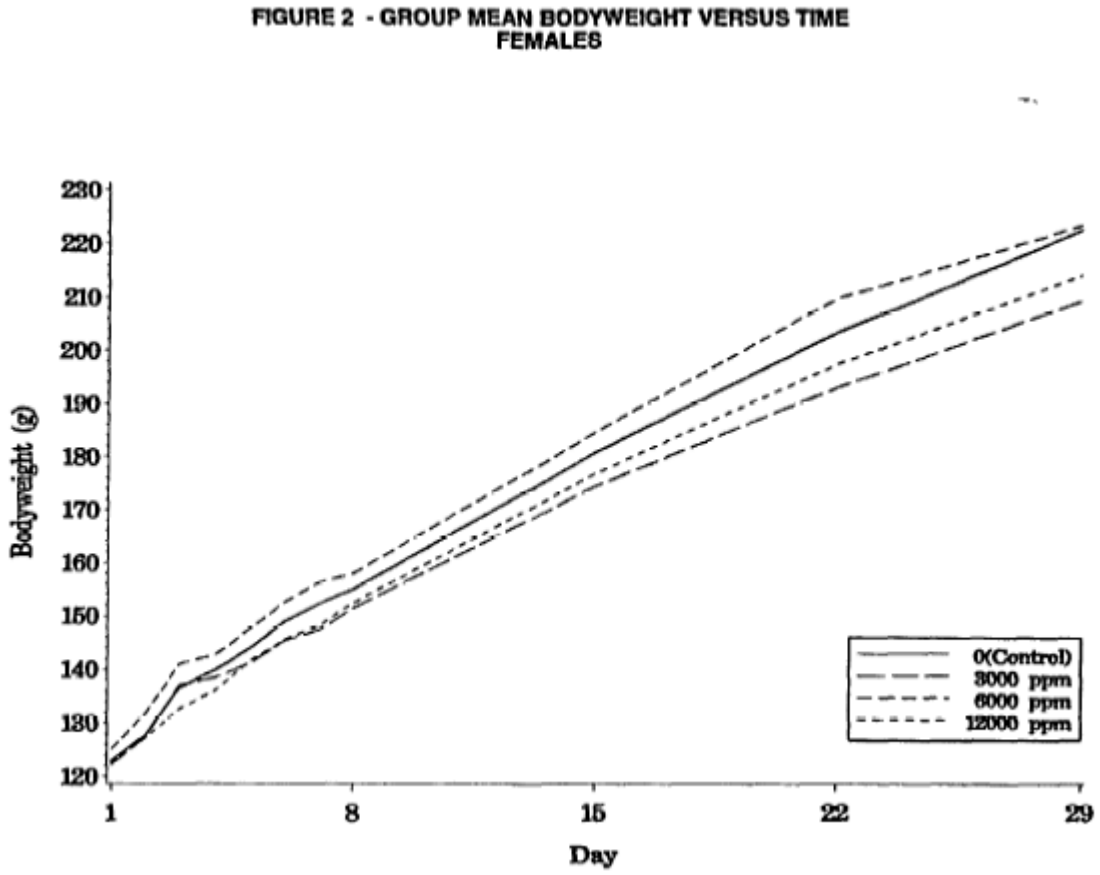


(8) Figure 4a. Body Weight Versus Time (Table 3-3) (Williams 2000a – Acetochlor OXA, 28-day dietary study) - Males

FIGURE 2 - GROUP MEAN BODYWEIGHT VERSUS TIME
MALES

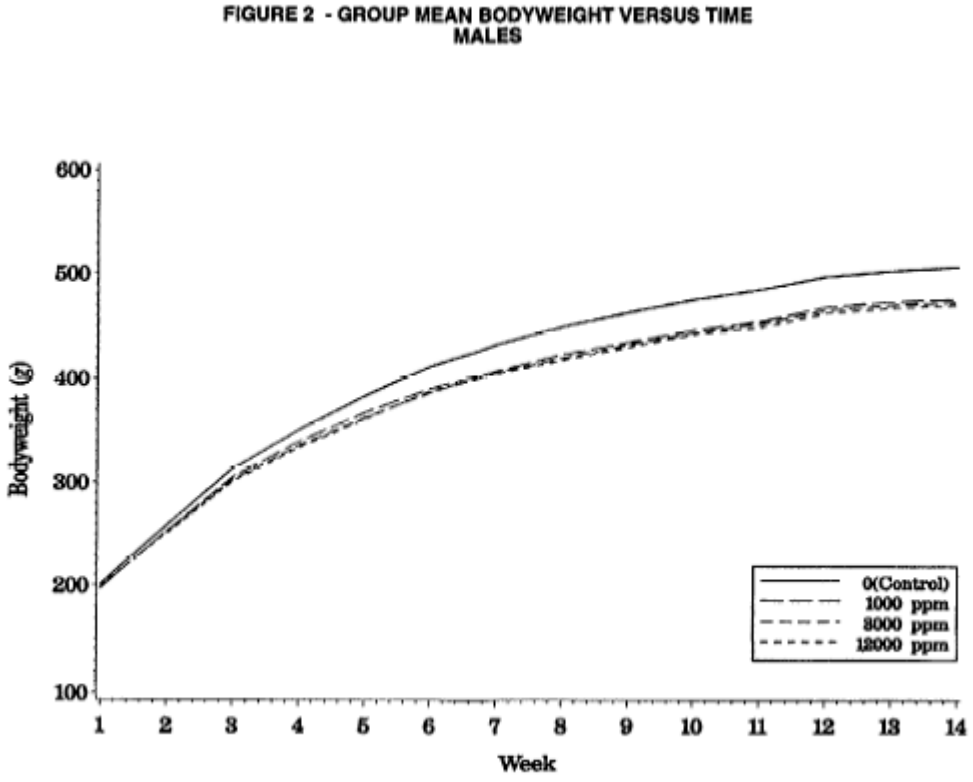


(9) Figure 4b. Body Weight Versus Time (Table 3-3) (Williams 2000a – Acetochlor OXA, 28-day dietary study) - Females

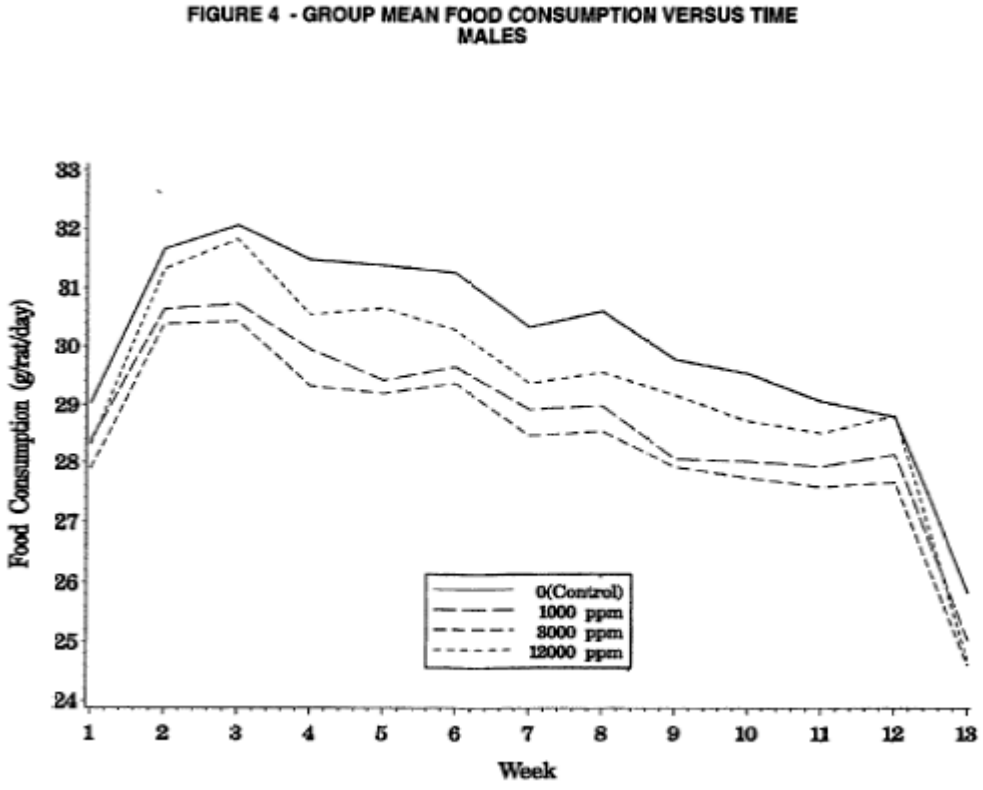


(10) Figure 5a. Body Weight Versus Time (Table 3-4) (Williams 2000b – Acetochlor OXA, 90-day dietary study) – Males

No figure for female data.

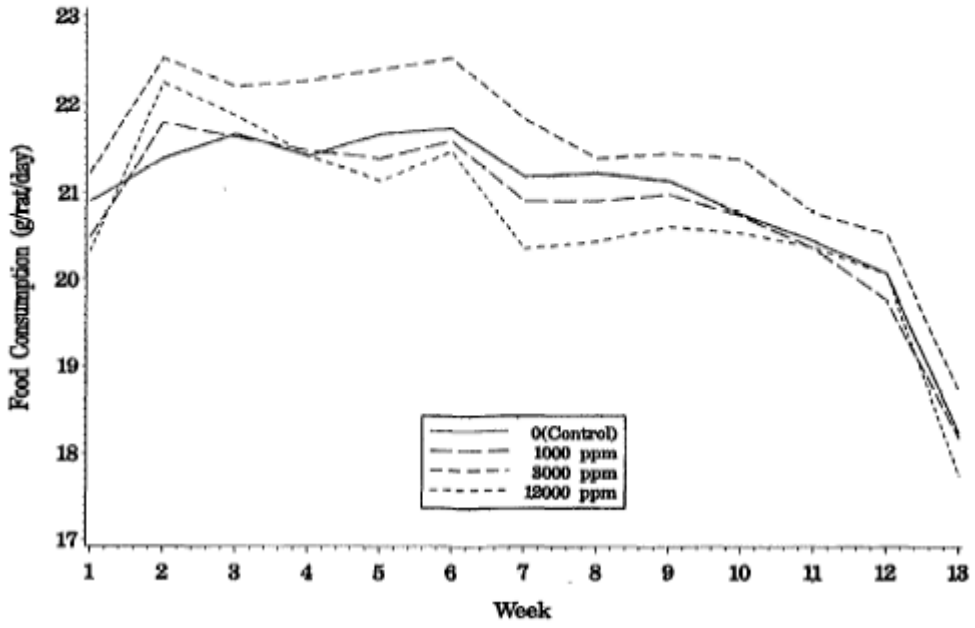


(11) Figure 5b. Food Consumption Versus Time (Table 3-4) (Williams 2000b – Acetochlor OXA, 90-day dietary study) - Males

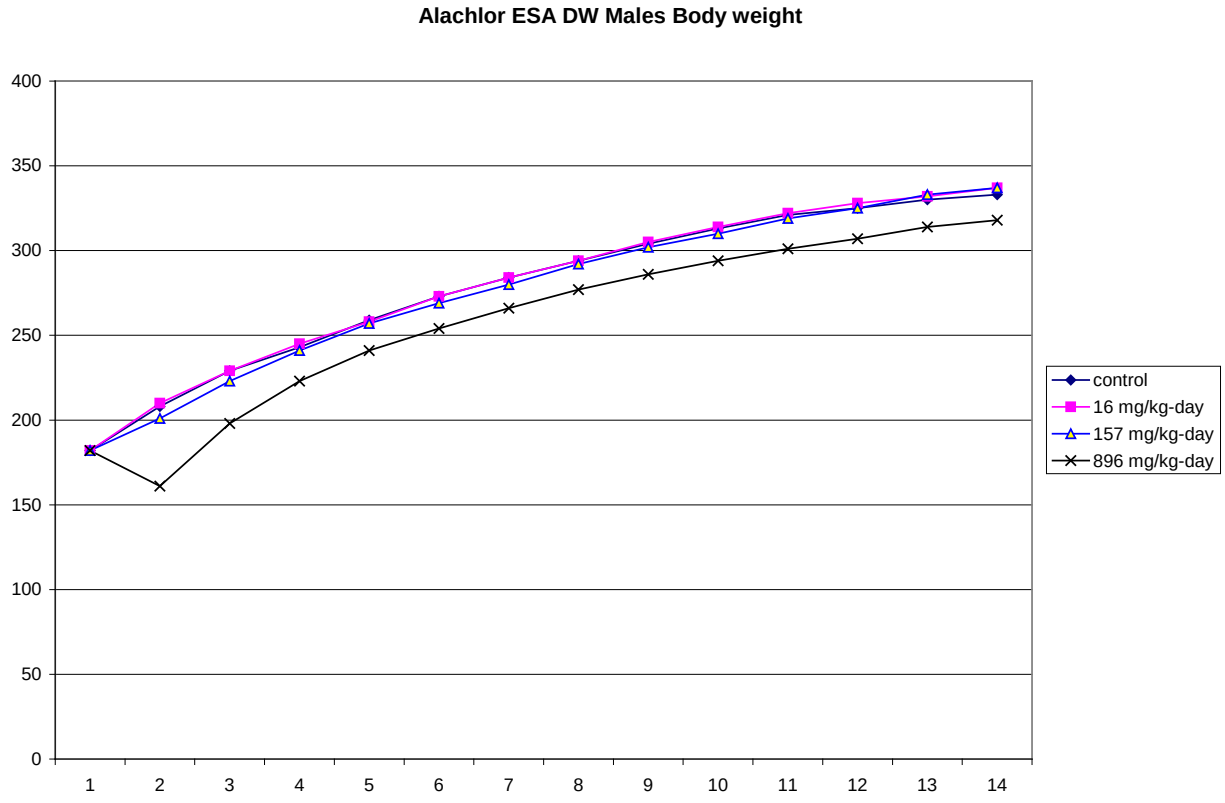


(12) Figure 5c. Food Consumption Versus Time (Table 3-4) (Williams 2000b – Acetochlor OXA, 90-day dietary study) - Females

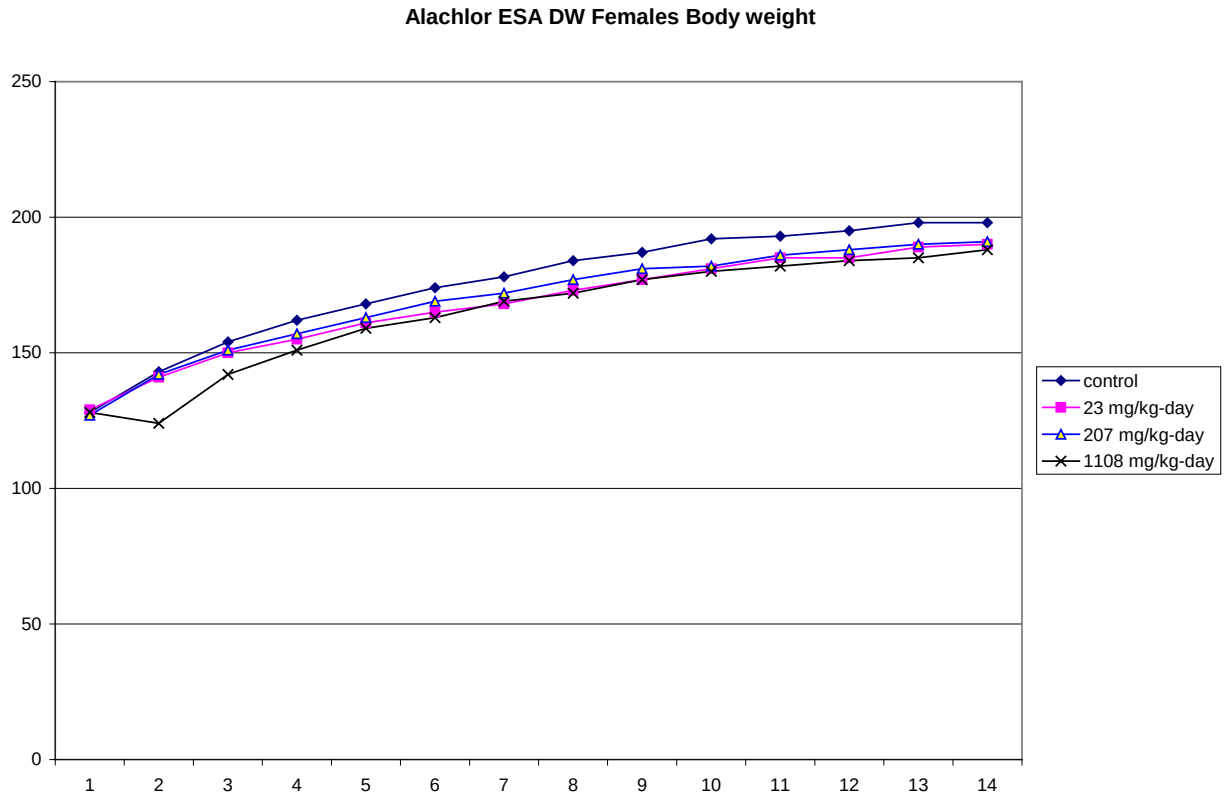
FIGURE 4 - GROUP MEAN FOOD CONSUMPTION VERSUS TIME
FEMALES



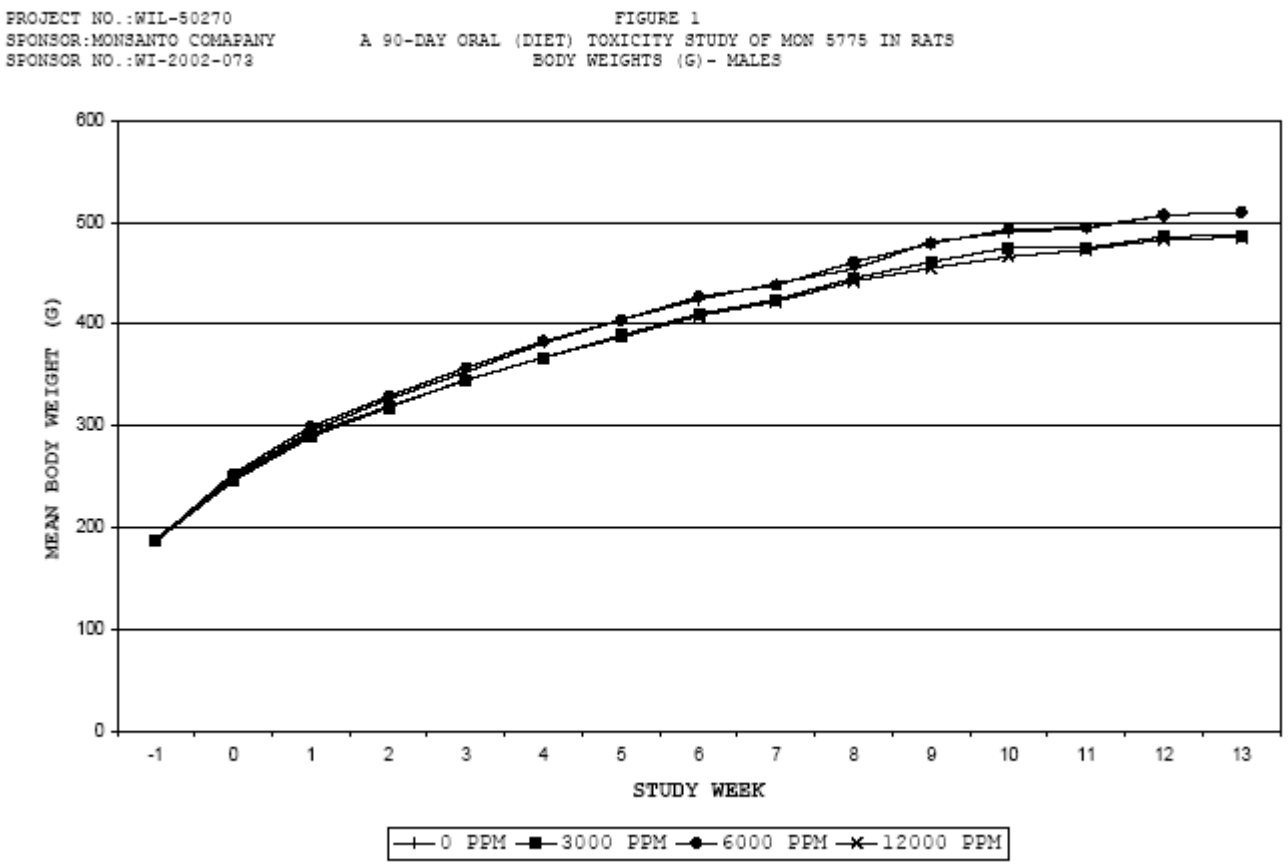
(13) Figure 6a. Body Weight Versus Time (Table 3-6) (Siglin, 1993 – Alachlor ESA, 91-day drinking water study) - Males



(14) Figure 6b. Body Weight Versus Time (Table 3-6) (Siglin, 1993 – Alachlor ESA, 91-day drinking water study) - Females



(15) Figure 7a. Body Weight Versus Time (Table 3-7) (Kirkpatrick 2002 – Alachlor ESA, 90-day dietary study) - Males



(16) Figure 7b. Body Weight Versus Time (Table 3-7) (Kirkpatrick 2002 – Alachlor ESA, 90-day dietary study) - Females

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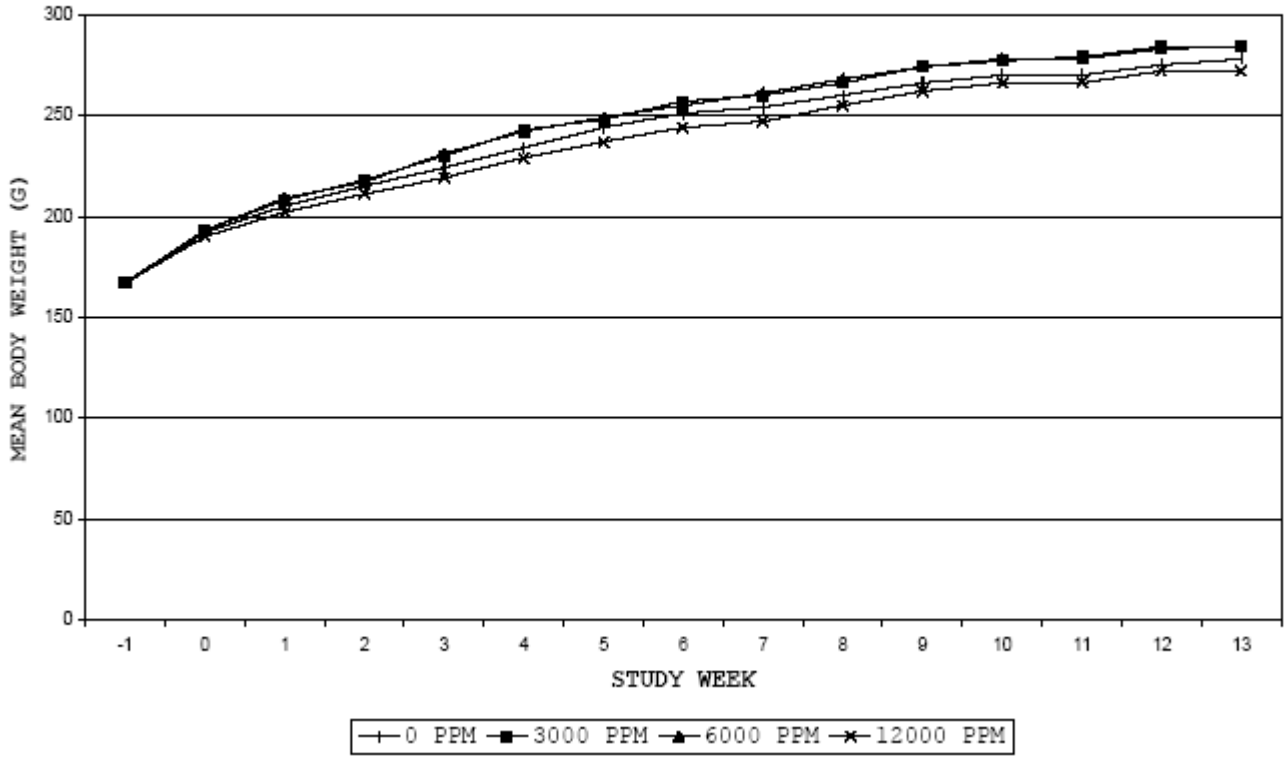
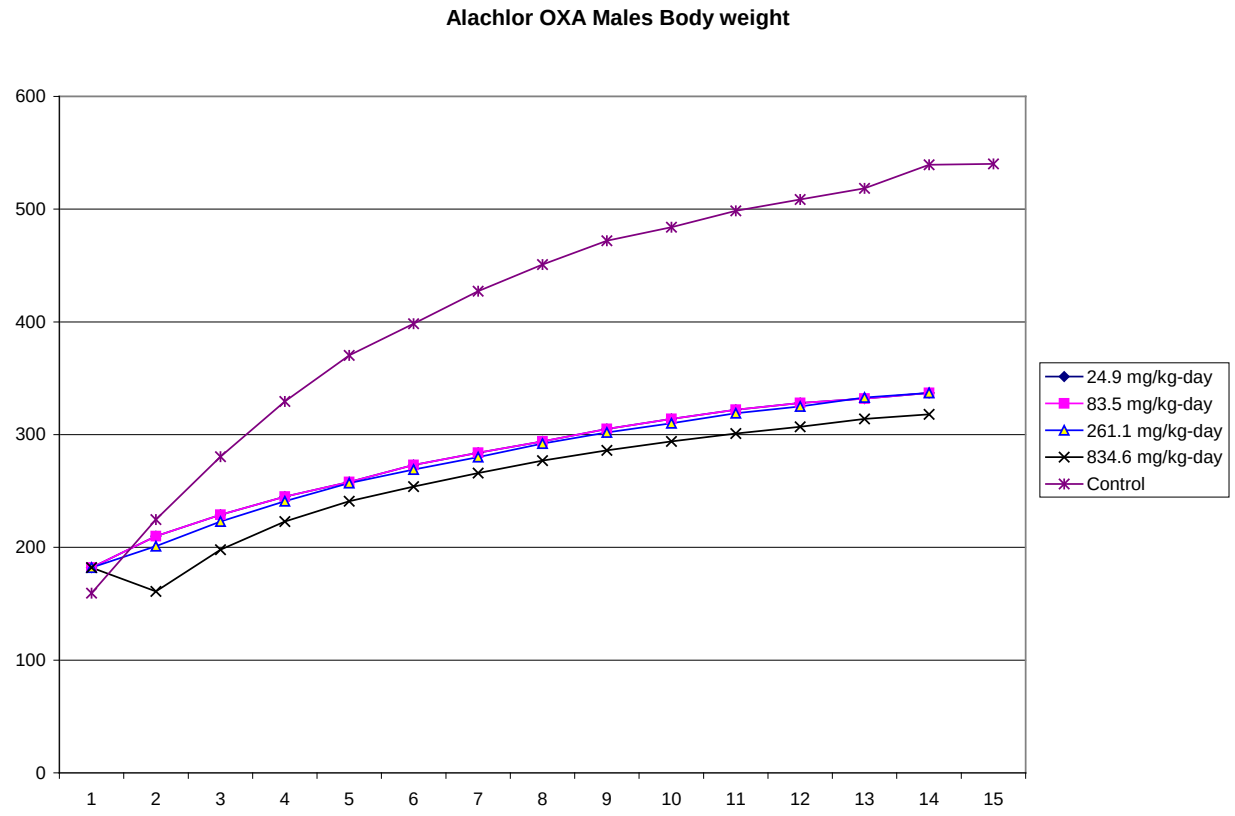
SPONSOR NO.:WI-2002-073

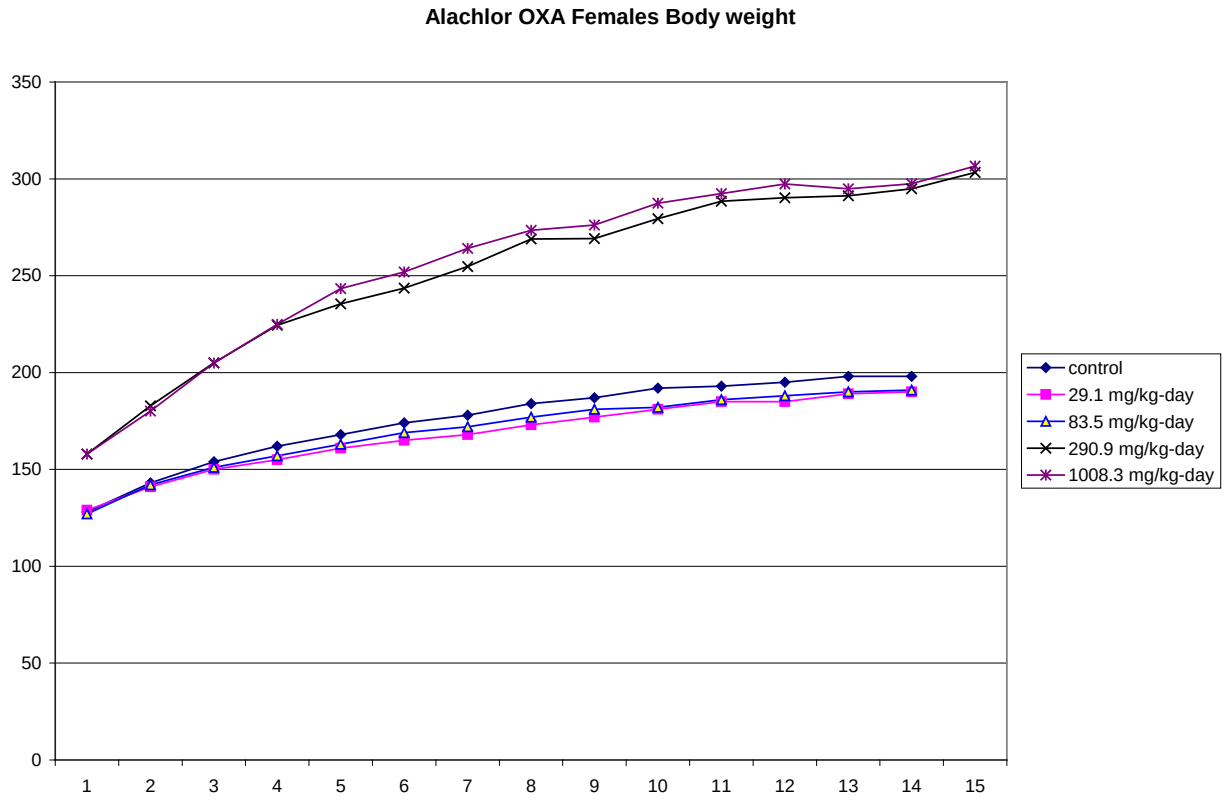
FIGURE 2
A 90-DAY ORAL (DIET) TOXICITY STUDY OF MON 5775 IN RATS
BODY WEIGHTS (G) - FEMALES



(17) Figure 8a. Body Weight Versus Time (Table 3-9) (Lemen et al., 2000 – Alachlor OXA, 90-day dietary study) - Males



(18) Figure 8b. Body Weight Versus Time (Table 3-9) (Lemen et al., 2000 – Alachlor OXA, 90-day dietary study) - Females



6.0 Potential Derivation of Oral RfD's for the Degradates

A. Benchmark Dose (BMD) Modeling Summary for Selected Endpoints

Approach for Modeling.

Endpoints with statistically significant changes or trends were chosen for modeling. Because BMDS 2.0 has stability problems, all modeling was done with BMDS 1.4. For each endpoint, all models of the relevant type (continuous or dichotomous) were run. Initially, the continuous endpoints were modeled with the power restricted on the Power model, signs not restricted on the Polynomial model, and, for all models, using both homogeneous and nonhomogeneous variances. Based on the results of the modeling and fit tests, we determined whether the homogeneous or nonhomogeneous variance was appropriate. In some cases, unrealistic results (e.g., nonmonotonic curves) were obtained with the polynomial model, and the polynomial model was re-run with the signs restricted. In some cases, the modeling results and more careful examination of the data indicated that further analysis was not worthwhile, and no additional modeling was done with the polynomial model, even though conducting the modeling with the restricted polynomial model would be necessary in order to obtain meaningful results. For all modeling re-runs, the modeling was initially done with a homogeneous variance, and a nonhomogeneous variance was used only if the output stated that homogeneous variance was not adequate. When adequate fit was not obtained by modeling all of the data points, the data were also modeled using the polynomial model and dropping the high dose. This approach often markedly changed the resulting BMD and BMDL, and provides some insight into the uncertainty related to the shape of the curve. Because none of the resulting BMDLs were chosen as the overall study BMDL, we did not run all of the available models with the high dose dropped for the relevant data sets. Further investigations could use the new models available in BMD 2.0, in an attempt to obtain better fits to the data, and could further investigate the implications of dropping the high dose.

Lees (2000b) – 90-Day Dietary Study in Rats – Acetochlor ESA

Body weight

Test 4 = Does the model fit (reject H0 if < 0.1)

Male MSW 6	BMDL	BMD	p (test 4)	AIC	res
Linear (nonconstant variance)	712	1160	0.58	665	0.15
Linear (constant variance)	706	1110	0.52	663	0.17
polynomial (constant variance, rest.)	706	1110	0.52	663	0.17
Power (nonconstant variance)	712	1160	0.58	665	0.15
Power (constant variance)	706	1110	0.52	663	0.17
Hill (nonconstant variance)	NA	1220	0.59	666	-0.1
Hill (constant variance)	NA	1270	0.6	664	-0.08

Female MSW 6	BMDL	BMD	p (test 4)	AIC	res
Linear (nonconstant variance)	1480	3400	0.79	527	0.08
Linear (constant variance)	1350	3240	0.94	526	0.06
polynomial (constant variance, restricted)	1270	3240	0.94	526	0.06
Power (nonconstant variance)	1100	3400	<0.001	525	0.079
Power (constant variance)	1100	3240	0.94	526	0.057
Hill (nonconstant variance)	NA	NA	<0.001	528	-0.1
Hill (constant variance)	NA	NA	1	528	1.1 E -07

Male **MSW 14**	BMDL	BMD	p (test 4)	AIC	res
Linear (nonconstant variance)	599	975	0.63	713	0.05
Linear (constant variance)	674	1040	0.61	712	0.04

Polynomial (nonconstant variance)	225	987	0.4	715	-0.07
polynomial (constant variance, rest.)	674	1040	0.61	712	0.04
Power (nonconstant variance)	599	975	0.63	713	0.05
Power (constant variance)	674	1040	0.6	712	0.04
Hill (nonconstant variance)	NA	908	0.42	715	-0.12
Hill (constant variance)	291	1070	0.34	714	-0.04

Female	**MSW 14**	BMDL	BMD	p (test 4)	AIC	res
Linear (nonconstant variance)		1270	2560	0.37	557	0.05
Linear (constant variance)		1170	2370	0.76	556	0.06
Polynomial (nonconstant variance)		NA	-9999	0.51	557	0.31
polynomial (constant variance, rest.)		1170	2370	0.76	556	0.06
Power (nonconstant variance)		1270	2560	0.37	557	0.05
Power (constant variance)		1170	2370	0.76	556	0.06
Hill (nonconstant variance)		NA	NA	1	555	-0.32
Hill (constant variance)		NA	NA	0.67	558	-1.9E-07

Males	**MS - food utilization**	BMDL	BMD	p (test 4)	AIC	res
Linear	constant variance, rest.	255	373	0.55	-5.6	0.71
Polynomial	constant variance, rest.	259	527	0.33	-3.9	0.32
Power	constant variance, rest.	258	558	0.31	-3.8	0.21
Hill	constant variance, rest.	257	558	NA	-1.8	0.21

Female	**MS - food utilization**	BMDL	BMD	p (test 4)	AIC	res
Linear	constant variance, rest.	538	1040	0.89	-1.4	-0.06
Polynomial	constant variance, rest.	782	1080	0.94	-1.5	0

Power	constant variance, rest.	543	1080	0.73	0.46	0
Hill	constant variance, rest.	NA	NA	NA	2.4	0

MS: Data from Main and Satellite Study Group combined.

MSW6 and MSW14: Data for Weeks 6 and Week 14 (i.e., at the end of the 13-week study period).

Williams (2000b) – 90-Day Dietary Study in the Rat – Acetochlor OXA

Body Weight

Male	**MSW 6**	BMDL	BMD	p (test 4)	AIC	res
Linear (nonconstant variance)		900	2070	0.08	651	0.43
Linear (constant variance)		1110	2440	0.06	650	0.36
Polynomial (nonconstant variance)		163	382	0.18	650	0.02
Polynomial (constant variance)		1110	2440	0.06	650	0.36
Polynomial (constant variance), no high dose		184	317	0.12	478	0.41
Power (nonconstant variance)		900	2070	0.08	651	0.43
Power (constant variance)		1110	2440	0.06	650	0.36
Hill (nonconstant variance)		NA	NA	NA	650	0.14
Hill (constant variance)		NA	NA	0.89	646	0.1

Female	**MSW 6**	BMDL	BMD	p (test 4)	AIC	res
Linear (nonconstant variance)		864	1470	0.57	560	-0.2
Linear (constant variance)		899	1480	0.58	558	-0.19
Polynomial (constant variance)		952	1280	0.83	557	-0.02
Power (nonconstant variance)		930	1100	0.86	559	0
Power (constant variance, parameters initialized)		961	1100	0.87	557	0

Hill (nonconstant variance)	NA	NA	NA	563	0
Hill (constant variance)	326	1120	0.6	559	0

Male **MSW 14**	BMDL	BMD	p (test 4)	AIC	res
Linear (nonconstant variance)	905	1900	0.04	700	0.37
Linear (constant variance)	1010	2010	0.05	698	0.34
Polynomial (nonconstant variance)	177	438	0.09	698	-0.2
polynomial (constant variance)	1011	2005	0.05	698	0.34
polynomial (constant variance), drop high dose	189	330	0.09	518	0.45
Power (nonconstant variance)	905	1900	0.04	700	0.37
Power (constant variance)	1010	2010	0.05	698	0.34
Hill (nonconstant variance)	NA	NA	NA	698	-0.25
Hill (constant variance)	NA	NA	0.95	694	-0.03

Female **MSW 14**	BMDL	BMD	p (test 4)	AIC	res
Linear (nonconstant variance)	887	1600	0.61	588	-0.19
Linear (constant variance)	957	1640	0.6	587	-0.16
Polynomial (nonconstant variance)	923	1280	0.54	590	0.02
Polynomial (constant variance)	1002	1350	0.8	586	-0.01
Power (nonconstant variance)	930	1230	0.49	590	0
Power (constant variance)	1010	1130	0.53	588	0
Hill (nonconstant variance)	NA	NA	NA	592	0
Hill (constant variance)	337	1130	NA	590	0

Food Utilization

Male MS	BMDL	BMD	p (test 4)	AIC	res
Linear (nonconstant variance)	457	595	0.02	-66.5	0.27
Linear (constant variance)	385	489	0	-62.7	0.46
Polynomial (nonconstant variance)	137	240	0.05	-68.9	0.1
Polynomial (constant variance) drop high dose	135	198	0.01	-40.6	0.68
Polynomial (nonconstant variance)	457	595	0.02	-66.5	0.27
Power (nonconstant variance)	457	595	0.02	-66.5	0.27
Power (constant variance)	385	489	0	-62.7	0.46
Hill (nonconstant variance)	32.7	166	0.09	-69.9	0.04
Hill (constant variance)	39.4	86.9	0.06	-71.2	-0.45

Female MS	BMDL	BMD	p (test 4)	AIC	res
Linear (nonconstant variance)	512	713	0	-47.7	-0.55
Linear (constant variance)	547	734	0	-48.9	-0.45
Polynomial (nonconstant variance)	687	863	0.02	-51.6	-0.05
Polynomial (nonconstant variance), drop high dose	138	322	0	-45.9	-1.34
Polynomial (constant variance)	719	882	0.01	-52.8	-0.04
Power (nonconstant variance)	671	1040	0.01	-49.9	0
Power (constant variance)	705	1050	0	-51.2	0
Hill (nonconstant variance)	290	1030	NA	-47.9	0
Hill (constant variance)	293	1030	NA	-49.2	0

MS: Data from Main and Satellite Study Group combined.

MSW6 and MSW14: Data for Weeks 6 and Week 14 (i.e., at the end of the 13-week study period).

Siglin (1993) and Heydens et al. (1996) – 91-day Drinking Water Study in Rats – Alachlor ESA

Male	**glucose**	BMDL	BMD	p (test 4)	AIC	res
Linear nonconstant variance		566	760	0.75	206	0.31
Linear constant variance		423	626	0.09	213	0.3
Polynomial nonconstant variance, not restricted		120	564	0.64	208	0.29
Polynomial constant variance, not restricted		77	131	0.91	210	0
Power nonconstant variance		566	760	0.91	204	0.31
Power constant variance		423	626	0.09	213	0.3
Hill nonconstant variance		NA	649	0.9	206	0.28
Hill constant variance		22.7	111	NA	212	0

Female	**glucose**	BMDL	BMD	p (test 4)	AIC	res
Linear nonconstant variance		1210	3270	0	267	0.01
Linear constant variance		1110	3050	0.999	266	0.01
Polynomial nonconstant variance, not restricted		1190	1760	0	269	0.01
Polynomial constant variance, not restricted		297	-9999	0.98	268	0
Power nonconstant variance		1120	1180	0.01	267	0
Power constant variance		1110	3050	0.999	266	0.01
Hill nonconstant variance		NA	NA	NA	271	0
Hill constant variance		1030	7160	0.98	268	0

Male	**Bilirubin**	BMDL	BMD	p (test 4)	AIC	res
Linear nonconstant variance		448	703	0.7	-170	0.12
Linear constant variance		434	649	0.54	-171	-0.16
Polynomial nonconstant variance		87.9	261	0.89	-169	-0.02
Polynomial constant variance		434	649	0.54	-171	-

					0.156
polynomial, constant variance, drop high dose	118	241	0.86	-125	0.13
Power nonconstant variance	448	703	0.7	-170	-0.12
Power constant variance	434	649	0.54	-171	0.16
Hill nonconstant variance	NA	303	0.93	-169	-0.01
Hill constant variance	49.9	287	0.91	-171	0

Female **Bilirubin**	BMDL	BMD	p (test 4)	AIC	res
Linear nonconstant variance	1130	6220	0.26	-149	0.12
Linear constant variance	1340	5790	0.45	-151	0.13
Polynomial nonconstant variance	1360	-9999	0.15	-148	-0.12
Polynomial constant variance	1280	-9999	0.35	-150	0
Power nonconstant variance	1130	6220	0.26	-149	0.12
Power constant variance	1340	5790	0.45	-151	0.13
Hill nonconstant variance	NA	NA	0.63	-149	0.08
Hill constant variance	NA	NA	NA	-148	0.13

Male **Albumin**	BMDL	BMD	p (test 4)	AIC	res
Linear nonconstant variance	336	570	0.1	-132	0.4
Linear constant variance	441	663	0.08	-133	0.3
Polynomial nonconstant variance	71.4	132	0.51	-134	0.12
Polynomial constant variance	79	137	0.42	-135	0
Polynomial constant variance	441	663	0.08	-133	0.3
polynomial, constant variance, drop high dose	113	141	0.55	-108	0
Power nonconstant variance	336	570	0.1	-124	0.4
Power constant variance	441	663	0.08	-133	0.3

Hill nonconstant variance	NA	152	NA	-132	0.13
Hill constant variance	NA	152	NA	-134	0

Female **Albumin**	BMDL	BMD	p (test 4)	AIC	res
Linear nonconstant variance	1520	4010	0	-112	0.51
Linear constant variance	1730	-9999	0.56	-113	-0.11
Polynomial nonconstant variance	1420	1870	0	-118	-0.49
Polynomial constant variance	1240	1550	0.44	-112	0
Power nonconstant variance	1130	4010	0	-114	0.51
Power constant variance	1130	1664	0.28	-111	0
Hill nonconstant variance	NA	NA	0.46	-125	-0.62
Hill constant variance	NA	NA	0.61	-112	-0.41

Stout and Thake (2000) – 28-Day Dietary Study in Rats – Alachlor OXA

Male **Gastric hyperplasia**	BMDL	BMD	p-value	AIC	residual
Gamma (restrict)	320	1190	0.9997	8.75	-0.1
Gamma (unrestrict)	288	1190	0.9997	8.75	-0.1
Logistic (log-restrict)	309	1390	1	8.73	0
Logistic (log-unrestrict)	298	1390	1	8.73	0
Logistic (unrestrict)	658	1460	1	10.7	0
Multistage (restrict)	272	954	0.96	9.29	-0.5
Multistage (unrestrict)	NA	NA	NA	NA	NA
Probit (log-restrict)	445	1340	1	10.7	0
Probit (log-unrestrict)	294	1340	1	10.7	0

Probit (unrestrict)	606	1390	1	10.7	0
Quantal-linear	294	1410	1	8.73	0
Weibull (restrict)	323	1410	1	8.73	0
Weibull (unrestrict)	294	1410	1	8.73	0

Female	**Gastric – Hyperplasia**	BMDL	BMD	p-value	AIC	residual
Gamma (restrict)		479	1100	0.996	8.84	0.23
Gamma (unrestrict)		479	1100	0.996	8.84	0.23
Logistic (log-restrict)		515	1380	1	8.73	-0.01
Logistic (log-unrestrict)		515	1380	1	8.73	-0.01
Logistic (unrestrict)		636	1490	1	10.7	0
Multistage (restrict)		267	831	0.88	9.89	0.33
Multistage (unrestrict)		NA	NA	NA	NA	NA
Probit (log-restrict)		536	1350	1	10.73	0
Probit (log-unrestrict)		536	1350	1	10.73	0
Probit (unrestrict)		593	1400	1	10.73	0
Quantal-linear		487	1410	1	8.73	-0.01
Weibull (restrict)		487	1410	1	8.73	-0.01
Weibull (unrestrict)		487	1410	1	8.73	-0.01

Male	**Gastric - Eosinophilic Inclusion**	BMDL	BMD	p-value	AIC	residual
Gamma (restrict)		511	947	0.33	16.5	-0.67
Gamma (unrestrict)		0	154000	0	28.5	-1.3
Logistic (log-restrict)		545	1270	0.34	16.4	-0.6

Logistic (log-unrestrict)	545	1270	0.34	16.4	-0.6
Logistic (unrestrict)	274	516	0.069	19.13	-1.2
Multistage (restrict)	247	687	0.22	17.9	-1.1
Multistage (unrestrict)	NA	NA	NA	NA	NA
Probit (log-restrict)	564	1220	0.14	18.4	-0.6
Probit (log-unrestrict)	564	1220	0.14	18.4	-0.6
Probit (unrestrict)	248	444	0.08	19.5	-1.3
Quantal-linear	504	1330	0.34	16.4	-0.6
Weibull (restrict)	504	1330	0.34	16.4	-0.6
Weibull (unrestrict)	504	1330	0.34	16.4	-0.6

Female	**Gastric - Eosinophilic Inclusion**	BMDL	BMD	p-value	AIC	residual
Gamma (restrict)		479	1100	0.996	8.84	-0.23
Gamma (unrestrict)		479	1100	0.996	8.84	-0.23
Logistic (log-restrict)		515	1380	1	8.73	-0.01
Logistic (log-unrestrict)		515	1380	1	8.73	-0.01
Logistic (unrestrict)		636	1490	1	10.73	0
Multistage (restrict)		267	831	0.88	9.89	-0.74
Multistage (unrestrict)		NA	NA	NA	NA	NA
Probit (log-restrict)		536	1350	1	10.73	0
Probit (log-unrestrict)		536	1350	1	10.73	0
Probit (unrestrict)		593	1400	1	10.73	0
Quantal-linear		487	1410	1	8.73	-0.01
Weibull (restrict)		487	1410	1	8.73	-0.01
Weibull (unrestrict)		487	1410	1	8.73	-0.01

Lees (2000a) – 28-Day Dietary Study in Rats - Acetochlor ESA

Mean Cell Volume (male)	BMDL	BMD	p	AIC	res
Linear	605	1030	0.04	52.8	-1.87
Polynomial	605	1030	0.04	52.8	-1.87
Polynomial (unrestrict.)	151	248	0.4	49.2	0.64
Power	605	1030	0.04	52.8	-1.87
Power (unrestrict.)	0	134	0.08	51.6	-0.03
Hill	77.2	370	0.41	49.2	0

Mean Cell Haemoglobin (male)	BMDL	BMD	p	AIC	res
Linear	530	845	0.03	7.25	-1.91
Linear (nonconstant var.)	629	1120	0.06	7.44	-2.07
Polynomial	530	845	0.03	7.25	-1.91
Polynomial (nonconstant var.)	629	1120	0.06	7.44	-2.07
Polynomial (unrestrict.)	142	226	0.39	3.29	-0.475
Polynomial (nonconstant var., unrestrict.)	140	286	0.3	4.81	-0.6
Power	530	845	0.03	7.25	-1.91
Power (nonconstant var.)	629	1120	0.13	5.44	-2.07
Power (unrestrict.)	0	120	0.08	5.69	-1.37
Power (nonconstant var., unrestrict.)	0	326	0.06	7.31	-1.56
Hill	111	366	0.55	2.89	-0.419
Hill (nonconstant variance)	207	383	0.69	3.9	-0.474

Mean Cell Volume (female)	BMDL	BMD	p	AIC	res
Linear	545	808	0.52	72.4	0.01

Polynomial	545	821	0.25	74.4	0.02
Power	547	848	0.26	74.4	0.04
Hill	259	293	NA	75.8	0

Williams (2000a) – 28-Day Dietary Study in Rats - Acetochlor OXA

Mean Cell Volume (males)	BMDL	BMD	p	AIC	res
Linear	888	2190	0.02	26.9	0.86
Polynomial	888	2190	0.02	26.9	0.86
Polynomial (unrestrict.)	131	217	0.83	21.4	0.07
Power	888	2190	0.02	26.9	0.86
Hill	0	0	0.14	23.5	0

Williams (2000b) – 90-Day Dietary Study in Rats - Acetochlor OXA

Mean Cell Volume (male)	BMDL	BMD	p	AIC	res
Linear (nonconstant var.)	482	636	0.76	63.7	0.26
Polynomial (nonconstant var.)	494	792	0.999	65.1	0.37
Power model (constant var.)	462	767	0.88	68.1	-0.002
Power (nonconstant var.)	494	790	0	63.1	0.365
Hill (nonconstant)	NA	784	0.99	65.1	0.37

Mean Cell Haemoglobin (male)	BMDL	BMD	p	AIC	res
Linear	555	874	0.73	-15.1	0.04
Polynomial	555	874	0.73	-15.1	0.04

Power	555	874	0.73	-15.1	0.04
Hill	160	774	0.47	-13.2	-0.03

Siglin (1993) – 90-Day Drinking Water Study in Rats – Alachlor ESA

Haemoglobin (male)	BMDL	BMD	p	AIC	res
Linear (nonconstant var.)	704	1510	0	5.18	0.45
Polynomial (nonconstant var.)	704	1510	0	5.18	0.45
Power (nonconstant var.)	704	1510	0	5.18	0.45
Hill (nonconstant var.)	NA	45.3	0.01	-20.4	-0.33

Haematocrit	BMDL	BMD	p	AIC	res
Linear (nonconstant var.)	381	560	0.29	65	-1.3
Polynomial (nonconstant var.)	381	560	0.29	65	-1.3
Power (nonconstant var.)	381	560	0.29	65	-1.3
Hill (nonconstant var.)	NA	160	0.38	65	-0.4

RBC	BMDL	BMD	p	AIC	res
Linear (nonconstant var.)	252	384	0	-74.3	-2.7
Polynomial (nonconstant var.)	252	384	0	-74.3	-2.7
Power (nonconstant var.)	252	384	0	-74.3	-2.7
Hill (nonconstant var.)	34	136	NA	-85.2	0.33

Stout & Thake (2000) – 90-Day Dietary Study in Rats – Alachlor OXA					
Haemogloblin (male)	BMDL	BMD	p	AIC	res
Linear	952	2240	0.05	7.95	0.57
Linear (nonconstant var.)	675	1880	0.01	8.46	-0.19
Polynomial (nonconstant variance)	675	1880	0.01	8.46	-0.19
Power (nonconstant variance)	645	1560	0.03	8.78	0
Hill (nonconstant variance)	0.01	6.83	0.46	1.2	0.07
Haematocrit (male)	BMDL	BMD	p	AIC	res
Linear (nonconstant variance)	914	3780	0	61.1	-0.38
Polynomial (nonconstant variance)	914	3780	0	61.1	-0.38
Power (nonconstant variance)	903	1590	0.33	61.2	0
Hill (nonconstant variance)	NA	62.6	0.72	50.9	-0.19
RBC (male)	BMDL	BMD	p	AIC	res
Linear	741	1370	0.09	-5.79	-0.16
Polynomial	744	1410	0.03	-3.64	-0.06
Power	741	1370	0.09	-5.79	-0.16
Hill	0	6.69	0.14	-6.19	0

B. Summary Table for Potential RfDs

Table 6 summarizes the potential key studies and the corresponding points of departure that may be considered for deriving RfDs for the acetanilide degradates. NOAELs were selected based on our conclusions drawn from the available results. The models' BMD lower limits (BMDL) were, where appropriate, selected for consideration as a potential point of departure.

(17) Table 6. Potential Key Studies for RfD Derivation for Acetanilide Degradates

Derivations of the Oral RfD for Acetochlor and Alachlor Degradates									
Reference	**Critical Effect**	**Critical Effect Level[a]**	**UF_A**	**UF_H**	**UF_L**	**UF_S**	**UF_D**	**Composite UF[b]**	**RfD**
Acetochlor ESA									
Lees (2000a) (28-day, rats, diet)	No toxicologically significant treatment-related effect	1578.7/1607.4 (NOAEL, M/F)							
Lees (2000b) (90-day, rats, diet)	Dec. BW (M), dec. food utilization (M&F)	225.4/259.1 (NOAEL, M/F)							
	Dec. BW (M at 14 weeks) *	599 ($BMDL_{1SD}$ in M)							
	*Adjusted BW provided without SD; hence, not modeled.								
	Dec. food utilization (M at 14 weeks)**	259 ($BMDL_{1SD}$ in M)							
	**Other endpoints (dec. BW and food utilization in F have higher BMDLs)								
Acetochlor OXA									
Williams (2000b)	Dec. BW (M&F)	230.2 / 268.0 (NOAEL, M/F)							

Derivations of the Oral RfD for Acetochlor and Alachlor Degradates									
Reference	**Critical Effect**	**Critical Effect Level[a]**	**UF_A**	**UF_H**	**UF_L**	**UF_S**	**UF_D**	**Composite UF[b]**	**RfD**
(90-day, rat, diet)	*Dec. BW (M&F)	1002 ($BMDL_{1SD}$, F)							
	*Adjusted BW provided without SD; hence, not modeled. No models adequately fit the data for food utilization.								
Holston (2000) (Developmental, oral gavage, rats)	Maternal mortality	500 (NOAEL)							
Alachlor ESA									
Siglin (1993); Heydens et al. (1996) (90-day, F344 rats, drinking water)	Dec. BW (marginal change in M&F) and clinical signs in males.	157 / 207 (NOAEL, M/F)							
	BMD modeling for clinical chemistry parameters (glucose, bilirubin, and albumin) in some cases were lower than the selected NOAEL. However, the degree of change was very small and 1SD BMR may not be appropriate.								
	RBC counts*	896/1108 (NOAEL, M/F)							
	Hemoglobin*	896/1108 (NOAEL, M/F)							
	Hematocrit*	896/1108 (NOAEL,							

Derivations of the Oral RfD for Acetochlor and Alachlor Degradates									
Reference	**Critical Effect**	**Critical Effect Level[a]**	**UF_A**	**UF_H**	**UF_L**	**UF_S**	**UF_D**	**Composite UF[b]**	**RfD**
		M/F)							
	*No acceptable BMDS model could fit the data.								
Kirkpatrick (2002) (90-day, rat, diet)	No toxicologically significant treatment-related effect	788 / 926 (NOAEL, M/F)							
Holson (1995) (Developmental, gastric intubation, rats)	No toxicologically significant treatment-related effect	1000 (NOAEL, maternal/developmental)							
Alachlor OXA									
Stout and Thake (2000) (28-day, rats, diet)	Hyperplasia of mucous cells and eosinophilic inclusions in the cytoplasm of epithelial cells in the stomachs of male and females	754.26 / 829.68 (NOAEL, M/F)							
	Hyperplasia of mucous cells and eosinophilic inclusions in the cytoplasm of epithelial cells in the stomachs of male and females	309/487 ($BMDL_{10}$, M/F)							
	BMD/DMBL ratio is over a value of 3, which reflects the small sample size (=5). This drives the BMDL estimate lower than would likely be seen with a larger sample. Modeling for eosinophilic inclusions did not yield a lower								

Derivations of the Oral RfD for Acetochlor and Alachlor Degradates									
Reference	**Critical Effect**	**Critical Effect Level[a]**	**UF_A**	**UF_H**	**UF_L**	**UF_S**	**UF_D**	**Composite UF[b]**	**RfD**
	critical BMDL.								
Lemen et al. (2000) (90-day, rat, diet)	No toxicologically significant treatment-related effect	834.6 / 1008.3 (NOAEL, M/F)							
[a]Oral effect levels are presented in units of mg/kg-day									

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8.0 Appendices

Appendix A: Detailed Description of the Studies Available for the Degradates

Acetochlor ethanesulfonic acid

An acute oral toxicity study and two oral subchronic (28- and 90-day) toxicity studies were available for this compound. No chronic reproductive/developmental toxicity studies were available for review. There were no inhalation or dermal toxicity studies and no human health effect studies were identified.

Acute oral toxicity study

An acute oral toxicity study reported a LD_{50} of greater than 2000 mg/kg body weight (MRID 44632704; Lees, 1997a). Two oral subchronic toxicity studies were identified.

Subchronic oral toxicity study

a. 28-day dietary study (Lees, 2000a).

In the 28-day dietary study, Sprague-Dawley rats (5 animals/sex/dose group) were fed diets containing 0 (control), 3000, 6000, or 12000 ppm R290131 (0, 370.3, 766.6 and 1578.7 mg/kg-day for males and 0, 374.6, 762.3, and 1607.4 mg/kg-day for females) for 28 consecutive days. Clinical signs of toxicity, body weight, and food consumption were recorded, clinical pathology (hematology, blood clinical chemistry, thyroid hormones) was conducted, hepatic T4-UDPGT activity was measured, organ weights were recorded and gross pathology and histopathology were conducted.

Body weight was reduced (maximum at approx. 6%) for males in the 12000 ppm group on day 2, reaching statistical significance from day 2 to day 5 for males and from day 2 to day 4 for females. At 6000 ppm, a maximal reduction in body weight of approx. 3% for males and 6% for females was observed on day 2, attaining statistical significance from day 2 to day 3 for males and from day 2 to day 4 for females. Body weight for males was also significantly lower than controls on day 22 and 29. No effects on body weight were observed at 3000 ppm. Because there were no clear treatment-related effects on body weights present at the end of the study, the initial reductions are considered to be of no toxicological significance.

TSH and free T3 levels increased in a dose-dependent manner in males, but the changes did not reach statistical significance at any dose level. There were also no dose-related changes in total T3. T4-UDPGT activity increased statistically significantly in females and to a minimal degree in males at 12000 ppm. Because of a lack of consistency between the hormone parameters and/or sexes or any related organ weight or pathology changes, increases in TSH, free T3 and T4-UDPGT are considered toxicologically insignificant.

Based on the results, the NOAEL in this study is 12000 ppm [1578.7 mg/kg-day, males; 1607.4 mg/kg-day, females], the highest dose tested (HDT).

b. 90-day dietary study (Lees, 2000b)

In the 90-day dietary study, CD Sprague-Dawley rats (12 animals/sex/group) were administered daily Acetochlor ESA at concentrations of 0, 1000, 3000, and 12000 ppm (0, 75, 225, and 919 mg/kg-day for males and 0, 85, 259, and 1073 mg/kg-day for females) for 90 days. Satellite groups (8/sex/group) were similarly dosed to evaluate the cell proliferation in the nasal passages by autoradiography. Clinical signs of toxicity and mortality were recorded daily, body weight and food consumption were recorded weekly, ophthalmoscopy was performed pre-test and in controls and high-dose animals during the week prior to termination, functional observation battery (FOB) and motor activity were preformed pre-test and in week 12 for all animals, clinical pathology (hematology and blood clinical chemistry) were performed in all animals at the end of the study, and urine clinical chemistry was performed during the week prior to study termination. At the time of sacrifice, gross necropsies were performed on all animals and organ weights (adrenals, brain, epididymes, heart, kidneys, liver, ovaries, spleen, testes, thymus, thyroid, and uterus) were recorded. Histopathology examination was performed on all tissues from control and high-dose groups.

There were no treatment-related mortalities, clinical signs of toxicity and ophthalmology findings, and no-dose dependent changes in FOB were observed. Some reduction in body weight and food consumption was reported at 3000 ppm in males but the reductions were considered not to be toxicologically significant because they were minor (<5%) and intermittent. Reduced growth and reduced food utilization in males and females and reduced food consumption in males were also reported at 12000 ppm. At this dose, females exhibited minimal changes in clinical pathology parameters (increases in hemoglobin and red blood counts and decreases in mean cell volume) while males exhibited changes in clinical chemistry parameters (increases in total bilirubin). These minimal changes in clinical pathology and chemistry parameters were considered by the author to only be equivocal evidence of toxicity.

In the satellite group, male rats exposed to 12000 ppm exhibited a statistically insignificant decrease in the unit length of labeling indices in all six levels of the nasal passages. Females in

this group also showed a decrease in the frequency of labeling indices in five levels of the nasal passages, but an increase was observed in the olfactory epithelium of level 5. However, considerable interanimal variability in the values rendered the decrease or the increase in cell proliferation in the females statistically insignificant compared to control values. Results, therefore, indicate no treatment-related effects on cell replication in the nasal epithelium. Other findings in the main study at the high dose included slight increase in relative liver weights for males and statistically significant reduction in relative uterus weights for females that was attributed to an increased proportion of animals in dioestrus. The study author considered the differences in the relative uterus weights to not be treatment-related given that the uterus weights are dependent on the stage of the estrus cycle at termination.

The NOAEL in this study is 3000 ppm [225 mg/kg-day, males; 259 mg/kg-day, females], with a LOAEL of 12000 ppm [919 mg/kg-day, males; 1073 mg/kg-day, females] based on reduced growth and food utilization for males and females and reduced food consumption for males.

Acetochlor Oxanilic Acid (OXA)

An acute oral toxicity study, two oral subchronic (28- and 90-day) toxicity studies, and a developmental toxicity study were available for this compound. No chronic and reproductive toxicity studies were available for review. There were no inhalation or dermal toxicity studies of any exposure duration and no human health effect studies were identified.

Acute oral toxicity study (Lees, 1997b)

An acute oral toxicity study reported a LD_{50} of greater than 2000 mg/kg body weight. Two oral subchronic toxicity studies were identified.

Subchronic oral toxicity study

a. ***28-day dietary study (Williams, 2000a)***

In the 28-day dietary study, Sprague-Dawley rats (5 animals/sex/dose group) were fed diets containing 0 (control), 3000, 6000, or 12000ppm R290130 (0, 373, 769, and 1468 mg/kg-day for males and 0, 367, 737, and 1507 mg/kg-day for females) for 28 consecutive days. Clinical observations, bodyweights and food consumption were measured throughout the study. At the end of the scheduled period, the animals were killed and subjected to an examination post mortem. Cardiac blood samples were taken for clinical pathology, selected organs were weighed and specified tissues were taken for subsequent histopathology.

There were no clinical signs of toxicity at any dose level. At 12000 ppm (1467.9 mg/kg-day, males, and 1506.5 mg/kg-day, females) body weight was significantly reduced in males (12% lower compared with the control value) and slightly reduced in females (4% lower compared to control levels). There were no effects on body weight in either sex at 6000 ppm. Body weight was decreased in both sexes (7% and 6% in males and females, respectively) at 3000 ppm towards the end of the study following adjustment for initial body weight differences. However, in the absence of an effect on body weight in the mid-dose group, the decrease in body weight at 3000 ppm was considered toxicologically insignificant. Food consumption was also slightly decreased for male rats in the top dose group during the study. TSH levels were decreased in males (not dose-dependent) and females (dose-dependent), but without statistical significant at any dose level. There was a dose-dependent decrease in total and free T3 levels in males, but with statistical significance only at the highest dose level (12000 ppm). T4-UDPGT activity was statistically significantly reduced in the in the liver of females only and at 12000 ppm only . Absolute thyroid weights was statistical significantly increased in males at 6000 ppm and 12000 ppm [1467.9 mg/kg-day], compared to controls, while thyroid weight relative to body weight was unaffected. The test material did not cause any macroscopic or microscopic lesions in either sex at any dose level.

The NOAEL in this study was 6000 ppm R290130 (769 mg/kg-day for males and 737 mg/kg-day for females), based on a LOAEL of 12000 ppm (1468 mg/kg-day for males and 1507 mg/kg-day for females) for significantly reduced bodyweights (12% decrease) in male rats.

b. ***90-day dietary study (Williams, 2000b)***

In the 90-day dietary study, CD Sprague-Dawley rats (12 animals/sex/group) were administered daily Acetochlor OXA in the diet at concentrations of 0, 1000, 3000, and 12000 ppm ([0, 77.2, 230.2, and 955.2 mg/kg-day, males; 0, 86.5, 268.0 and 1082.7 mg/kg-day for females) for 90 days. Satellite groups (8 animals/sex/group) were similarly dosed to evaluate the cell proliferation in the nasal passages by autoradiography. Clinical signs of toxicity and mortality were recorded daily, body weight and food consumption were recorded weekly, ophthalmoscopy was performed pre-test and in controls and high-dose animals during the week prior to termination, functional observation battery (FOB) and motor activity were preformed pre-test and in week 12 for all animals, clinical pathology (hematology and blood clinical chemistry) were performed in all animals at the end of the study, and urine clinical chemistry was performed during the week prior to study termination. At the time of sacrifice, gross necropsies were performed on all animals and organ weights (adrenals, brain, epididymes, heart, kidneys, liver, ovaries, spleen, testes, thymus, thyroid, and uterus with cervix) were recorded. Histopathology examination was performed on all tissues from control and high-dose groups.

There were no treatment-related mortality, clinical signs of toxicity and ophthalmology findings reported. No treatment-related changes in FOB were observed. Motor activity during week 12 was statistically significantly increased in males at the high dose. The author indicated that the values for these animals were not dissimilar to the control values (342 ±118, overall mean + SD) from a concurrent study in the same strain of rat. Therefore, th e toxicological significance of this finding is equivocal. Decreases in clinical pathology parameters (some hematological parameters and in some blood clinical pathology) were minor and small in magnitude, and were considered to be of no toxicological significance due to the absence of associated changes in other parameters.

Body weights for both sexes were decreased throughout the study at 12000 ppm (combined main and satellite groups) (maximally 7% and 5% for males and females, respectively). Body weights were also significantly reduced for males in the 3000 ppm group for some timepoints during the study. Food consumption was generally lower for males compared to the controls at 1000 ppm and 3000 ppm, but no decrease in this parameter was observed in the high-dose group. Food utilization was slightly (7 to 9%) but significantly reduced in both sexes at the high dose, with a slight decrease in males only at 3000 ppm. However, the effect at 3000 ppm was reported by the study author to be predominantly due to reductions during the first 4 weeks of the study. There were no effects on food utilization in the 1000 ppm group.

There were no treatment-related effects on cell replication rates in the nasal passages at any level in either sex.

Other changes in animals at the high dose included minor decreases in some hematological and clinical chemistry parameters. However, these clinical pathology changes were small in magnitude and because no associated changes in other parameters were reported, these minor decreases are considered to be of no toxicological significance. Relative adrenal weight was slightly increased while absolute liver and heart weights were slightly decreased at the high dose. Treatment did not cause any macroscopic or microscopic lesions in any sex.

The NOAEL in this study is 3000 ppm [230 mg/kg-day for males and 268 mg/kg-day for females], with a LOAEL of 12000 ppm [955 mg/kg-day for males and 1083 mg/kg-day for females], based on statistically significant decrease in body weight in both sexes.

Prenatal developmental toxicity study in rats (Holson, 2000)

Pregnant rats (25 animals/dose group) were administered orally, by gavage, the test material dissolved in deionized water at dose levels of 0, 250, 500, and 1000 mg/kg-day on gestation days (GDs) 6 through 19. Mortality, clinical signs of toxicity and food consumption were recorded daily while body weights were recorded on days 0, and daily on GDs 6 through 20. Mean body

weight change was reported for each corresponding interval and also for GDs 6 through 20 and 0 through 20. Animals were killed on GD 20. Gross morphological examination was conducted on the thoracic, abdominal and pelvic cavities. Uterus was excised and weighed prior to removal of fetuses. Organ weights (liver, kidneys) were recorded and organs were placed in formalin. Uteri and ovaries were examined to determine number of corpora lutea, numbers of fetuses, total implantations, and early and late resorptions. Fetal parameters (weight, sex) and developmental variations and malformations (external, visceral, and skeletal) were recorded. Statistical analyses were performed.

Two dams in the 1000-mg/kg-day group were found dead approximately 30-60 minutes following dosing on GDs 8 and 9. There were no adverse clinical signs or postmortem findings noted for these animals. The cause of death could not be determined in any of these animals, but because spontaneous deaths are a rare occurrence in rats, the deaths were considered equivocal, but potentially test article-related.

Treatment-related clinical signs of toxicity observed in the 1000 mg/kg-day group included slight to severe wet, clear matting around the mouth one hour following dosing during gestation days 10-19. However this finding was not considered to be evidence of systemic toxicity.

Body weights and body weight gains were not adversely affected at any dose level. Although food consumption was reduced at 1000 mg/kg-day during GDs 6-7, the reduction was transient, and so not considered to be an adverse effect.

A statistically significant but slight reduction (5.6%) in food consumption (g/kg-day) was observed in the 1000 mg/kg-day group when the entire treatment period (GDs 6-20) was evaluated. However, in the absence of any significant reductions in maternal body weight gain, this slight reduction in food consumption was not considered to be an adverse effect of treatment. No test article-related macroscopic findings were observed in any treated animal including the two that died. No organ (liver, kidney and spleen) weight differences between treated groups and controls were observed.

No test article-related effects on intrauterine growth parameters – postimplantation loss, viable litter size, fetal sex ratios, mean fetal body weight, and the mean number of corpora lutea and implantation sites – and survival of products of conception were observed at any dose level evaluated.

Malformations and developmental variations observed in fetuses in this study were considered to be spontaneous in origin and not related to test article administration.

The NOAEL in this study is 500 mg/kg-day, with a LOAEL of 1000 mg/kg-day, based on maternal mortality in two dams. In the absence of any adverse effects on fetuses and their development, the NOAEL for developmental toxicity is 1000 mg/kg-day.

Alachlor ethanesulfonic acid (ESA)

An acute oral toxicity study, two oral subchronic (90-day, drinking water and diet) and developmental toxicity studies (a range-finding study and a main study) were available for this compound. No 28-day, chronic, reproductive toxicity studies were available for review. There were no inhalation or dermal toxicity studies and no human health effect studies were identified.

Acute oral toxicity study (Bonnette 1993)

An acute oral toxicity study in rat reported a LD_{50} of greater than 6000 mg/kg body weight (Bonnette 1993).

Subchronic oral toxicity study

a. 28-day drinking water study (Siglin 1993)

A preliminary range-finding study was conducted to evaluate the potential toxicity of MON 5775 (alachlor ESA) when administered to rats by the oral (drinking water) route over the course of 91 days. In this study, Fischer 344 rats (6 animals/sex/dose group) received alachlor ESA (MON 5775) in drinking water at concentrations of 0, 700, 2000, 7000, or 20000 ppm (equivalent to 0, 69, 183, 656, and 2217 mg/kg-day for males and 0, 75, 205, 749, and 2378 mg/kg-day for females) for 28 days. Clinical signs of toxicity were monitored daily. Body weights were measured on day -1 and weekly thereafter. Food consumption and water intake were measured weekly during the study. All animals were subjected to a complete gross necropsy at the time of death or scheduled euthanasia. Surviving rats were killed the following day (day 29).

At 20000 ppm: one male and one female died on study days 17 and 12, respectively. Adverse clinical signs observed included decreased activity, dehydration, rough coat, hunched posture, unkempt appearance, emaciation, dark material around the nose and mouth, and increased incidence of urine staining and few and/or small feces. Body weight, weight gain and food consumption were statistically significantly decreased in males and females. These decreases were associated with a marked reduction in water intake in the 20,000 ppm rats during week 1. However, subsequent water intake in the 20,000 ppm males and females exceeded respective control values. The only effect observed at lower doses was a minor, but statistically significant reductions in water intake in the 2000 ppm males and females, and in the 7000 ppm males during week 1. There were no treatment-related gross necropsy findings in surviving animals.

The NOAEL in this study was 7000 ppm (656 mg/kg-day for males and 749 mg/kg-day for females), with a LOAEL of 20000 ppm (2217 mg/kg-day for males and 2378 mg/kg-day for females) based on mortality, clinical signs of toxicity, significant decreases in body weight, food consumption, and significant changes in water intake.

b. ***91-day drinking water study (Siglin 1993; Heydens et al., 1996)***

In the 91-day drinking water study, Fischer 344 rats (10 animals/sex/group) were administered daily Alachlor ESA (MON 5775) at concentrations of 0, 200, 2000, and 10000 ppm (0, 16, 157, and 896 mg/kg-day for males and 0, 23, 207, and 1108 mg/kg-day for females).

Clinical signs of toxicity were monitored daily and mortality, twice daily. Body weight and food consumption (weekly), water consumption (once or twice weekly), and ophthalmoscopy (Days -6 and 90) were recorded. Clinical pathology (hematology and clinical chemistry) were performed in all animals at the end of the study. Complete gross necropsies were performed on all animals at the time of sacrifice or scheduled euthanasia. Organ weights (liver, kidneys, testes, ovaries, adrenal glands, thyroid/parathyroid, brain and heart) were recorded for surviving animals. In addition, the nasal turbinates from surviving animals were processed for microscopic examination. Tissues collected at necropsy from control animals, high-dose animals and all animals found dead during the study, as well as the lungs, liver, kidneys and gross lesions from all low and mid-dose animals, were processed for histopathological examination.

One male rat of the 10,000 ppm group was found dead on day 13, while no other spontaneous deaths occurred during the study. In both sexes at 10,000 ppm, adverse clinical signs were observed primarily during the first two weeks of the study and included few and/or small feces, urine staining, dehydration, emaciation, rough coat and dark material around the eyes. At the 200 and 2000 ppm levels, clinical signs were generally less severe and limited in occurrence.

Mean body weight was statistically decreased in the 10,000 ppm males and females throughout the study, beginning on study day 8. These decreases correlated with statistically significant body weight losses in the 10,000 ppm males and females during the first week of the study. Other body weight changes observed included: increases in weekly weight gain in the 10,000 ppm males during weeks 2 and 3, and in the 10,000 ppm females during week 2; and statistically increased weight gain in week 3 in the 10,000 ppm males compared to the control males. Mean weight gain was decreased slightly in 2000 ppm males during week 1, but the decrease was not statistically different from the control group. Occasional statistical differences in mean body weight and/or weight gain were noted at the 200 and 2000 ppm levels, but these differences did not follow any consistent pattern which would indicate a relationship to treatment.

Food consumption (grams/animal-day) was statistically decreased in the 10,000 ppm males and females during the first week of the study. These decreases correlated with body weight losses observed in the 10,000 ppm males and females during week 1. While food consumption was statistically increased in the 10,000 ppm females during week 2, and statistically decreased in the 2000 ppm females during weeks 8 and 9, these differences were relatively minor and transient. In addition, the decrease in food consumption of the 2000 ppm females did not follow any apparent dose-response relationship.

Changes in water intake (grams/kg-day) observed in males included statistical decrease during week 1, and statistical increase during weeks 2-13 in males at 10,000 ppm and slight but statistically insignificant decrease at 2000 ppm during week 1. In females, water intake was statistically decreased at 2000 and 10,000 ppm during study week 1, with additional statistical decreases in the 2000 ppm during weeks 2-7, these differences were not considered toxicologically relevant in the absence of similar effects in the 10,000 ppm females. An incidental statistical increase in mean water intake was observed in 200 ppm females during week 12, but this increase was not considered meaningful in the absence of similar changes at higher treatment levels.

No test article-related ophthalmological changes in the study animals.

Small changes (2-5%) in terminal hematological parameters included: statistically significant decrease in erythrocyte counts in the 2000 and 10,000 ppm males; decrease in hemoglobin and hematocrit in the 10,000 ppm males; and increase in mean corpuscular hemoglobin (MCH) in the 10,000 ppm males. These changes did not correlate with other hematological or histopathological changes. More importantly, for each measured hematologic parameter which was statistically different in males, the respective control value exceeded the normalized historical control range for male rats of this strain and age. The relatively high hematology values in controls is highlighted by the fact that even though hemoglobin in high-dose males was statistically significantly lower than in controls, it was higher than the upper-limit of the historical control range. As such, although the values were statistically significantly lower than controls, the biological significance of the slightly lower value is not clear. In females, statistically significant, but relatively minor, increase in total leukocyte count was noted in the 10,000 ppm group.

Changes in clinical chemistry parameters observed in the study included statistically significant decrease in potassium and aspartate aminotransferase (AST) in the 200 ppm females, and decreased calcium in the 2000 ppm females. No such differences were observed at 10,000 ppm, rendering the change toxicologically insignificant. In males, statistically significant decreases in glucose, increase in total bilirubin, and an increase in phosphorus levels were noted in the 10,000 ppm group. No abnormal histopathology accompanied these effects in the males. Albumin levels in the 2000 and 10,000 ppm males were statistically decreased and, because the decreases were small (2.7 to 4%) compared to controls, they are not considered to be biologically significant.

Gross necropsy findings of surviving animals were generally unremarkable. There were no statistically significant differences in absolute or relative organ weight data among the groups. Histopathological examination did not reveal any test article-related findings in any dose group.

The NOAEL in this study is 2000 ppm (157 mg/kg-day for males and 207 mg/kg-day for females), with a LOAEL of 10,000 ppm (896 mg/kg-day for males and 1108 mg/kg-day for females) for systemic toxicity.

c. 90-day dietary study (Kirkpatrick, 2002)

In a 90-day oral dietary study, alachlor ESA (MON 5775) was administered to male and female Sprague-Dawley rats (15 animals/sex/dose group) at dose levels of 0, 3000, 6000 and 12000 ppm

(0, 195, 389, and 788 mg/kg-day for males and 0, 222, 454, and 926 mg/kg-day for females). All animals were observed twice daily for mortality and moribundity. Clinical examinations were performed daily and detailed physical examinations were performed weekly. Individual body weights and food consumption were recorded weekly. Functional Observational Battery (FOB) and Motor Activity (MA) data were recorded for 10 animals/sex/group prior to randomization and during study week 12. Clinical pathology evaluations (hematology and serum chemistry) were performed on all rats euthanized at the scheduled necropsy (study week 13). Ophthalmic examinations were performed prior to the initiation of dose administration and during study week 12. Complete necropsies were conducted on all animals, and selected organs were weighed at the scheduled necropsies. Selected tissues were examined microscopicallyfrom 10 animals/sex/group in the control and 12000 ppm groups.

All animals survived to the scheduled necropsy. A low incidence of clinical findings, typically in single animals, was observed similarly in treated and control groups and was not present in a dose-related manner. Therefore, these clinical findings were not considered to be test article-related.

A statistically significant ($p<0.05$) increase in mean body weight gains was noted in the 6000 ppm group males, from study weeks 7 to 8 when compared to the control group. In addition, a statistically significant ($p<0.01$) decrease in mean body weight gains was noted in the 3000, 6000 and 12000 ppm group males from study weeks 8 to 9 when compared to the control group. Because these differences were transient, did not occur in a dose-related manner, and were not consistent between the sexes, they were not considered to be meaningful. Cumulative weight gain was also not affected. Overall, there were no test article-related effects on body weights or body weight gains.

All food consumption values in the test article-treated groups were similar to control group values. There were no test article-related effects on FOB or motor activity. Mean overall ambulatory counts (a measure of motor activity) was statistically significantly decreased ($p<0.01$ or $p<0.05$) in males in the 3000, 6000 and 12000 ppm group at the study week 12 evaluation when compared to the control group. However, the decreases were not dose-related. In addition, the pretest values for the 3000 and 12000 ppm groups were also decreased compared to the control group. No statistically significant changes were observed when ambulatory counts at study week 12 were expressed relative to pretest value. Similar changes were not observed in females and, therefore, the changes observed in the males were not considered to be test article-related. Total motor activity counts in the 6000 ppm group males were decreased at the study week 12 evaluation when compared to the control group (statistically significant at $p<0.05$); however, the study week 12 value and the pretest value were similar and the decrease was not noted in the 12000 ppm group. The changes were not considered to be test article-related.

Although no test article-related effects on hematology were observed, mean absolute and percent reticulocytes were increased in the 6000 and 12000 ppm group males relative to the control group. However, since reticulocyte counts are often highly variable and there were no correlating changes in other hematology parameters (red blood cells and indices) or microscopic findings, the increase in the reticulocytes was not considered test article-related. An increase in mean absolute lymphocyte counts was observed in males at 6000 ppm but not at 12000 ppm. Since the

change in lymphocyte counts was not accompanied by a change in % lymphocytes, this change was not attributed to test article administration.

The only change in serum chemistry parameters was a statistically significant decrease ($p<0.05$) in mean triglyceride levels in males at 12000 ppm group males when compared to the control group. However, the difference from the control group was small, did not occur in a dose-related manner and increases, instead of decreases, in triglyceride levels are typically considered to be of toxicological significance. Therefore, the change was not considered to be test article-related.

No oculopathic findings indicative of a test article-related effect were observed at any dose level. No test article-related macroscopic findings were observed at the scheduled necropsy. No test article-related effects on organ weights were observed, with the exception of a statistically significant ($p<0.05$) increase in mean testis weight relative to final body weight in the 3000 ppm group males. This increase was not accompanied by any change in the absolute testis weight, there were no changes in the 6000 or 12000 ppm group males and no histopathologic alterations were noted. Therefore, this change was not attributed to test article administration. There were no test article-related histopathologic effects at the scheduled necropsy.

The NOAEL in this study is 12000 ppm (approximately 788 and 926 mg/kg-day for males and females, respectively), the HDT.

Developmental toxicity (Holson 1995)

Range-finder

A dose range-finding developmental toxicity study of Alachlor ESA (MON 5775) was performed in rats. In this study, the test article was administered dissolved in corn oil at dose levels of 0, 100, 300, 400, 600 and 1000 mg/kg-day to Sprague-Dawley female rats (8 animals/dose group) once daily from GDs 6 through 15. Clinical observations and body weights were recorded. Animals were killed on GD 20 and the uteri and ovaries were examined and the numbers of fetuses, early and late resorptions, total implantations and corpora lutea were recorded. Mean gravid uterine weights and net body weight changes were calculated for each group. The kidneys, spleen and liver of each female were weighed. The fetuses were weighed, sexed, examined for external malformations and variations.

An increased incidence of rales was observed in the high dose group (1000 mg/kg-day) and one and two instances in the 400 and 600 mg/kg-day groups, respectively. The occurrence of rales was observed exclusively at the one hour post-dosing examinations. There were no rales observed in animals of the control, 100 and 300 mg/kg-day groups. Although the occasional occurrences of rales in the 400, 600 and 1000 mg/kg-day groups were considered to be test article-related, they were not considered to be definitive signs of maternal toxicity. As concluded in the main study, such an effect is not uncommon in rats receiving high doses of test material by oral gavage, and probably results from trauma associated with the dosing procedure combined with a non-specific reaction to a large volume of a chemical.

There were no statistical differences in body weights, body weight gains, gravid uterine weights, net body weights and net body weight gains at any dose level compared to controls.

No gross pathology findings were noted at the scheduled necropsy. No statistically significant differences in organ weights between treated and control groups were observed.

Intrauterine growth and survival were not adversely affected by compound administration at any dose level. The only difference observed was a slightly lower, but statistically insignificant, mean fetal body weight in the 1000 mg/kg-day group (3.4 grams) compared to the control group value (3.6 grams). The author attributed the difference primarily to a decrease in male fetal body weights (no difference in females). According to the author, the 1000 mg/kg-day group value was within the range of the performing laboratory's historical control data (3.3-3.8 grams). Therefore, no treatment-related effects were evident.

There were no test article-related external malformations and no development variations observed in fetuses in this study. Although one fetus in the 1000 mg/kg-day group had a filamentous tail, the author indicated that the defect occurs spontaneously in control animals; therefore, the single occurrence is not considered a treatment-related effect.

The only treatment-related effect observed in this study was clinical signs (rales) in the 400, 600, and 1000 mg/kg-day groups. Since no other signs of toxicity on quantitative endpoints (body weight data) were observed, the author considered this single clinical sign not to be a conclusive indication of maternal toxicity. Furthermore, as concluded in the main study, such an effect is not uncommon in rats receiving high doses of test material by oral gavage, and probably results from trauma associated with the dosing procedure combined with a non-specific reaction to a large volume of a chemical. Based on the results, no test substance related maternal or developmental toxicity was observed at dose levels up to 1000 mg/kg-day.

Main Study

In the main developmental toxicity study, Alachlor ESA (MON 5775), dissolved in corn oil, was administered by oral gavage to three groups of female Sprague-Dawley rats (25 animals/dose group) once daily at dose levels of 0, 150, 400, and 1000 mg/kg-day from GDs 6 through 15. All females were observed twice daily for moribundity and mortality. Detailed clinical observations were recorded daily throughout gestation (Days 0 through 20). Animals were observed for signs of toxicity at the time of dosing and approximately one hour following dosing. Body weights and food consumption were recorded on GDs 0, 6, 9, 12, 16, 18, and 20. Animals were killed on GD 20 and the liver, kidneys and spleen of each female were weighed. The uteri and ovaries were examined and the numbers of fetuses, early and late resorptions, total implantations and corpora lutea were recorded. Mean gravid uterine weights and net body weight changes were calculated for each group. Fetuses were weighed, sexed and examined for external, visceral and skeletal malformations and developmental variations.

All animals survived to the scheduled necropsy on GD 20. The predominant clinical sign in the 1000 mg/kg-day group was rales. The rales were noted in five animals in this dose group on one to three occasions between GDs 9 and 17. The authors concluded that the rales probably resulted

from trauma associated with the dosing procedure combined with a non-specific reaction to a large volume of a chemical.

No adverse effects were noted on mean gestation body weights, body weight gains, gravid uterine weights, net body weights or net body weight gains at any dose level.. There were no treatment-related effects on food consumption at any dose level. No treatment-related internal findings were observed at the scheduled necropsy. Organ (liver, kidney, and spleen) weights did not differ statistically significantly between treated and control groups. Treatment did not affect intrauterine growth and survival, measured as mean postimplantation loss, viable litter size, fetal body weights, fetal sex ratios and numbers of corpora lutea and implantation sites. The mean fetal body weight in the 400 mg/kg-day group was slightly reduced (3.4 g) and statistically significant at $p < 0.05$ when compared to the control group value (3.6 g). However, because fetal body weight changes were not observed in the 1000 mg/kg-day group, the slight reduction at 400 mg/kg-day was not considered treatment-related. No compound-related increases in external, visceral and skeletal variations or malformations were observed.

Although rales observed in the dams following administration of test material, and the rales appear to be treatment-related, it was concluded that they were not directly related to the inherent toxicity of the test substance, but likely due to local effects from oral gavage of large amounts of the test article. Therefore, the NOAEL for maternal toxicity is $\geq$1000 mg/kg-day (HDT). Since the test material did not produce any evidence of developmental toxicity at dose levels up to 1000 mg/kg-day, the NOAEL for developmental toxicity is also $\geq$1000 mg/kg-day, the HDT. Since the test substance was approximately 90% pure, the NOAEL was corrected to $\geq$900 mg/kg-day.

Alachlor Oxanilic Acid (OXA)

An acute oral toxicity study and two oral subchronic (28- and 90-day dietary) were available for this compound. No reproductive/developmental or chronic toxicity studies were available for this compound. There were no inhalation or dermal toxicity studies and no health effect studies in humans were identified.

Acute oral toxicity study (Blaszcak, 1995)

An acute oral toxicity study in Sprague-Dawley rats reported a LD_{50} of greater than 5000 mg/kg body weight.

Subchronic oral toxicity study

a. 28-day dietary study (Stout and Thake, 2000)

A subchronic, 28-day dietary study was performed in Sprague-Dawley albino rats. Alachlor OXA (MON 5760) was administered in the diet to the animals (5 animals/sex/dose group) at concentrations of 0, 1000, 10000 or 20000 ppm (0, 74.21, 754.26 and 1539.32 mg/kg-day for

males and 0, 83.35, 829.68 and 1595.26 mg/kg-day for females). Obvious signs of toxicity were observed at least once daily while detailed observations for signs of toxicity were conducted every 6-8 days. Motor activity and a complete FOB were performed or measured on all animals prior to exposure and again in Week 4. Body weights were recorded 5 days before study start, on Day 1, and every 6-8 days thereafter. Food consumption was measured every 6-8 days. Clinical pathology (hematology, blood chemistry, and clotting potential) was performed on all animals at termination of study. Gross pathology was conducted on all animals at the scheduled necropsy (Day 30). External and internal examinations were conducted, organ weights were recorded, and microscopic examination was performed on several organs and tissues from animals in the control and 20000 ppm groups and on stomachs from animals at 1000 and 10000 ppm.

There were no test article-related clinical signs of toxicity observed at any dose levels. Group mean body weights and/or cumulative weight gains were increased in males at 1000 ppm throughout the study (statistically significant at weeks 1, 3 and 4). Males from 10000 and 20000 ppm groups did not exhibit any changes in these parameters when compared to control. There were also no treatment-related effects on body weights and/or cumulative weight gains in females at any dietary concentration.

Food consumption was statistically significantly increased in males at all dietary concentrations during the last week of the study. However, no significant differences in food consumption by females were observed at any dietary concentration.

The only significant differences in the Week 4 FOB data were the presence of focal loss of hair in a female at 10000 ppm, and subcutaneous mass in a control female, and alopecia in one control male. There were no significant differences in motor activity.

Hematology parameters that were statistically significantly altered in males at 20000 ppm included increased numbers of lymphocytes, basophils and large unstained cells (154%, 282% and 174% of controls, respectively**),** increased mean corpuscular volume (105% of controls) and decreased red blood cell counts (91% of controls). In females, mean corpuscular hemoglobin was decreased (95% of controls) only at 20000 ppm. These increases in lymphocytes, basophils, and large unstained cells in males were not considered toxicologically relevant due to individual variations which often occur in these parameters, together with the small numbers of animals in this study, and the absence of similar changes in females. Because the magnitude of changes in total erythrocytes in males and mean corpuscular hemoglobin in females at 20000 ppm, and in the mean corpuscular volume in males at 20000 ppm is small, these changes are considered to be toxicologically irrelevant. In addition, there were no corroborative changes for any of these changes in blood cells.

The only blood chemistry parameter that was affected was creatinine, in which statistically significant increase (133% of controls) were reported in females at 1000 ppm but not at higher concentrations. No such changes were observed in males at any concentration level. Therefore, the change in females at 1000 ppm is not toxicologically relevant.

There were no significant differences in activated partial thromboplastin times.

Absolute and relative (to body weight) spleen weights were statistically significantly increased in males at all levels, while liver weights were increased in males at 20000 ppm only (absolute: 112% of controls; relative: 111 % of controls). However, the increases were not dose-dependent. The author attributed the increase to an inordinately low spleen weight for two control males. Although liver weights increased (≤112% of controls) in males at 20000 ppm, there were no treatment-related hepatic abnormalities observed microscopically. Therefore, the increase is not considered to be toxicologically relevant. Organ weights in females did not differ significantly from controls.

No gross pathological findings related to treatment were observed. The only treatment-related microscopic changes observed were in the stomach. Hyperplasia of mucous cells (primarily in the fundic region of the stomach) and eosinophilic inclusions in the cytoplasm of epithelial cells (primarily in the fundic region, but also present to some extent in pyloric epithelium) were observed in the stomachs of males and females at 20000 ppm. One or both of these changes, described as generally of mild or moderate severity, occurred in four males and three females from the 20000 ppm group. Eosinophilic inclusions of minimal severity occurred in a single control male. According to the authors, these gastric changes appear to have been the result of altered mucous production in the epithelium of the glandular stomach.

The NOAEL in this study is 10000 ppm (754.26 and 829.68 mg/kg-day in males and females, respectively), with a LOAEL of 20000 ppm (1539.32 and 1595.26 mg/kg-day for males and females, respectively), based on gastric changes (hyperplasia and eosinophilic inclusions of epithelial cells) in males and females.

b. 90-day dietary study (Lemen et al., 2000)

In a 90-day oral dietary study, Alachlor OXA (MON 5760) was administered to groups of male and female Sprague-Dawley rats (10 animals/sex/dose group) daily at dose levels of 0, 400, 1300, 4000 or 13,000 ppm (0, 24.9, 83.5, 261.1, and 834.6 mg/kg-day, males; 0, 29.1, 95.4, 290.9, and 1008.3 mg/kg-day, females). All animals were observed once daily during acclimation and twice daily during the study for mortality and moribundity. Detailed clinical examinations, including observations in an open field, were performed and food consumption was measured every 6 to 8 days of the study. An ophthalmic examination was conducted at pretest (Day -8) and Day 80. A neurobehavioral evaluation, motor activity (MA) and functional observational battery (FOB) were conducted on all animals at pretest and Week 11. Clinical pathology (hemoglobin, blood chemistry, and clotting potential) was performed at the end of the exposure. Animals were then killed and a complete necropsy was then conducted, organs were weighed and tissues were collected from all animals. The tissues from the control and high dose animals were examined microscopically.

All animals survived until scheduled kill. Clinical observations revealed no substance-related effects. However, isolated occurrences of non-test related clinical signs (discharge from the nose and eyes, malocclusion, swollen mouth, focal loss of hair, scabs and decreased defecation) were observed in animals from various groups during the study. No test-related body weight differences or body weight changes or food consumption were noted. Ophthalmoscopic findings

related to treatment were not observed. There were no significant changes in FOB attributable to the test substance at any dose level. Motor activity was increased in the 1300 ppm group as a percent of pretest baseline. The authors attributed this effect to reduced activity at pretest rather than a test-substance related increase. Activity counts at Week 11 were similar in all groups, indicating that the test substance did not affect the FOB. No significant changes in clinical pathology parameters were noted at any dose level. There were no treatment-related differences in absolute or relative organ weights and treatment did not cause any macroscopic or microscopic changes compared to controls.

The NOAEL in this study is 13000 ppm (834.64 mg/kg-day for males and 1008.29 mg/kg-day for females), the HDT.

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Appendix B: Analyses Related to other Potential Endpoints

This section presents potential issues regarding gastric changes observed in a 28-day dietary study with alachlor OXA (Stout and Thanke, 2000) and a position statement by the Acetochlor Registration Partnership (ARP) regarding neurotoxic effects noted in one dog study.

i. **Gastric Histopathology**

Summary of Key Data

In rats, alachlor is known to cause gastric mucosal atrophy in the fundic region that ultimately results in the development of glandular stomach tumors. The mode of action for development of such tumors in the rat by alachlor was supplemented using data developed for the related chloroacetanilide compound and a close structural analog of alachlor, butachlor, which also caused an increased incidence of these tumors. At environmentally relevant doses, the mode of action of alachlor-induced gastric tumor formation is not relevant for assessing human cancer hazard, since the mechanism is highly threshold dependent and could only occur in experimental studies where high doses were administered over a prolonged period of time (Thake et al. 1996, Heydens et al. 1999). USEPA classifies alachlor as "likely to be carcinogenic to humans at high doses, but not at low doses" (Federal Register/Vol. 72, No. 168/Sept 26, 2007: pp.. 54579-54584), recognizing the non-genotoxic threshold mode-of-action of alachlor. IARC (http://monographs.iarc.fr/ENG/Publications/reports.php) has also evaluated the human relevance of gastric neoplasms observed after treatment with alachlor and determined the mechanism is highly threshold dependent and operable only at high doses. Treatment-related gastric neoplasms have not been observed after long-term administration of acetochlor.

Bridging studies indicate that alachlor shares a similar mode of action for the formation of these tumors with butachlor. For both alachlor and butachlor, these tumors were produced in rats chronically exposed in their diet at the highest dose level (126 mg/kg-day for alachlor and 3000 ppm/138.5 mg/kg-day (females) for butachlor) (Heydens et al., 1999; U.S. EPA, 1998). For butachlor, such an exposure first resulted in progressive gastric mucosal atrophy. Biochemical studies show depletion of glutathione in glandular stomach associated with administration of 3000 ppm alachlor. The mucosal atrophy resulted in loss of parietal cells, resulting in reduced gastric acid secretion and elevation of intragastric pH, leading to increased gastrin secretion. This response induces hormonally mediated cellular proliferation that results eventually in the formation of carcinoid tumors in the glandular stomach. The cell proliferation was consistently increased at the base of the gastric fundus, the magnitude of which was substantially greater than that observed in the neck of the gastric fundus (Thake et al., 1995).

In a 28-day dietary study, alachlor OXA caused treatment-related microscopic changes in the stomach (Stout and Thake, 2000). These changes include hyperplasia of mucous cells (primarily in the fundic region of the stomach) and eosinophilic inclusions in the cytoplasm of epithelial cells (primarily in the fundic region, but also present to some extent in pyloric epithelium) in males and females at 20,000 ppm (1539 mg/kg-day for males and 1595 mg/kg-day for females). This dose is at least 12 times higher than the dose at which alachlor caused stomach tumors in rats. Inclusions were confined to the surface epithelium and the neck of the gastric glands. One or both of these changes, described as generally of mild or moderate severity, occurred in four males and three females, while the eosinophilic inclusions of minimal severity occurred in a single control male. The NOAEL in this study is 10,000 ppm (754.26 and 829.68 mg/kg-day in males and females, respectively). According to the authors, these gastric changes appear to have been the result of altered mucous production in the epithelium of the glandular stomach. Additionally, the stomach pathological changes observed in the 28-day study with alachlor OXA are different (hyperplasia of mucus cells and eosiniphilic inclusions) than those observed after treatment of rats with alachlor (mucosal atrophy and loss of parietal cells).

No treatment-related pathological changes in the rat stomach were observed in the 90-day rat study with alachlor OXA, at the highest dose tested (1008.3 mg/kg-day).

Mechanistic data that evaluated the potential of alachlor OXA to induce the glandular tumors as observed in studies with the parent, alachlor, were not available. However, such a potential was retrospectively evaluated for alachlor ESA to determine if it causes the same preneoplastic effects (mucosal atrophy, as measured by decreased thickness and increased cell proliferation) which resulted in gastric-tumor development following chronic alachlor and butachlor administration. Stomach tissues from control and high-dose animals from the alachlor ESA drinking water study were histopahologically reevaluated. In the original study, alachlor ESA was administered in drinking water to female rats – the sex in which alachlor preferentially induced stomach tumors – at 0 or 10,000 ppm (1108 mg/kg-day, females), the highest dose tested, for 91 days (Heydens et al., 2000; Iatropoulos and Wang, 1995). This dose was approximately 5 times higher than the butachlor dose (190 mg/kg-day; Thake et al., 1995) that produced changes in mucosal thickness and regenerative cell proliferation prior to tumor formation and 9-times higher than the dose that produced stomach tumors in the alachlor bioassay. Alachlor ESA at this dose produced a significant increase in cell proliferation in the fundic neck, although the degree of increased cell turnover was relatively low (26% above controls). No significant increase in cell proliferation in the fundic base – the region most affected by alachlor – was observed in alachlor ESA-treated animals compared to controls. There was no difference in the mucosal thickness of the fundus between treated and control animals. Based on these results, alachlor ESA did not produce any atrophy or biologically-relevant change in cell turnover in the fundic mucosa.

Chronic studies for acetochlor do not suggest that the gastric mucosa is a critical target of non-cancer or cancer effects.

Key Points for Consideration

- The stomach was identified as target organ in the 28-day study with alachlor OXA, but only at a dose that exceeded the limit dose.

- Similar pathological changes were not observed in the 90-day study with alachlor OXA, at doses up to and including a limit dose.

- The pathological changes in the stomach observed in the 28-day study with alachlor OXA are different than the pathological changes that are associated with the development of gastric tumors in the rat stomach after treatment with the parent alachlor.

- The gastric tumors observed after alachlor treatment are recognized by the USEPA and IARC as forming via a mechanism that is not relevant for assessing human cancer hazard at environmentally relevant doses.

In the context of hazard characterization:

- Given the differences in predominant gastric target site and the current MOA understanding, are gastric changes likely to be a potential critical effect for the alachlor degradates? Are the available data for alachlor ESA and alachlor OXA sufficient to evaluate the potential for chronic non-cancer effects on the gastric epithelium for the alachlor degredates? Are there data that suggest concern regarding this endpoint for the acetochlor degredates?

- Are other studies related to this endpoint for the alachlor or acetochlor degradates likely to impact the risk assessment? If so, what studies would be recommended to fill the existing data need?

ARP Position Statement Regarding Neurotoxic Effects Noted in One Dog Study

Neurotoxic effects were observed in one of two one-year dog studies. In that study, acetochlor was administered via capsule at dose levels of 0, 2, 10 and 50 mg/kg/day. Six of the ten dogs at 50 mg/kg/day were sacrificed prematurely between days 39 to 51 due to excessive signs of toxicity, including emaciation and numerous clinical signs of neurotoxicity (including ataxia, swaying, hind limb rigidity, etc). High-dose animals also exhibited degenerative lesions of the brain (cerebellum). No clinical signs of neurotoxicity or brain lesions were noted at 10 mg/kg/day, although increased salivation was noted, primarily in one animal.

The brain lesions and clinical signs of neurotoxicity noted in this study were highly likely to be secondary to renal toxicity. The neurological effects were noted only in high dose animals, all of which exhibited significant renal pathology (nephritis, hyperplasia of the collecting ducts and pelvic epithelium, cortical atrophy and/or fibrosis, vasculitis, and sometimes necrosis). According to the report, "the cortical and collecting duct changes in dogs treated at 50 mg/kg/day were considered to be potentially life threatening and it is probable that the renal toxicity seen would have proved fatal if treatment had continued." Surviving high-dose animals exhibited significantly increased levels of urea, creatinine and BUN. Thus, it is possible that the brain lesions noted in high-dose animals may have been the result of uremic encephalopathy. The renal toxicity would have resulted in less efficient renal clearance and thus substantially higher blood concentrations of acetochlor and/or its metabolites, which could have contributed to the neurological effects observed. In either case, the brain lesions and definitive clinical signs of neurotoxicity occurred only at a dose level (50 mg/kg/day) that was clearly excessively toxic.

In a second one-year dog study, acetochlor was administered via capsule at dose levels of 0, 4, 12 and 40 mg/kg/day. High-dose animals in this study exhibited markedly decreased weight gain, increased liver and kidney weights, testicular atrophy and possible fatty infiltration of the liver. No evidence of brain or kidney histopathology was noted in this study at any dose level.

No evidence of neurotoxicity was noted in either of two subchronic dog studies. In the first study, acetochlor was administered by capsule at dose levels of 0, 25, 75 and 200 mg/kg/day for approximately 4 months. The high-dose level was excessively toxic, as indicated by a high rate of mortality, emaciation, bloody diarrhea, decreased body weight, and histopathological lesions of the liver, kidneys and bone marrow. No clinical or histopathological indications of neurotoxicity were noted at any dose level. In the second study, acetochlor was administered by

capsule for 3 months at dose levels of 0, 2, 10 and 60 mg/kg/day. There was no effect on survival but high-dose dogs exhibited decreased weight gain and numerous clinical signs of toxicity including diarrhea, mucus in the feces, salivation, emesis and vocalization during defecation. There were a number of clinical pathology changes but no effect on brain cholinesterase and no histopathological findings in any tissue, including the brain.

Therefore, the overall weight of evidence suggests that the neurotoxic effects noted at 50 mg/kg/day in a one-year dog study occurred only at an excessively toxic dose and were likely secondary to renal toxicity. Thus, they are not considered to be a relevant endpoint for human risk assessment.