Independent Expert Peer Workshop for the Toxicological Assessment and Development of RfDs for Acetanilide Degradates: A Workshop Using the Alliance For Risk Assessment (ARA) Collaborative Model

Bernard Gadagbui[1], Andrew Maier[1], Michael Dourson[1], Ann Parker[1], Alison Willis[1], John P. Christopher[2], Lebelle Hicks[3]
[1]Toxicology Excellence for Risk Assessment, [2]Department of Toxic Substances Control, California Environmental Protection Agency, [3]Maine Board of Pesticides, Department of Agriculture

Abstract

The workshop was organized to provide a diverse group of independent experts' review of toxicity data to develop RfDs for tertiary-ethanesulfonic acid (ESA) and tertiary-oxanilic acid (OXA) degradates of acetochlor and alachlor. The workshop was open to the public; interested persons were invited to attend the meeting either in person or via a real-time Internet webcast. Observers were provided the opportunity to provide written or oral technical comments before and during the meeting. *TERA* compiled data into a series of comprehensive tables which included key data summary tables, critical endpoint summary tables, benchmark dose modeling results, potential RfD summary tables, and copies of key references for the parent chemicals (acetochlor and alachlor) and their degradates (acetochlor ESA, acetochlor OXA, alachlor ESA, and alachlor OXA). The panel assessed the critical effect, appropriate NOAEL, LOAEL, or BMD and recommended uncertainty factors for the above acetanilide degradates using the compiled tables and supporting materials during the 2-day workshop. The panel had an active discussion on the adequacy of the data, critical effects, mode of action, uncertainty factor selection, and derivation of reference values. The panel deliberated and concluded that an RfD for each degradate should be developed for a total of 4 RfDs resulting from the workshop.

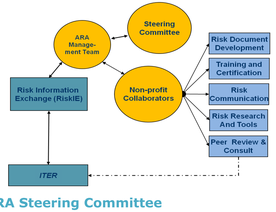
This project was conducted under the auspices of the Alliance for Risk Assessment (ARA), a collaboration of stakeholders representing government, academic, industry, environmental and consulting perspectives. As an ARA project, this assessment was vetted for scientific relevance and was conducted by an independent, nonprofit organization, using state-of-the-science chemical risk assessment methods to protect public health. ARA risk assessments are performed in a transparent manner, and made publicly available upon completion.

Alliance for Risk Assessment Collaboration

This project was conducted under the auspices of the Alliance for Risk Assessment (ARA), a collaboration of stakeholders representing government, academic, industry, environmental and consulting perspectives. Given a limited supply of time, resources, and know-how, public health protection is an effort that requires cooperation, organization, and prioritization. The Alliance helps focus these resources to increase the output of risk values.

The ARA works toward this goal by striving for:

- **Improved communication among groups**
- **Transparency in development of products**
- **Harmonization and consistency in risk assessments**
- **Shared costs and human resources**



ARA Steering Committee

A project submitted to the Alliance, is first reviewed by the ARA Steering Committee, a balance of Federal, State, and Tribal governments, Environmental NGOS and non-profits, and Academia. Current Steering Committee members include:

- Anita Meyer, United States Army Corps of Engineers
- Barbara Harper, Confederated Tribes of the Umatilla Indian Reservation
- Bette Meek, University of Ottawa
- Edward Ohanian, United States Environmental Protection Agency
- Michael Dourson, Toxicology Excellence for Risk Assessment (TERA)
- Michael Honeycutt, Texas Commission on Environmental Quality (TCEQ)
- Phil Wexler, National Library of Medicine (NLM)
- Ruthann Rudel, Silent Spring
- William Hayes, State of Indiana

The Steering Committee reviews projects for mission relatedness, impact to the broader risk assessment community, and helps identify relevant work being conducted by groups in their respective sectors.

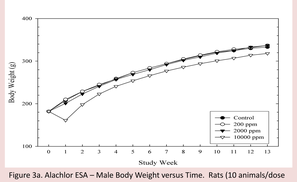
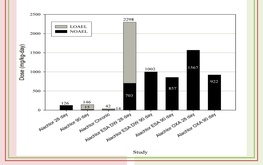


Figure 3a. Alachlor ESA – Male Body Weight versus Time. Rats (10 animals/dose group) were administered alachlor ESA in their drinking water at a concentration of 0, 200, 2000, or 10000 ppm (0, 16, 157, and 896 mg/kg-day) for 91 days (Siglin, 1993; Heydens et al., 1996). Graph represents group mean body weight versus time.

Alachlor ESA

- Degradate not formed in vivo, metabolic pathways are different in soil than in mammals
  - Frequently detected in groundwater
  - No federal regulations
- Toxicokinetic data
  - Poorly absorbed
  - Rapidly eliminated
  - Excreted largely untransformed
- Toxicity of parent chemical is greater than toxicity of degradates
  - Consistent with recent EPA assessments
- Key effects
  - Mild clinical effects
  - Slight body weight changes
  - Initial rapid decreases in body weight for high dose group
  - Effects suggest palatability issues
- Low to medium confidence RfD

Figure 2a. Effect Levels for Body Weight - Alachlor and Degradates. Differences in NOAEL and LOAEL values identified from dietary or drinking water (DW) studies in rats using alachlor and its ESA and OXA degradates. Values are means for both male and female animals. The references for alachlor 28-day, 90-day, and chronic toxicity studies are Hotz et al. (1993), Wolf (1966), and Daly et al. (1981), respectively.



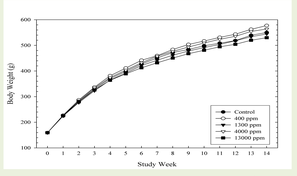
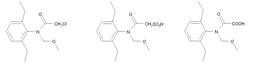


Figure 3b. Alachlor OXA – Male Body Weight versus Time. Rats (10 animals/dose group) were administered alachlor OXA in the diet at a concentration of 0, 400, 1300, 4000, or 13000 ppm (0, 24.9, 83.5, 261.1, and 834.6 mg/kg-day) for 90 days (Lemen et al., 2000). Graph represents group mean body weight versus time for the more sensitive sex.

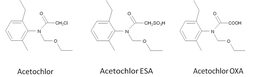
Alachlor OXA

- Degradate not formed in vivo, metabolic pathways are different in soil than in mammals
  - Frequently detected in groundwater
  - No federal regulations
- Toxicokinetic data not available
  - Other degradates' toxicokinetic data can be used as a surrogate
    - Poorly absorbed
    - Rapidly eliminated
    - Excreted largely untransformed
- Toxicity of parent chemical is greater than toxicity of degradates
  - Consistent with recent EPA assessments
- Key effects
  - Absence of a consistent pattern of body weight changes
- Low to medium confidence RfD

Alachlor and Degradate Structures



Acetochlor and Degradate Structures



Alachlor ESA Available Studies

Duration of Study	Animal Model Species	Route of Administration	Dosing Regimen	Reference
28 days	Rat	Diet	0, 700, 2000, 7000, and 20,000 ppm [Males – 0, 68, 183, 656, and 2217 mg/kg-day; Females – 0, 75, 205, 749, and 2378 mg/kg-day]	Siglin (1993)
90 days	Rat	Diet	0, 3000, 6000, and 12,000 ppm [Males – 0, 195, 389, and 788 mg/kg-day; Females – 0, 222, 454, and 926 mg/kg-day]	Kirkpatrick (2002)
91 days	Rat	Drinking water	0, 200, 2000, and 10,000 ppm [Males – 0, 16, 157, and 896 mg/kg-day; Females – 0, 23, 207, and r 1108 mg/kg-day]	Siglin (1993); Heydens et al. (1996)

Composite Uncertainty Factor (UF)

- 10 • Human variability in sensitivity
- 10 • Interspecies differences in sensitivity
- 10 • Subchronic to chronic and • Database deficiency combined
- 1000 Composite UF

Alachlor ESA Key Studies and Points of Departure (POD) for RfD Derivation

Critical Effect(s)	NOAEL mg/kg-day, males / females	LOAEL mg/kg-day, males / females	POD* mg/kg-day	Reference
No adverse effects on body weight	788 / 926	NA	788	Kirkpatrick (2002)

Alachlor ESA RfD Derivation

$$\frac{788 \text{ mg/kg-day}}{1000} = 0.8 \text{ mg/kg-day}$$

Alachlor OXA Key Studies and Points of Departure (POD) for RfD Derivation

Critical Effect(s)	NOAEL mg/kg-day, males / females	LOAEL mg/kg-day, males / females	POD* mg/kg-day	Reference
No adverse effects on body weight	834 / 1008	NA	834	Lemen et al., (2000)

Alachlor OXA RfD Derivation

$$\frac{834 \text{ mg/kg-day}}{1000} = 0.8 \text{ mg/kg-day}$$

Composite Uncertainty Factor (UF)

- 10 • Human variability in sensitivity
- 10 • Interspecies differences in sensitivity
- 10 • Subchronic to chronic and • Database deficiency combined
- 1000 Composite UF

Alachlor OXA Available Studies

Duration of Study	Animal Model Species	Route of Administration	Dosing Regimen	Reference
28 days	Rat	Diet	0, 1000, 10,000, and 20,000 ppm [Males – 0, 74.21, 754.26, and 1539.32 mg/kg-day; Females – 0, 83.35, 829.68, and 1595.26 mg/kg-day]	Stout and Thake (2000)
90 days	Rat	Diet	0, 400, 1300, 4000, and 13,000 ppm [Males – 24.9, 83.5, 261.1, and 834.6 mg/kg-day; Females – 0, 29.1, 95.4, 290.9, and 1008.3 mg/kg-day	Lemen et al. (2000)

Alachlor ESA 0.8 mg/kg-day | **Alachlor OXA 0.8 mg/kg-day**

RfD Values

Acetochlor ESA 0.2 mg/kg-day | **Acetochlor OXA 0.2 mg/kg-day**

Expert Panel Workshop

- An expert panel met publicly over two days to develop oral RfDs for the acetanilide degradates.
  - The panel was highly experienced in the areas of dose-response assessment and pesticide toxicology.
- Members of the panel
  - Dr. Michael Dourson, Toxicology Excellence for Risk Assessment (*TERA*)
  - Dr. John P. Christopher, Department of Toxic Substances Control, California Environmental Protection Agency
  - Dr. Lebelle Hicks, Maine Board of Pesticides, Department of Agriculture
  - Dr. Santhini Ramasamy, Office of Water, U.S. Environmental Protection Agency
  - Dr. Stephen M. Roberts, Center for Environmental and Human Toxicology, University of Florida
- The panel received a data package for the parent chemicals (acetochlor and alachlor) and their degradates from *TERA*
  - The package included: charge questions, issue descriptions, data summary tables from relevant studies, key findings on the selection of potential critical effects, and benchmark dose modeling results.
  - Final recommendations were not provided by *TERA*; the panel made independent decisions.
  - Summary information available at http://www.tera.org/ART/Degradates/index.html
- Panel concluded that the degradates are less likely to be biologically reactive than the parent chemicals because they:
  1. Are more polar
  2. Have relatively low absorption
  3. Undergo little biotransformation
  4. Are rapidly eliminated
  5. Are not likely to undergo conjugation reactions due to lack of a reactive dehalogenation site as is present in the parent chemicals, and
  6. The presence of oxamic acid or ethane sulfonate moieties that prevent the chemicals from being metabolized to a reactive quinoneimine like the parent chemicals

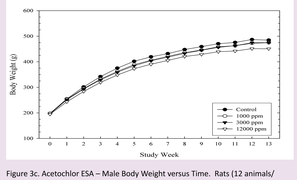


Figure 3c. Acetochlor ESA – Male Body Weight versus Time. Rats (12 animals/dose group) were administered acetochlor ESA in the diet at a concentration of 0, 1000, 3000, or 12000 ppm (0, 75.0, 225.4 or 919.4 mg/kg-day) for 90 days (Lees, 2000b). Graph represents group mean body weight versus time for the more sensitive sex.

Acetochlor ESA

- Degradate not formed in vivo, metabolic pathways are different in soil than in mammals
  - Frequently detected in groundwater
  - No federal regulations
- Toxicokinetic data
  - Poorly absorbed
  - Rapidly eliminated
  - Excreted largely untransformed
- Toxicity of parent chemical is greater than toxicity of degradates
  - Consistent with recent EPA assessments
- Key effects
  - Decrease in body weight of 10% or greater
  - Significantly decreased food utilization in males and females
  - 4% change in adjusted body weight in the mid-dose group
- Low to medium confidence RfD

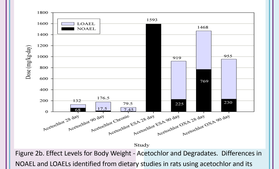


Figure 2b. Effect Levels for Body Weight - Acetochlor and Degradates. Differences in NOAEL and LOAELs identified from dietary studies in rats using acetochlor and its ESA and OXA degradates. Values are means for both male and female animals except for the 28-day studies for acetochlor and acetochlor OXA and the 90-day studies for acetochlor ESA and OXA where values represent the lower values in males. The references for the 28-day, 90-day, and chronic toxicity studies for acetochlor are Broadmeadow (1985), Broadmeadow (1986), and Virgo and Broadmeadow (1988), respectively.

Acetochlor ESA Available Studies

Duration of Study	Animal Model Species	Route of Administration	Dosing Regimen	Reference
28 days	Rat	Diet	0, 3000, 6000, and 12,000 ppm [Males – 0, 370.3, 766.6, and 1578.7 mg/kg-day; Females – 0, 374.6, 762.3, and 1607.4 mg/kg-day]	Lees (2000a)
90 days	Rat	Diet	0, 1000, 3000, and 12,000 ppm [Males – 0, 75.0, 225.4, and 919.4 mg/kg-day; Females – 85.2, 259.1, and 1073.2 mg/kg-day]	Lees (2000b)

Composite Uncertainty Factor (UF)

- 10 • Human variability in sensitivity
- 10 • Interspecies differences in sensitivity
- 10 • Subchronic to chronic and • Database deficiency combined
- 1000 Composite UF

Acetochlor ESA Key Studies and Points of Departure (POD) for RfD Derivation

Critical Effect(s)	NOAEL mg/kg-day, males / females	LOAEL mg/kg-day, males / females	POD* mg/kg-day	Reference
Decreased body weight gain, decreased food consumption, and decrease food utilization	225 / 259	919 / 1073	225	Lees (2000b)

Acetochlor ESA RfD Derivation

$$\frac{225 \text{ mg/kg-day}}{1000} = 0.2 \text{ mg/kg-day}$$

Acetochlor OXA

- Degradate not formed in vivo, metabolic pathways are different in soil than in mammals
  - Frequently detected in groundwater
  - No federal regulations
- Toxicokinetic data
  - Poorly absorbed
  - Rapidly eliminated
  - Excreted largely untransformed
- Toxicity of parent chemical is greater than toxicity of degradates
  - Consistent with recent EPA assessments
- Key effects
  - Significant reductions in body weights, 7% for males and 5% for females
  - Clear effect on reduced food utilization and adjusted body weight
- Low to medium confidence RfD

Acetochlor OXA Key Studies and Points of Departure (POD) for RfD Derivation

Critical Effect(s)	NOAEL mg/kg-day, males / females	LOAEL mg/kg-day, males / females	POD* mg/kg-day	Reference
Decreased body weight gain and decrease food utilization	230 / 268	955 / 1082	230	Williams (2000b)

Acetochlor OXA RfD Derivation

$$\frac{230 \text{ mg/kg-day}}{1000} = 0.2 \text{ mg/kg-day}$$

Composite Uncertainty Factor (UF)

- 10 • Human variability in sensitivity
- 10 • Interspecies differences in sensitivity
- 10 • Subchronic to chronic and • Database deficiency combined
- 1000 Composite UF

Acetochlor OXA Available Studies

Duration of Study	Animal Model Species	Route of Administration	Dosing Regimen	Reference
28 days	Rat	Diet	0, 3000, 6000, and 12,000 ppm [Males – 0, 372.6, 768.5, and 1467.9 mg/kg-day; Females – 0, 367.2, 737.3, and 1506.5 mg/kg-day]	Williams (2000a)
90 days	Rat	Diet	0, 1000, 3000, and 12,000 ppm [Males – 0, 77.2, 230.2, and 955.2 mg/kg-day; Females – 86.5, 268.0, and 1082.7 mg/kg-day]	Williams (2000b)

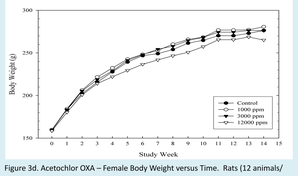


Figure 3d. Acetochlor OXA – Female Body Weight versus Time. Rats (12 animals/dose group) were administered acetochlor OXA in the diet at a concentration of 0, 1000, 3000, or 12000 ppm (0, 86.5, 268.0, and 1082.7 mg/kg-day) for 90 days (Williams, 2000b). Graph represents group mean body weight versus time for the more sensitive sex.

Panel Observations

- LOAELs were at least five-times higher than those of the parent chemicals and NOAELs that ranged from five- to 60-times higher for the degradates compared to the parent chemicals.
- The underlying mode of action for decreased body weights is uncleaar, and relative impacts of different mechanisms were not readily apparent from the available data.
- Observed clinical signs were considered to be consistent with dehydration as an underlying cause for the alachlor ESA drinking water study.
- No treatment-related adverse effects on the thyroid were seen for acetochlor and alachlor degradates.
- Developmental toxicity doesn't appear to be a concern for these degradates, but recognized that lack of data for the untested degradates continues to represent a data gap.
- A composite UF of 1000 for each degradate was considered reasonable, but noted that an argument could be made for an UF of 3000 ($10_L \times 10_A \times 10_{H/D}$).

Funded by Monsanto and Dow AgroSciences, with in-kind support from US EPA, State of Maine and TERA