

Report From Agency

REPORT TO LEGISLATURE

NR 140, Wis. Adm. Code
Groundwater quality standards (Alachlor ESA)

Board Order No. DG-18-07
Clearinghouse Rule No. 07-034

Basis and Purpose of the Proposed Rule

Amendments are being proposed to Wisconsin Administrative Code Chapter NR 140, Groundwater Quality. Chapter NR 140, Wis. Adm. Code, establishes Wisconsin state groundwater quality standards for substances of public health and welfare concern. Amendments to NR 140 are proposed to add groundwater quality standards for a substance of public health concern, alachlor ethane sulfonic acid (alachlor-ESA).

Wisconsin's groundwater law, State Statute Chapter 160, was created in May of 1984, as part of the 1983 Wisconsin Act 410. NR 140 was adopted by the Natural Resources Board in 1985 to comply with ch. 160, Stats. Chapter 160, Stats., requires the Department to develop groundwater quality standards for substances detected in, or having a reasonable probability of entering, the groundwater resources of the state. Alachlor-ESA has been detected in Wisconsin in a significant number of water supply wells.

Alachlor-ESA is a degradation product of the broadleaf herbicide alachlor. Alachlor has been used in Wisconsin primarily on corn and soybean crops. Alachlor-ESA was detected in approximately 28% of the private water supply wells tested in a 2000/2001 Wisconsin Department of Agriculture and Consumer Protection (DATCP) statewide groundwater sampling survey. In a 1999/2000 DATCP groundwater sampling survey of wells known or suspected to be impacted by agricultural chemicals, alachlor-ESA was detected in 91% of private water supply wells tested and 48% of the municipal water supply wells tested.

NR 140 establishes groundwater quality standards at two levels, enforcement standard (ES) and preventive action limit (PAL). In accordance with ch. 160, Stats., health based ES groundwater quality standards are established based on recommendations developed by the Department of Health and Family Services (DHFS). PAL groundwater quality standards for substances of public health concern are set at either 20% of the concentration of the established ES, or at 10% of the concentration of the established ES if the substance has carcinogenic, mutagenic or teratogenic properties or interactive effects.

These proposed amendments to NR 140, to establish state groundwater standards for alachlor-ESA, are based on recommendations received from DHFS. Because no federal number, as defined by statute, or health based reference dose (acceptable daily intake level) has been established for alachlor-ESA, DHFS developed their recommendations for an alachlor-ESA ES using the applicable methodology in s. 160.13, Stats. DHFS has recommended an alachlor-ESA ES of 20 micrograms per liter ($\mu\text{g/L}$), and a PAL, set at 20% of the recommended ES, of 4 $\mu\text{g/L}$.

The Natural Resources Board has approved amendments to NR 140 in: 1988, 1990, 1991, 1993, 1995, 1996, 1998, 1999, 2003 and 2006. These amendments were made to add and revise groundwater quality standards and to clarify rule language. There are currently groundwater quality standards for 122 substances of public health concern, 8 substances of public welfare concern and 15 indicator parameters in NR 140.

SUMMARY OF THE RULE

New NR 140 public health based groundwater quality standards are proposed for alachlor-ESA, a degradation product of the broadleaf herbicide alachlor. DHFS has recommended an ES of 20 µg/L and a PAL of 4 µg/L for alachlor-ESA. A concentration of 20 µg/L has been used as an interim health advisory level for alachlor-ESA in Wisconsin since 1993.

Amendments to NR 140 are proposed to add groundwater quality standards for alachlor-ESA, as indicated below:

<u>Substance</u>	<u>Current Standards (in µg/L)</u>		<u>Proposed Standards (in µg/L)</u>	
	<u>ES</u>	<u>PAL</u>	<u>ES</u>	<u>PAL</u>
Alachlor-ESA	no standard	no standard	20	4

Summary of Public Comments

In March of 2007, the Natural Resources Board authorized the Department to hold public hearings and solicit comments on the proposed amendments to NR 140. A public hearing was held on May 11, 2007, in Madison, Wisconsin. One member of the public attended the hearing and signed a hearing appearance slip "in opposition" to the proposed amendments. No oral comments were presented at the public hearing.

5. Summary of Written Public Comments

Written comments on the proposed rule revisions were accepted through May 18, 2007. Correspondence was received by the Department expressing comments on the proposed NR 140 amendments. A total of four comment letters/memos were received by the Department:

- 1) a memo, dated 5/14/2007, from the Alachlor ESA Coalition
- 2) a letter, dated 5/17/2007, from the Wisconsin Crop Production Association
- 3) a letter, dated 5/16/2007, from the Monsanto Company
- 4) a letter, dated 5/18/2007, from the Wisconsin Farmers Union

The Department received written comments both in opposition to, and in support of, the proposed NR 140 alachlor-ESA groundwater quality standards.

Comments received in opposition to the proposed groundwater quality standards for alachlor ESA focused on the methodology used by DHFS to develop their ES groundwater standard recommendation. Because no federal number (federal drinking water standard, suggested no adverse response level or cancer risk level) or Wisconsin state drinking water standard has been established for alachlor-ESA, DHFS, in accordance with Wisconsin's groundwater law, used the methodology specified in s.s. 160.07 and 160.13, Stats., to develop its recommended alachlor-ESA ES.

Use of the s. 160.13, Stats., methodology to develop a NR 140 ES recommendation requires DHFS to determine a no-observable-effect level (NOEL) for alachlor-ESA, and a "suitable" uncertainty factor that the NOEL can be divided by to calculate a reference dose (RfD)/acceptable daily intake (ADI) value. The calculated RfD/ADI is then used to develop a recommended enforcement standard. The majority of the comments received in opposition to the proposed alachlor-ESA groundwater standards challenged DHFS' determination of an alachlor-ESA NOEL, and the uncertainty factor used in the RfD/ADI calculations.

DHFS reviewed relevant toxicological studies and determined an alachlor-ESA NOEL from the results of a 1993 91-day rat study of the toxicity of alachlor-ESA administered in drinking water. Different opinions have been expressed on the selection of a NOEL from the results of this study. Comments were received suggesting that an alternative NOEL from the 1993 rat study be used by DHFS to develop their recommended alachlor-ESA enforcement standard. The Monsanto Company, the manufacturer of alachlor, initiated a new (2003) 90-day rat study of the toxicity of alachlor-ESA administered in food.

Comments were received suggesting that the results of this study be used, instead of the results of the 1993 drinking water study, as the basis for an alachlor-ESA ES recommendation.

The enforcement standard development methodology in s. 160.13, Stats., requires DHFS to determine a suitable uncertainty factor to be used in the calculation of a recommended enforcement standard. DHFS is required to consider a number of specific factors, listed in the statute, when establishing a suitable uncertainty factor. Comments were received questioning DHFS' determination of the uncertainty factor used to develop their recommended alachlor-ESA enforcement standard and suggesting that a different uncertainty factor would be more appropriate.

In determining the uncertainty factor used to calculate their alachlor-ESA ES recommendation DHFS included a factor for "data gaps, including lack of a carcinogenicity study for the metabolite of a potentially carcinogenic parent compound". Comments were received questioning use of this specific factor in determining the uncertainty factor to be used in development of an alachlor-ESA ES recommendation. Commenters suggested that DHFS reconsider use of this factor based on the current EPA alachlor cancer classification.

Because of concerns with DHFS' determination of the NOEL and uncertainty factor used to develop their recommended alachlor-ESA ES, commenters suggested that an independent panel conduct a peer review of the studies and methodology used by DHFS to develop their recommended standard.

Commenters also asked that a "trigger" be placed in the rule that would automatically/immediately revise alachlor-ESA groundwater quality standards as soon as a health advisory level or reference dose (acceptable daily intake) for alachlor-ESA was established by the U.S. Environmental Protection Agency.

Comments were received generally supporting the protection of groundwater resources in Wisconsin. Comments were also made supporting the proposed groundwater standards for alachlor-ESA and stating that farm family health is critical to the health of Wisconsin's rural economy.

A separate Response to Public Comments (Attachment 1) provides responses to comments received on the proposed NR 140 amendments. DHFS has provided responses to comments received related to their development of groundwater standard recommendations for alachlor-ESA (Attachment 2). DHFS has also updated the scientific support documentation that was prepared for their alachlor-ESA groundwater standard recommendations (Attachment 3).

Modifications Made

No modifications were made as a result of the public hearing. The Natural Resources Board requested the Department to add a directive that the Department was required to initiate rulemaking to revise the existing state groundwater quality standards for Alachlor-ESA if a new reference dose or federal number was adopted by the U.S. Environmental Protection Agency.

Appearances at the Public Hearing

In support – none

In opposition

Amy Winters, Monsanto, P.O. Box 771, Madison, WI 53701

As interest may appear - none

Changes to Rule Analysis and Fiscal Estimate

None were required.

Response to Legislative Council Rules Clearinghouse Report

The recommendations were accepted.

Final Regulatory Flexibility Analysis

The Department does not believe that the proposed rule will have a significant economic impact on a substantial number of small businesses. The compliance and reporting requirements in NR 140 are not changed by the proposed amendments. If a groundwater quality standard is exceeded, the owner or operator of a facility, practice or activity, including any small business, must report the violation to the appropriate regulatory agency. The proposed amendments to NR 140 would add one new substance that a facility may have to monitor for, and report exceedances of, if sampled levels attain or exceed proposed standards.

Chapter 160, Stats., requires establishment of both design and performance standards. Individual regulatory programs (DATCP, COMM, DNR-Waste Management, DNR-Watershed Management, etc.) establish design and operational standards in their program rules. Performance standards (groundwater quality standards) are contained in NR 140. Chapter 160, Stats., does not allow for less stringent schedules, deadlines or reporting requirements, or for exemptions to remedial action, when a groundwater quality standard is attained or exceeded, based on the size of the business causing the contamination.

There would be adverse impacts on public health, welfare, safety and the environment if small businesses were not required to meet regulatory reporting requirements and implement remedial responses. The more quickly contamination can be evaluated and responses initiated, the less likely that public health, safety and welfare will be adversely affected. If small businesses were exempt from these requirements groundwater contamination would continue unabated at least until the Department could appropriate sufficient resources to undertake this work. The delay, or possibility that nothing would be done, would lead to adverse impacts on public health, welfare, safety and the environment.

The type of small businesses that are typically impacted by NR 140 include dry cleaners, small manufacturers, agricultural cooperatives, farmers, underground storage tank owners, small solid waste disposal facilities, small wastewater treatment operations, as well as others. In effect, any small business that has an authorized or unauthorized discharge of a substance exceeding the health or welfare groundwater quality standards listed in NR 140 is responsible for responding to the release consistent with the requirements of NR 140.

With the proposed amendments to NR 140 there would be new groundwater quality standards for one new substance. The new groundwater standards would be used, along with existing NR 140 standards, to establish system and facility design standards, for compliance purposes, and as clean up goals in the event of a spill or unpermitted discharge. If remedial action or other response is necessary, the individual programs which regulate the facility, practice or activity would determine the appropriate level of clean-up required. As the cost of remedial options varies, the cost of remediation of groundwater contamination for small businesses will vary, depending on the complexity of the site, the contamination at the facility, practice or activity, and the federal and state laws being used to guide the remedial action.

The new substance for which groundwater quality standards are proposed has been detected in groundwater in Wisconsin. The adoption of state groundwater quality standards that can be used for design, compliance and clean-up activity purposes might aid small businesses in number of ways. Groundwater standards provide specifications for facility and activity design and management, as well as inform a business whether or not substance concentrations detected in groundwater exceed levels determined to be protective of public health and welfare. If concentrations of a substance in a potential drinking water source are elevated and remediation is required, established groundwater quality standards let a small business know when clean-up efforts are completed. When substances are detected in groundwater for which a NR 140 standard does not exist, the Department may require clean-up of groundwater "to the extent practicable". This may result in overly conservative clean-up depending upon the actual toxicity of the substance detected.

Attachment #1

RESPONSE TO PUBLIC COMMENTS

July 13, 2007

**Revisions to ch. NR 140, Wis. Adm. Code, to amend
NR 140.10 Table 1 and Appendix 1, relating to groundwater quality standards for Alachlor-ESA**

Natural Resources Board Order No. DG-18-07

Introduction

In March of 2007, the Natural Resources Board (NRB) authorized the Department to hold public hearings and solicit comments on proposed revisions to Ch. NR 140, "Groundwater Quality", that would establish new state groundwater quality standards for alachlor ethane sulfonic acid (alachlor-ESA).

A public hearing on proposed revisions to NR 140 was held on Friday May 11, 2007. One person attended the hearing. That hearing attendee did not present oral comments, but did register "in opposition" to the proposed NR 140 revisions.

Written comments on the proposed rule revisions were accepted through May 18, 2007. Correspondence was received by the Department expressing comments on the proposed NR 140 revisions. A total of four comment letters/memos were received by the Department:

- 1) a memo, dated 5/14/2007, from the Alachlor ESA Coalition [submitted attached to 5/17/2007 e-mail (from Ms. Amy Winters, President, Capitol Strategies, LLC)]
- 2) a letter, dated 5/17/2007, from the Wisconsin Crop Production Association [submitted attached to 5/17/2007 e-mail (from Mr. Mike Turner, Executive Director, Wisconsin Crop Production Association); copy of letter also submitted via conventional mail]
- 3) a letter, dated 5/16/2007, from the Monsanto Company [submitted attached to 5/18/2007 e-mail (from Ms. Amy Winters, President, Capitol Strategies, LLC and Monsanto Contract Lobbyist)]
- 4) a letter, dated 5/18/2007, from the Wisconsin Farmers Union [submitted via fax on 5/18/2007]

The following acronyms and abbreviations are used to identify commenting organizations below:

AEC	Alachlor ESA Coalition
WCPA	Wisconsin Crop Production Association
MON	Monsanto Company
WFU	Wisconsin Farmers Union

The majority of comments that were received by the Department on this rule relate to DHFS' development of recommendations for alachlor-ESA groundwater quality standards. A copy of comments received by the Department were forwarded to DHFS for their review and response. DHFS has prepared a document with responses to comments related to their development of alachlor-ESA groundwater standard recommendations. This document is attached to the NRB Agenda Item (Green Sheet) background memo as Attachment 2. DHFS has also revised its alachlor-ESA scientific support documentation. The revised DHFS scientific support documentation is attached to the NRB Agenda Item background memo as Attachment 3.

Below are responses to comments received by the Department on the proposed rule, with DHFS responses (from their response to comments document) referenced as appropriate. Comments related to rule language clarity, grammar, punctuation and use of plain language were also received from the Wisconsin Legislative Council Rules Clearinghouse.

I. Written comments received on proposed ch. NR 140, Wis. Adm. Code, revisions:

1. **Comment:** (AEC) "As we have previously stated during the CR 02-095 rule review, we fully support Wisconsin's goal of protecting groundwater resources and ensuring the safety of drinking water and have no objection to the establishment of a scientifically sound, health-based groundwater quality standard. We only ask that the state ensure that sound science is being utilized in establishing this standard and that the state is ensuring the accuracy, integrity, objectivity, and consistency of the data that is being used to prepare the rule as required by the Data Quality Act (State statute 227.14 2m)."

Response: *The Department is proposing that the groundwater quality standard recommendations developed by the Wisconsin Department of Health and Family Services (DHFS) for alachlor-ESA be adopted in ch. NR 140, Wis. Adm. Code. As required under Wisconsin's groundwater law, DHFS followed the methodology in s. 160.13, Stats., in developing its recommendation for an alachlor-ESA groundwater quality enforcement standard.*

Section 227.14(2m), Stats., addresses the quality of data used in the preparation and analysis of a proposed rule. The scientific data that DHFS used in developing their recommendation for an alachlor-ESA groundwater quality enforcement standard were primarily the results of toxicology studies funded by the Monsanto Company, the manufacturer of alachlor. The standard recommended by DHFS is based on the results of valid scientific studies, and the methodology used to develop it is specified in state statute. There is no reason to believe that the accuracy, integrity, objectivity or consistency of the data used by DHFS in developing its alachlor-ESA enforcement standard recommendation is in question.

2. **Comment:** (AEC, MON) "... believe that the DHFS recommendations are at odds with the scientific evidence and are therefore erroneous in two key respects: (1) DHFS's conclusions regarding the toxicity of alachlor ESA, particularly DHFS' determination of a No Observable Effect Level (NOEL) ignore recent study results; (2) DHFS did not select an appropriate uncertainty factor for use in calculating an Enforcement Standard. In both instances, DHFS' conclusions are at odds with and considerably more conservative than those of USEPA and other federal, state, and international regulatory agencies. The net effect of these two decisions by DHFS is a proposed Enforcement Standard (20ppb) that is at least 30-fold, and perhaps over 100-fold, more restrictive than would have been set had the DHFS followed EPA's guidance for conducting risk assessments and setting water quality standards or utilized EPA's conclusions regarding the toxicity of alachlor and alachlor ESA."

Response: *DHFS has reviewed comments related to the NOEL and uncertainty factor used to develop its recommendation for an alachlor-ESA groundwater quality enforcement standard. DHFS has provided responses to comments related to the NOEL and uncertainty factor it utilized - see DHFS (NRB Agenda Item background memo - Attachment 2) response to comments: A, B, D, E & G.*

3. **Comment:** (AEC) "DHFS has justified the additional 10-fold uncertainty factor on the basis of the carcinogenicity of the parent alachlor. However, contrary to DHFS' justification, alachlor is NOT classified by EPA as a "probable human carcinogen". In 1997, following review of extensive mechanistic information and evaluation by the Science Advisory Panel, the EPA re-classified alachlor as "likely to be a human carcinogen at high doses, but not likely at low doses." The scientific justification for this reclassification was clearly outlined in the RED [Dec. 1998 EPA Reregistration Eligibility Decision (RED) Alachlor]."

Response: *DHFS has reviewed comments related to the uncertainty factor used to develop its recommendation for an alachlor-ESA groundwater quality enforcement standard. DHFS has provided responses to comments related to the uncertainty factor it utilized - see DHFS (NRB Agenda Item background memo - Attachment 2) response to comments: B, C & F.*

4. **Comment:** (AEC, MON) "The March 2006 EPA Cumulative Risk Assessment for Chloroacetanilides was also not utilized in establishing the proposed standard. The assessment summarizes the latest EPA cancer risk assessment for combined residues from alachlor and acetochlor in food and water. 2 key elements in this assessment are: (1). The ESA and OXA metabolites were not included in the cancer risk assessment. As stated in the third paragraph on page 19, "These compounds [the metabolites] ... are not included in this cumulative risk assessment because extensive data are available (USEPA 2004b) to show that these compounds show a different toxicological profile than the respective parents and do not contribute to the development of nasal olfactory epithelium tumors in rats." (2). The EPA did NOT apply any additional safety factor for carcinogenicity, even though both alachlor and acetochlor are known to be carcinogenic to rats. As indicated at the top of pages 5 and 30, the Agency considers a Margin of Exposure greater than 100 to be outside their "level of concern" (LOC) for the tumors produced by these chemicals. This is equivalent to utilizing a total uncertainty factor (UF) of 100, based on two values of 10 each to account for interspecies and intraspecies differences. No additional uncertainty factor was applied due to concerns about carcinogenicity. This is clearly in contrast to the WI approach of adding an extra 10X due to the DHFS/DNR "concern" about potential carcinogenicity of alachlor ESA."

Response: *DHFS has reviewed the March 2006 EPA Cumulative Risk Assessment for Chloroacetanilides document and has provided a response to comments related to this document - see DHFS (NRB Agenda Item background memo - Attachment 2) response to comments G.*

5. **Comment:** (AEC) "... we believe that the proposed rule/groundwater standard is not based on sound science and will needlessly alarm Wisconsin residents. It will also set an irresponsible precedent for the groundwater standard process and potentially unnecessarily tap into limited financial resources for remediation efforts."

Response: *The alachlor-ESA groundwater quality standards recommended by DHFS were developed using the appropriate methodology specified in Wisconsin's groundwater law, ch. 160, Stats. The scientific data used in developing the recommendations were primarily the results of toxicology studies funded by the Monsanto Company, the manufacturer of alachlor. The standard recommended by DHFS is based on the results of valid scientific studies, and the methodology used to develop it is specified in state statute. There is no reason to believe that the data or methodology used by DHFS is in question. The alachlor-ESA enforcement standard recommended by DHFS is consistent with past standards, and is based on review and consideration of the best science available.*

6. **Comment:** (AEC, WCPA) ... ask that "DNR/DHFS reconsider its recommendation of 20 ppb and propose a more reasonable and science based alternative as is required under section 227.14 (2m) of the Wisconsin State Statutes."

Response: *This comment is somewhat vague and confusing. Section 227.14(2m), Stats., addresses the quality of data used in the preparation and analysis of a proposed rule. The comment presented is related to the 20 part per billion (ppb)/milligram per liter (mg/L) alachlor-ESA groundwater quality enforcement standard recommendation developed by DHFS. As required under Wisconsin's groundwater law, DHFS followed the methodology in s. 160.13, Stats., in developing its recommendation for an alachlor-ESA groundwater quality enforcement standard.*

The comment appears to suggest that the 20 mg/L enforcement standard recommendation developed by DHFS is unreasonable and not science based. In developing their recommendation DHFS followed the applicable methodology specified in Wisconsin's groundwater law, ch. 160, Stats. The scientific data used in developing the recommendation were primarily the results of toxicology studies funded by the Monsanto Company, the manufacturer of alachlor. The standard recommended by DHFS is based on the results of valid scientific studies, and the methodology used to develop it is specified in state statute. There is no reason to believe that the accuracy, integrity, objectivity or consistency of the data used by DHFS in developing its alachlor-ESA enforcement standard

recommendation is in question. Thealachlor-ESA enforcement standard recommended by DHFS is reasonable, consistent with past standards, and is based on the best science available.

7. **Comment:** (AEC, WCPA) ... ask that DNR/DHFS conduct "an unbiased independent scientific peer review of the proposed groundwater standard foralachlor ESA".

(MON) "Monsanto requests that prior to taking final rulemaking action DNR convene an independent, scientific review panel to conduct an external unbiased scientific peer review of the toxicology data onalachlor ESA, and of the methodology used and conclusions drawn by DHFS."

Response: *The recommendation for analachlor-ESA groundwater quality enforcement standard was developed by DHFS in accordance with the methodology specified in s. 160.13, Stats. This methodology is applicable in cases where no federal number or state drinking water standard has been established for a substance. DHFS is required by state statute to utilize this methodology, and it has consistently been employed by DHFS in the past to establish state groundwater quality standards.*

There is no provision in ch. 160, Stats., for peer review of state groundwater standard recommendations developed by DHFS. DHFS' recommendation for analachlor-ESA groundwater quality enforcement standard of 20 µg/L was established in accordance with the applicable provisions of ch. 160, Stats., and it is consistent with past development of state groundwater quality standards. There is no justification for requiring a peer review of the scientific studies and methodology used by DHFS to develop their recommended standard.

8. **Comment:** (AEC, WCPA, MON) ... ask that a "trigger" be placed in the rule that would automatically/immediately revise the groundwater standard and PAL as soon as a health advisory level or reference dose (acceptable daily intake) for Alachlor-ESA is established by the federal environmental protection agency.

Response: *Ch. 160 Stats. directs that Wisconsin state groundwater enforcement standards are generally established based on "federal numbers" which represent EPA consensus risk-based values such as maximum contaminant levels, cancer potency factors and health-based reference doses. However, the statute directs that groundwater standard recommendations are initiated at DHFS to ensure their adequacy and appropriateness for a particular compound. The imposition of a trigger that would bypass the authority of DHFS to review and recommend appropriate ES and PAL values would represent a violation of the statute. Wisconsin groundwater quality standards are routinely adjusted to reflect new or revised federal guidance. A "trigger", as proposed in the comments, would not conform with Wisconsin law and, as revisions to state groundwater standards are now routinely made, is not necessary.*

9. **Comment:** (MON) "Monsanto fully supports Wisconsin's goal of protecting groundwater resources and ensuring the safety of drinking water and has no objection to the establishment of scientifically sound, health-based groundwater quality standards. However, we strongly oppose the proposal to establish a 20 ppb Enforcement Standard and 4 ppb Preventive Action Limit foralachlor ESA as it is not based on sound science nor is it consistent with standard scientific or regulatory practices. It also conflicts with the conclusions of other state, federal and international regulatory agencies."

Response: *The Wisconsin state groundwater quality standards proposed foralachlor-ESA are based on recommendations developed by DHFS. These recommendations were developed in accordance with methodologies specified in state statute. DHFS considered all available, applicable scientific information related to the toxicology ofalachlor-ESA when it developed its recommendations. No federal or international standards or health advisory levels have been established foralachlor-ESA.*

At least two states, Minnesota and North Carolina, have established health based guidance levels for alachlor-ESA. The health based guidance level (Health Based Value) established for alachlor-ESA in Minnesota is 40 µg/L. The health based guidance level (recommended Interim Maximum Allowable Concentration) established in North Carolina for total alachlor plus its metabolites (including alachlor-ESA) is 0.4 µg/L. The health based groundwater quality standards for alachlor-ESA recommended by DHFS are not inconsistent with the health advisory levels established in these states.

10. **Comment:** (MON) "The state clearly needs to take appropriate caution to ensure public health, however, erroneous decisions by DHFS, if adopted, may unnecessarily alarm Wisconsin residents about the safety of their drinking water supplies and could have a significant impact on Wisconsin's agricultural industry. It also sets an irresponsible precedent for establishing groundwater standards in Wisconsin."

Response: *The Department is charged with establishing state groundwater quality standards for substances detected in, or having a reasonable probability of entering, the groundwater resources of the state. Water supply well sampling, done by the Wisconsin Department of Agriculture, Trade and Consumer Protection, has shown alachlor-ESA to be one of the most commonly detected pesticide related compounds in Wisconsin groundwater. Alachlor-ESA has been found in approximately 28% of the water supply wells tested in alachlor use areas.*

In order to provide adequate safeguards for public health and welfare, state groundwater law clearly justifies development of state groundwater standards for alachlor-ESA. Chapter 160, Stats., establishes a strict process for generating and promulgating state groundwater quality standards that ensures that these standards are based on sound science, and that available, pertinent information is considered in their development. This statutory process has been followed in the development of the proposed state groundwater quality standards for alachlor-ESA.

11. **Comment:** (MON) "... belief that DHFS did not ensure the accuracy, integrity, objectivity and consistency of the data underpinning its recommendations. We believe an objective review of the data, consistent with the State's Data Quality statute, will show that DHFS 1) misinterpreted a key study concerning the toxicity of alachlor ESA, 2) disregarded the results of a follow-up study that was specifically designed and conducted to address DHFS' concerns, 3) did not utilize U.S. Environmental Protection Agency (EPA) conclusions concerning the toxicity of alachlor and alachlor ESA; and 4) did not follow standard scientific and regulatory practices or EPA guidelines with regard to selection of a suitable uncertainty factor."

Response: *Section 227.14(2m), Stats., addresses the quality of data used in the preparation and analysis of a proposed rule. The scientific data used by DHFS in developing its recommendation for an alachlor-ESA enforcement standard were primarily the results of toxicology studies funded by the Monsanto Company. The standard recommended by DHFS is based on the results of valid scientific studies, and the methodology used to develop it is specified in state statute. There is no reason to believe that the accuracy, integrity, objectivity or consistency of the data used by DHFS in developing its alachlor-ESA enforcement standard recommendation is in question.*

12. **Comment:** (MON) "Monsanto provided extensive scientific and legal comments on this proposal during the public hearing process on CR02-095. As DNR's Response to Public Comments on CR02-095 document shows, many of our comments were supported by other agricultural interests, through public testimony and written comments. We are disappointed to see that these comments had no impact on the proposal. DHFS' recommendations for the Enforcement Standard and Preventive Action Limit remain unchanged. We also note that many of these comments appear to have been summarily dismissed without sufficient rationale. Monsanto's September 2002 written comments (attached) also detailed the many ways in which the procedures followed by DHFS in developing its recommendation fail to comply with the requirements of Chapter 160, the state groundwater law. We ask that those comments be reconsidered/utilized in the review/reassessment of CR07-034".

Response: DHFS has received a copy of all comments that were sent to the Department related to this rule. DHFS has reviewed those comments and has provided responses to comments related to their development of recommendations for alachlor-ESA groundwater quality standards - see DHFS response to comments document (NRB Agenda Item background memo - Attachment 2). DHFS has also revised the scientific support documentation that details the development of its alachlor-ESA groundwater standard recommendations - see DHFS June 2007 alachlor-ESA scientific support documentation (NRB Agenda Item background memo - Attachment 3).

13. **Comment:** (MON) "DHFS has concluded that the NOEL for the 1993 rat study conducted with alachlor ESA was 20 mg/kg/day. This value is almost 10-fold lower than the NOEL (182 mg/kg/day) determined for the same study by USEPA and by the European Union. DHFS has now acknowledged the USEPA conclusion, but justified its conclusion on the basis of the "criteria specified in Ch. 160" See September 2005 Green Sheet Attachment 2, DHFS responses [to comments received on Natural Resources Board Order No. DG-37-02] #1, 8 and 21 (attached). It appears that DHFS is referring to section 160.13(c), which defines the term NOEL. However, this definition is essentially the same as that used by USEPA as well as other regulatory agencies and toxicologists throughout the world, and does not justify DHFS' decision to ignore USEPA's conclusion."

Response: DHFS has reviewed comments related to the NOEL used to develop its recommendation for an alachlor-ESA groundwater quality enforcement standard. DHFS has provided responses to comments related to the NOEL it utilized - see DHFS (NRB Agenda Item background memo - Attachment 2) response to comments: A & E.

14. **Comment:** (MON) "DHFS previously justified its NOEL decision on the basis of statistics (see November 2001 draft Recommendation, included as Attachment B to Monsanto's September 20, 2002 written comments). However, as discussed in Monsanto's written comments of September 20, 2002, that position conflicted with a previous DHFS statement that statistical significance was not intended to be used as the sole determinant of whether or not a finding is biologically significant or meaningful. The reference to statistical significance has now been dropped from DHFS' August 2005 Scientific Support Documentation for Cycle 8 Revisions of NR 140.10 (2005 DHFS Recommendation) but DHFS' conclusion regarding the NOEL remains the same. DHFS provides no alternative explanation in either the 2005 DHFS Recommendation or in DHFS' Response To Public Comments other than to assert that the conclusion results from "application of the criteria in Ch. 160"."

Response: DHFS has reviewed comments related to the NOEL used to develop its recommendation for an alachlor-ESA groundwater quality enforcement standard. DHFS has provided responses to comments related to the NOEL it utilized - see DHFS (NRB Agenda Item background memo - Attachment 2) response to comments: A & E.

15. **Comment:** (MON) "... DHFS appears to consider suspect the fact that USEPA has revised its conclusions about the 1993 study. Monsanto believes these concerns are unwarranted. USEPA revised its conclusions after receipt of additional information and further scientific input and review. This is not an unusual occurrence. In addition, the final USEPA conclusions regarding the NOEL for this study were included in the alachlor Reregistration Eligibility Decision (RED) document that was published in 1998 following both internal USEPA peer review and a standard public comment period. DHFS had previously been in contact with USEPA about this study and any further concerns should have been expressed at that time."

Response: DHFS has reviewed comments related to the NOEL used to develop its recommendation for an alachlor-ESA groundwater quality enforcement standard. DHFS has provided responses to comments related to the NOEL it utilized - see DHFS (NRB Agenda Item background memo - Attachment 2) response to comments: A & E.

16. **Comment:** (MON) "In 2002, following a series of meetings with and at the suggestion of DHFS, Monsanto initiated a new 90-day rat study with alachlor ESA (at a cost of approximately \$200,000), in

an attempt to resolve this issue. The results of the 2003 study clearly demonstrated that alachlor ESA is markedly (10- to 40-fold) less toxic than believed by DHFS. DHFS has acknowledged this marked difference but has chosen to ignore the new results and to continue to base their calculations only on their original conclusions from the 1993 study. DHFS justifies this decision (2005 DHFS Recommendation, page 5) on the basis that alachlor ESA was administered via the drinking water in the first study and via the diet in the second study. However, dietary administration was utilized in the second study to avoid the water palatability problem that greatly complicated the interpretation of the results in the first study. It is highly unlikely that this difference in methodology, which was discussed with and agreed to by DHFS prior to study initiation, would have had a significant impact on the study results. Furthermore, results from studies conducted via dietary administration have been used by state, national and international authorities to establish numerous groundwater standards, including the overwhelming majority of those for pesticides (including alachlor)."

Response: *DHFS has reviewed and considered the results of all available scientific studies related to the toxicity of alachlor-ESA. These studies included the new Monsanto initiated 90-day rat study [A 90-day oral (diet) toxicity study of MON 5775 in rats, conducted by WIL Research Laboratories] - see DHFS June 2007 alachlor-ESA scientific support documentation (NRB Agenda Item background memo - Attachment 3).*

17. **Comment:** (MON) "DHFS' utilization of a 10,000-fold uncertainty factor differs greatly from the 1000-fold uncertainty factor used for alachlor ESA in the alachlor RED and thus violates 160.13(2)(b) which requires DHFS to utilize available information from USEPA. Please also see our September 2002 comments for detailed explanation of the specific deficiencies."

Response: *DHFS has reviewed comments related to the uncertainty factor used to develop its recommendation for an alachlor-ESA groundwater quality enforcement standard. DHFS has provided responses to comments related to the uncertainty factor it utilized - see DHFS (NRB Agenda Item background memo - Attachment 2) response to comments: B, C & D.*

18. **Comment:** (MON) "Contrary to the statement on page viii of the 2005 DHFS Recommendation, uncertainty factors of 10,000 are not typically used, even in cases where the data are limited or there are some unresolved concerns. EPA's general guidance is that uncertainty factors greater than 3000 should not be used in establishing standards because they are "too uncertain." (e.g., EPA Office of Drinking Water, 2000)."

Response: *DHFS has reviewed comments related to the uncertainty factor used to develop its recommendation for an alachlor-ESA groundwater quality enforcement standard. DHFS has provided responses to comments related to the uncertainty factor it utilized - see DHFS (NRB Agenda Item background memo - Attachment 2) response to comments D.*

19. **Comment:** (MON) "DHFS's response to the above two comments [*Monsanto comments on Natural Resources Board Order No. DG-37-02 related to DHFS' use of a 10,000-fold uncertainty factor*] (DHFS Responses #6 and 10) is only that they are "required to employ the methodology outlined in Ch. 160 for deriving uncertainty factors". The methodology provided in Ch. 160 does not justify this decision. Section 160.13 lists the types of information that should be considered when determining a suitable uncertainty factor; it does not provide any guidance as to what the magnitude of such a factor should be."

Response: *Chapter 160 does not provide guidance on the magnitude of the uncertainty factor used in the calculation of an acceptable daily intake/RfD. Section 160.13(2)(b)3, Stats., lists the types of information that must be considered in establishing a suitable uncertainty factor. This information was considered by DHFS in establishing a suitable uncertainty factor to be used to calculate an acceptable daily intake/RfD value for alachlor-ESA - see DHFS June 2007 alachlor-ESA scientific support documentation (NRB Agenda Item background memo - Attachment 3)*

20. **Comment:** (MON) "The use of an additional ten-fold uncertainty factor to account for DHFS' concern about possible carcinogenicity of alachlor ESA is contrary to a specific recommendation made to DHFS by USEPA in 1994, and ignores the USEPA conclusion that "alachlor ESA is unlikely to be carcinogenic" (alachlor RED, 1998), a conclusion that DHFS agreed to in a 2001 meeting. It is also contrary to the policies expressed in the USEPA Guidelines for Carcinogen Risk Assessment (USEPA, 2005). In fact, there are numerous examples of USEPA Category B2 (Probable) or C (Possible) carcinogens for which no additional uncertainty factor has been applied."

Response: *DHFS has reviewed comments related to the uncertainty factor used to develop its recommendation for an alachlor-ESA groundwater quality enforcement standard. DHFS has provided responses to comments related to the uncertainty factor it utilized - see DHFS (NRB Agenda Item background memo - Attachment 2) response to comments: B, C & F.*

21. **Comment:** (MON) "DHFS either does not fully understand or does not accept USEPA's revised cancer classification for alachlor. This classification was changed in late 1997 following extensive peer review of the data by numerous senior scientists at USEPA, as well as the USEPA Science Advisory Panel. This classification now represents the official USEPA regulatory position. However, the 2005 DHFS Recommendation as well as DHFS' Response #9 [*to comments received on Natural Resources Board Order No. DG-37-02*] continues to rely on the outdated, B2 (Probable Human Carcinogen) classification that was assigned in 1986."

Response: *DHFS has reviewed comments related to the uncertainty factor used to develop its recommendation for an alachlor-ESA groundwater quality enforcement standard. DHFS has provided responses to comments related to the uncertainty factor it utilized -see DHFS (NRB Agenda Item background memo - Attachment 2) response to comments F.*

22. **Comment:** (MON) "DHFS continues to rely on highly misleading and outdated examples as precedent for use of a 10,000-fold uncertainty factor (DHFS Responses #5 and 23 [*to comments received on Natural Resources Board Order No. DG-37-02*]). All four examples cited in the 2005 DHFS Recommendation were based on decisions prior to the USEPA policy decision in the year 2000 that uncertainty factors greater than 3000 should not be employed. More importantly, the unusually large uncertainty factor DHFS utilized for these chemicals was based either on the fact that a NOEL for the chemicals had not been determined or because the chemicals were classified by the USEPA as a Probable (B2) and/or Possible (C) human carcinogens. Neither of these situations applies to alachlor ESA."

Response: *DHFS has reviewed comments related to the uncertainty factor used to develop its recommendation for an alachlor-ESA groundwater quality enforcement standard. DHFS has provided responses to comments related to the uncertainty factor it utilized - see DHFS (NRB Agenda Item background memo - Attachment 2) response to comments: D & F.*

23. **Comment:** (MON) "In addition to not addressing any of the factual issues raised about the four examples, DHFS' Response #23 [*to comments received on Natural Resources Board Order No. DG-37-02*] erroneously states that Monsanto claims "EPA has no RfDs with a UF of 10,000 based on a subchronic LOAEL". This is incorrect. Monsanto commented that the only examples in which USEPA applied a 10,000-fold uncertainty factor in determining the RfD were a few chemicals for which a subchronic NOEL could not be determined and a subchronic LOEAL had to be used instead. As previously explained, this is not the situation for alachlor ESA. USEPA has established numerous RfD's based on subchronic toxicity studies and uncertainty factors of 1000 or 3000."

Response: *Thank you for clarification of Monsanto's position on this issue.*

24. **Comment:** (MON) "Comments at September 5th 2006 DNR Board Meeting by Dr. Anderson - Dr. Anderson, Department of Health and Family Services, stated that "The rats who were fed this [Alachlor ESA] in their drinking water suffered from anemia." and that ".....Monsanto argues that

anemia is not a serious enough affect [sic] to base the standard on." Monsanto has never argued that anemia is not a serious health effect or that it shouldn't be used to establish health-based standards. Rather, Monsanto disagrees with the DHFS/DNR conclusion that alachlor ESA caused anemia in rats, especially at the dose levels cited by DHFS. The DHFS conclusion is also in contrast to the conclusions of the USEPA and EU, both of which concluded that the slight numerical differences cited by DHFS were not biologically relevant and/or were not caused by alachlor ESA. This conclusion is further supported by the clear lack of anemia in a repeat study conducted at the request of DHFS with even higher dose levels of alachlor ESA."

Response: *Thank you for clarification of Monsanto's position on this issue.*

25. **Comment:** (MON) "In addition, the rule background statement that current levels of alachlor ESA in WI groundwater would lead to adverse impacts on public health is in contrast to the following statement by USEPA: "Chronic dietary risk from alachlor from food containing residues of alachlor and from consumption of water containing residues of alachlor per se and/or residues of alachlor ESA is not of concern." By their overly conservative proposal, DHFS/DNR will create a false public health concern and trigger unnecessary mitigation expenses that will have no meaningful impact on public health."

Response: *The (Feb. 26, 2007) rule background memo statement that refers to "adverse impacts" (page 4, second paragraph) is a discussion of adverse impacts on public health, welfare, safety and the environment that would result if small businesses were not required to meet the regulatory requirements (reporting, remedial response) of Wisconsin's groundwater law, ch. 160, Stats. The rule background memo does not state that current levels of alachlor ESA in WI groundwater would lead to adverse impacts on public health.*

26. **Comment:** (WFU) " Wisconsin Farmers Union supports the DHFS groundwater standard for alachlor ESA as proposed. The standard was developed as required in the Wisconsin Groundwater Protection law, just as it has been for more than 100 other chemicals. It uses the best science available and has been 15 years in the making. Farm family health is critical to the health of Wisconsin's rural economy and our well waters are important."

Response: *Thank you for the comment supporting the proposed groundwater quality standards for alachlor-ESA. See DHFS (NRB Agenda Item background memo - Attachment 2) response to comments H.*

Attachment #2

**Recommendation for Groundwater Enforcement Standard
and Preventive Action Limit for Alachlor-ESA**

**Summary of Comments
June, 2007**

A. *DHFS' conclusions regarding the NOEL for alachlor-ESA are in direct conflict with the conclusions of the U.S. EPA and the European Commission.*

In the most recent opinion of EPA's Office of Pesticide Programs about the toxicity of alachlor-ESA, it was concluded that the effects observed at the middle dose of 200 mg/kg/day in the 1993 subchronic toxicity study were "minor, generally not dose-related, and not biologically meaningful." In reviewing the data provided by Monsanto from this study in accordance with the criteria established in Ch. 160 Stats., DHFS continues to find that the effects observed at the 200 mg/kg/day dose level constitute a lowest observed effect level (LOEL) and an appropriate endpoint for deriving an enforcement standard and preventive action limit for this compound.

B. *DHFS' use of an uncertainty factor of 10,000 is flawed and unsupported, and does not meet the criteria in Stats. 160.13(2)(b)3. The use of an additional UF for concern about possible carcinogenic potential is inappropriate since the acceptable daily intake is typically based only on non-cancer endpoints and is not intended to address carcinogenic risk, which should be evaluated separately.*

As in the case of several compounds for which enforcement standards have been recommended by DHFS and ultimately adopted, uncertainty and suspicion about carcinogenic activity has been addressed by inclusion of an uncertainty factor where one was deemed necessary to protect public health. In this case, no suitable data exist on which to evaluate the carcinogenic potency of alachlor-ESA in a quantitative way.

C. *DHFS' assessment ignores the substantial body of evidence that demonstrates that alachlor ESA is less toxic than parent alachlor and is unlikely to be carcinogenic.*

DHFS is recommending an enforcement standard for alachlor-ESA that is ten times higher than the corresponding enforcement standard for alachlor. While the database for alachlor-ESA is not robust enough to warrant a reduction of the uncertainty factor, DHFS finds the data sufficient to derive a separate standard for alachlor-ESA rather than to recommend that it be regulated in tandem with its parent compound at the more restrictive ES level of 2 µg/L. D. DHFS ignores substantial regulatory precedent for utilizing uncertainty factors of 1000 to 3000 when establishing an ADI or RfD based on a NOEL from a subchronic toxicity study. No appropriate regulatory precedent exists for applying an uncertainty factor of 10,000 in this situation.

The background document lists several compounds for which uncertainty factors of 10,000 have been incorporated into recommendations for enforcement standards. As described in Monsanto's comments on the proposed rule, DHFS has only rarely made recommendations that incorporate such a large uncertainty factor. Each of the previous cases where DHFS has employed a UF of 10,000 has been for a compound for which there was a reasonable amount of data about the health effects related to exposure, but there were specific data gaps that required the use of a larger uncertainty factor. The known carcinogenic potential of alachlor and the absence of data on the carcinogenicity of a closely-related degrade of alachlor

represents a uniquely troubling gap in the database that, in the view of DHFS, requires that particular caution be taken in regulation.

E. *DHFS fails to consider the most recent and scientifically available information, including its current opinion on the establishment of a NOEL for alachlor-ESA.*

As described in the background document, DHFS' application of the criteria in Ch. 160 yields a different no-observed-effect level (NOEL) than was determined by EPA in the most recent of the three opinions offered by their Office of Pesticide Programs.

F. *DHFS fails to recognize EPA's classification of alachlor under its new cancer classification system and its conclusion that alachlor is unlikely to be carcinogenic at low doses.*

EPA has proposed revisions to the system by which it classifies carcinogens. At the same time, EPA has maintained its maximum contaminant limit goal (MCLG) of zero for alachlor, a value reserved for compounds that are considered by EPA to be carcinogenic. As such, it is concluded that EPA's current regulatory position about the carcinogenicity of alachlor as a drinking water contaminant reflects sufficient concern to warrant classification as a carcinogen. Alachlor is listed as a B2 carcinogen in EPA's 2006 table of drinking water standards and health advisories. Revised cancer descriptors based on its new approach to cancer classifications are provided in this table for several compounds. However, no such revision is noted for alachlor.

A reference to the opinion of EPA's Office of Pesticide Programs that alachlor is unlikely to be carcinogenic at low doses is included in the background document. No guidance is provided, however, to determine the threshold at which a dose is to be considered 'low'. Opinions such as this may ultimately be considered in a revision of how alachlor is regulated by EPA as a drinking water contaminant. Giving such a finding priority over an existing EPA drinking water regulation would, however, be premature.

G. *DHFS has not considered all available studies on alachlor-ESA, including EPA's recently-published "Cumulative Risk from Chloroacetanilide Pesticides".*

DHFS staff were not aware of the publication of this document until May of 2007, and a reference to the document has been added to the background document. This document summarizes the findings of a screening-level cumulative risk assessment of the chloroacetanilide pesticides developed based on the common carcinogenic mechanism observed between alachlor, acetochlor and butachlor. While the document itself was published in 2006, the references to alachlor ESA are not based on new data or a new degradate-specific assessment of relative toxicity. As such, none of the data gaps referenced by DHFS in developing an uncertainty factor have been reduced, and no corresponding modification to the DHFS recommendation is warranted.

H. *The proposed standard for alachlor-ESA was developed as required by the applicable statute, and serves to ensure the protection of the health of farm families.*

DHFS acknowledges and appreciates the support expressed in this comment.

**SCIENTIFIC SUPPORT DOCUMENTATION
FOR GROUNDWATER ENFORCEMENT STANDARD AND
PREVENTIVE ACTION LIMIT RECOMMENDATIONS
FOR ETHANE SULFONIC ACID METABOLITE OF ALACHLOR
(ALACHLOR-ESA)**

Prepared by:

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Henry Anderson, MD, Chief Medical Officer**

**Wisconsin Department of Health and Family Services
Division of Public Health**

June 2007

ETHANE SULFONIC ACID METABOLITE OF ALACHLOR (ALACHLOR-ESA)

Introduction

Alachlor-ESA is a metabolite of the herbicide alachlor. Alachlor is a broadleaf preemergent acetanilide herbicide used widely on corn and soybeans in Wisconsin.

Chemical Profile

Chemical Name: Alachlor, ethane sulfonic acid metabolite
Molecular Formula: C₁₃H₂₀NO₅
Molecular Weight: 302.37
Synonyms: MON 5775
2',6'-diethyl-N-methoxymethyl-2-sulfoacetanilide, sodium salt
2-[2,6-diethylphenyl (methoxymethyl) amino]-2-oxoethane sulfonic acid, sodium salt

Occurrence

Alachlor-ESA has been detected in groundwater and surface waters in Wisconsin and elsewhere in the Midwest. In a 1994 study of acetochlor and related herbicides in 12 Midwestern states, alachlor-ESA was found in each of 104 surface water samples at median concentrations of 0.80 µg/L (pre-application) and 5.2 µg/L (post-application).¹ Alachlor-ESA was detected in 65.8% of groundwater samples at a median concentration of 0.28 µg/L.

Human Exposure

In a 1994 Wisconsin survey of private wells considered at risk for contamination, alachlor-ESA was detected in 206 of 293 samples. Observed concentrations ranged from 1.1 to 26.7 µg/L (average = 4.9 µg/L).² Alachlor was detected in only 12 of these 293 samples.

In 2000, the Wisconsin Department of Agriculture, Trade and Consumer Protection (DATCP) conducted a survey of chloroacetanilide herbicides and their degradates in monitoring wells, private drinking water wells and municipal wells considered at risk for herbicide contamination.³ The survey yielded the following results:

<i>Well Type</i>	<i>Wells Sampled</i>	<i>Wells with Detects</i>	<i>Percent w/Detects</i>	<i>Average Detect (µg/L)</i>	<i>Highest Detect (µg/L)</i>
Monitoring Wells	27	22	81	4.7	33
Private DW Wells	22	20	91	3.5	9.0
Municipal Wells	23	11	48	1.9	4.4

In a separate Wisconsin survey, 336 private water supplies selected in a random, stratified fashion were sampled for atrazine, alachlor and other herbicides as well as their degradates. Alachlor-ESA was detected in 27.8% of surveyed wells, and was detected in a higher percentage of wells than any other contaminant. The mean observed concentration of alachlor-ESA was 1.0 µg/L, with the highest concentration observed at 14.8 µg/L.⁴

Toxicity

Acute

An acute oral LD₅₀ of greater than 6000 mg/kg was observed for alachlor-ESA in rats.⁵

Subchronic

Two oral subchronic rat studies have been conducted on the toxicity of alachlor-ESA.

In a 91-day study, alachlor-ESA was administered to male and female Fischer F-344 rats (10 per sex per dose level) in drinking water at doses of 0, 20, 182 or 1002 mg/kg/day.^{6,7} Effects observed in the study included changes in physical appearance of test animals, decreased body weight, ophthalmic effects and alterations in clinical chemistry and hematological measures.

- Physical appearance. Increased incidence was reported versus controls for the following endpoints at all dose levels: decreased activity, rapid/shallow breathing, few feces, feces small in size, dehydration, urine staining, emaciation, hunched posture, rough coat, unkempt appearance, dark material/stain on pads of forelimb, around eyes, mouth and nose, clear and red ocular discharge, and hair loss around eyes.
- Decreased body weight. Female rats in the lowest dose group showed a statistically significant decrease in body weight relative to controls on days 22 through 85 of the study, although food and water intakes were similar. Similarly, body weights in the high-dose group were significantly lower on days 8 through 91. Body weights for mid-dose females were lower as well. Two-sample t tests conducted by the Wisconsin Department of Health and Social Services (now DHFS) showed significant differences between the body weights of controls and animals in each of the three dose groups ($p = 0.016, 0.044$ & <0.001 , respectively).⁸
- Ophthalmic changes. Both dacryoadenitis (inflammation of the lacrimal gland) and chorioretinopathy (lesions on the retina and/or chorion) were observed with increased frequency in exposed animals versus controls. In laboratory studies assessing the toxicity of alachlor, ocular lesions and molting of retinal pigmentation (described as *uveal degeneration syndrome*) have been seen in Long-Evans rats.⁵ Because the Fischer 344 rat has an unpigmented eye, the full range of alachlor-related ocular effects could not be assessed in this experiment.
- Clinical chemistry indices. Low-dose females had a statistically significant decrease in levels of aspartate aminotransferase relative to controls ($p < 0.01$). Low- and mid-dose females also had significantly lower levels of potassium ($p < 0.05$) and calcium ($p < 0.01$). Effects were not consistent at higher dose levels.
- Hematological effects. Male rats in the middle dose group had a statistically significant decrease in erythrocyte counts ($p < 0.05$). This finding was more pronounced ($p < 0.01$) in test animals at the highest dose. Hematocrit values and hemoglobin levels, both of which were significantly lower at the high dose vs. controls ($p < 0.05$), were moderately lower than controls at the mid-dose, consistent with a dose-response relationship. Bilirubin, a by-product of the breakdown of hemoglobin, was increased at statistically-significant levels in both mid-dose and high-dose animals.

In a more recent 90-day study, alachlor-ESA was administered to three groups of Cr1:CD(SD)IGS BR rats in the diet at dosage levels of 3000, 6000 and 12,000 ppm (209, 422 and 857 mg/kg/day, respectively).⁹ Observed effects included changes in sensory observations, testis weight, serum chemistry and hematological effects.

- Sensory observations. Unresponsiveness to touch response was measured in control and test animals. The mean number of times animals had no reaction to the touch response was increased in males in the high-dose group ($p < 0.05$). No dose-related change was observed in other sensory observations such as tail pinch response, startle response and approach response.
- Organ weights. Relative testis weight was found to be increased in low-dose males ($p < 0.05$). No corresponding increase was seen in mid-dose and high-dose males, and no increase in absolute testis weight was observed.

- Serum chemistry. Mean triglyceride levels were significantly lower in high-dose males when compared to controls ($p < 0.05$). There were no significant changes in triglyceride levels among the low-dose and mid-dose groups.
- Hematological effects. Mean absolute and relative reticulocyte counts were elevated in both mid-dose and high-dose males ($p < 0.05$). These values were also elevated in low-dose males, but the increase at this dose level was not statistically significant.

Chronic

No data on the chronic toxicity of alachlor-ESA are available.

Carcinogenicity

No data from long-term carcinogenicity studies are available for alachlor-ESA.

In oral feeding studies, alachlor has been shown to cause tumors in nasal epithelium, stomach and thyroid. Among the primary metabolites of alachlor of concern for nasal tumors is 2-chloro-*N*-(2,6-diethylphenyl)acetamide (CDEPA), which can be metabolized to 2,6-diethylaniline (DEA). DEA can be oxidized to form a diethylbenzoquinone imine (DEBQI), which binds to cellular protein, leading to cell death. Ensuing regenerative cell proliferation has been hypothesized by EPA to lead to neoplasia through fixation of spontaneous mutations.⁵ The mechanism by which rats and humans form the DEBQI metabolite is similar.¹⁰

Alachlor-ESA has been demonstrated to show less affinity for accumulation in nasal turbinates than alachlor.¹¹ A 91-day study failed to show nasal cell proliferation following administration of alachlor-ESA at a dose level of 157 mg/kg/day.¹² A separate 91-day study showed no apparent fundic mucosal atrophy upon exposure to alachlor-ESA, an effect which precedes cell proliferation and stomach tumors upon alachlor exposure.¹³ Cell proliferation in the stomach resulting from alachlor-ESA exposure was described by the investigators as minimal.

Mutagenicity

Chromosomal effects of alachlor-ESA were evaluated in the mouse micronucleus test. Single oral doses of 500, 1000 or 2000 mg/kg alachlor-ESA were administered to five male CD-1 mice by gavage.^{5,7} Animals were sacrificed at 24 or 48 hours after administration. Bone marrow cells were harvested and examined for the presence of micronucleated polychromatic erythrocytes. No treatment-related increase was observed in the frequency of polychromatic erythrocytes with micronuclei. A range of other tests have failed to demonstrate any substantive mutagenic potential for alachlor-ESA.^{14,15}

Reproductive and Developmental Toxicity

Single doses of alachlor-ESA in doses of 0, 150, 400 and 1000 mg/kg/day in corn oil were administered by gavage to bred female rats (25 at each dose level) on gestational days 6 through 15.^{5,7} Animals were euthanized on gestational day 20 and examined for uterine and ovarian abnormalities. Fetuses were sexed, weighed and examined for gross developmental abnormalities. Rales were observed in some dams at the highest dose, and body weight of mid-dose pups was decreased relative to controls ($p < 0.05$). No treatment-related changes were observed between test and control animals in food consumption or organ weight among dams or fetuses, and no increase in external, visceral or skeletal variations or malformations were seen in fetuses.

Interactive Effects

No data on interactive effects of alachlor-ESA are available.

Environmental Fate

Atmospheric

The vapor pressure of alachlor-ESA has not been determined. Given its chemical similarity to alachlor (vapor pressure = 2.2×10^{-5} mm Hg), the volatility of alachlor-ESA is likely to be relatively low.

Terrestrial

In a study of the behavior of alachlor and metolachlor and their metabolites in soil following a single application, alachlor-ESA was found to penetrate more deeply in soil than its parent compound. In the upper 15 cm of soil, alachlor-ESA concentrations reached peak levels at 9 to 10 weeks after application at 60% of parent concentration. Conversely, alachlor-ESA concentrations were more than 10 times greater than alachlor at depths of 60 to 75 cm after six weeks.¹⁶

Aquatic

Alachlor-ESA was found to be very mobile in studies conducted with Sable silty clay loam soils and Sarpy sandy loam soils mixed and equilibrated with calcium chloride.⁵ Alachlor-ESA is highly persistent in surface water, with long-term declines in surface water concentration attributed more directly to dilution than degradation.¹⁷

Analytical Methods

Alachlor-ESA can be quantified in water samples by high-performance liquid chromatography / mass spectrometry. This method yields detection limits as low as 0.10 $\mu\text{g/L}$.¹⁸

U.S. EPA Regulatory Position

	<u>Alachlor-ESA</u>	<u>Alachlor</u>
EPA MCL & MCLG:	None	2 $\mu\text{g/L}$ (MCL), 0 $\mu\text{g/L}$ (MCLG)
EPA Reference Dose:	None	0.01 mg/kg/day
EPA Reference Concentration:	None	None
EPA Lifetime Health Advisory:	None	None
EPA Carcinogenicity Classification:	No classification	B2, probable human carcinogen ¹⁹

EPA Office of Pesticide Program (OPP) Reviews

In its 1998 Reregistration Eligibility Document (RED) for alachlor, the hematological effects observed at the middle and high doses in the 91-day subchronic oral study for alachlor-ESA were acknowledged to be of statistical significance, but were described as “minor, mostly not dose related and...not considered to be biologically relevant, especially in the absence of any organ or tissue pathology”.⁵ In addressing the development of a reference dose for alachlor-ESA, two alternative methods with default assumptions were offered: (1) the use of the RfD for alachlor of 0.01 mg/kg/day, which is based on observations of hemolytic anemia and hemosiderosis at various organ sites in a one-year study in dogs, and (2) a value based on the agency’s NOEL and an uncertainty factor of 1000 to account for “interspecies extrapolation, intraspecies variability and a lack of a complete database”. In the RED, alachlor is described as “likely to be a human carcinogen at high doses but not likely at low doses”. No quantitative benchmark is provided to distinguish between ‘high doses’ and ‘low doses’. Alachlor-ESA is described in the RED as “unlikely to be carcinogenic”.

In 2006, OPP published a screening-level cumulative risk assessment for chloroacetanilide pesticides.²⁰ The document sought to characterize risks from exposure to acetochlor and alachlor in food and water based on their designation by OPP as a “common mechanism group.” This designation was based on

their common mode of action for the production of tumors of the nasal olfactory epithelium in rats. In the document, OPP declined to include alachlor-ESA or other degradates of alachlor and acetochlor in its risk assessment, stating that the ethane sulfonic acid and oxanilic acid degradates of alachlor and acetochlor show a different toxicological profile than their parent compounds and do not contribute to the nasal epithelial tumors on which the designation of a common mechanism group was based.

Recommendations and Conclusions for Alachlor-ESA

Ch. 160 Stats. defines a “no-observable-effect-level” (NOEL) as “that level of intake of a substance which, when administered to a group of humans or experimental animals, does not produce any of the effects observed or measured at any higher level of intake and produces no significant difference between the test groups and an unexposed control group of humans or animals maintained under identical conditions”. In reviewing the available data on alachlor-ESA, the two subchronic studies represent the best available data on which to identify a NOEL. The results from these studies show a marked difference in observed toxicity, which may be due to differences in the route of exposure. Test compound was administered in drinking water in the 1993 study, was administered with food in the 2003 study. Given that the route of exposure in the older study matches that of concern for a groundwater enforcement standard, and the sharp difference in observed toxicity between the two studies, it is appropriate to give deference to the 1993 study as a better representation of the toxicity of alachlor-ESA in drinking water than the more recent subchronic. Therefore, based on Ch. 160 Stats. and our analysis of data from studies of the subchronic toxicity of alachlor-ESA, the hematological findings in the study by Siglin *et al* at the dose of 182 mg/kg/day constitute the lowest level at which effects are observed, thereby establishing a no-observed-effect-level (NOEL) of 20 mg/kg/day.

In establishing an uncertainty factor, DHFS is directed in Ch. 160 Stats. to consider a range of factors, including the quality and quantity of available data, potential interactions with environmental chemicals and known chronic or subchronic effects of exposure to similar or related compounds. In the case of alachlor-ESA, the lack of data on chronic or carcinogenic effects and the frequency with which alachlor-ESA is found in drinking water with alachlor, metolachlor and acetochlor and other degradates of these chloroacetanilide herbicides, require special consideration.

Based on these considerations, an uncertainty factor of 10,000* (10 for interspecies variability, 10 for intraspecies variability, 10 for use of a subchronic study and 10 for data gaps, including lack of a carcinogenicity study for the metabolite of a potentially carcinogenic parent compound) is applied.

$$\frac{(20 \text{ mg/kg/day}) (10 \text{ kg})}{(1 \text{ L/day}) (10,000)} = 0.02 \text{ mg/L} (20 \text{ } \mu\text{g/L})$$

In accordance with Chapter 160 of Wis. Stats., the Department of Health and Family Services recommends adoption of a groundwater enforcement standard and preventive action limit for alachlor-ESA as follows:

Recommended enforcement standard:	20 μ g/L**
Recommended preventive action limit factor:	20%
Recommended preventive action limit:	4 μ g/L

*Uncertainty factors of 10,000 have been previously used in developing groundwater enforcement standards for methyl-tert-butyl ether and n-hexane; they have also been used by EPA in establishing the MCLs for lindane and styrene that were adopted as Wisconsin groundwater enforcement standards.

**Corresponds to an acceptable daily intake value of 20 μ g/day.

References:

1. Kolpin DW, Nations BK, Goolsby DA and Thurman EM. 1994. Acetochlor in the hydrologic system in the Midwestern United States, 1994. *Environ Sci Tech* 30:1459-1464.
2. Wisconsin Department of Agriculture, Trade and Consumer Protection (WI DATCP). 1994. 1994 groundwater survey for alachlor in southern Wisconsin. Final Report.
3. Rheineck B and Postle J. 2000. Chloroacetanilide herbicide metabolites in Wisconsin groundwater. Final report, 2000. Wisconsin Department of Agriculture, Trade and Consumer Protection (WI DATCP).
4. Wisconsin Department of Agriculture, Trade and Consumer Protection. 2001. Agricultural chemicals in Wisconsin groundwater.
5. U. S. Environmental Protection Agency (EPA). 1998. Reregistration eligibility decision: alachlor. EPA 738-R-98-020.
6. Siglin JC. 1993. A 91-day drinking-water toxicity study in rats with MON 5775. Springborn Laboratories, Spencerville, OH.
7. Heydens WF, Siglin JC, Holson JF and Stegeman SD. 1996. Subchronic, developmental and genetic toxicology studies with the ethane sulfonate metabolite of alachlor. *Fundam Appl Toxicol* 33:173-181.
8. Knobloch LM. 1994. Letter to William F. Heydens, Monsanto Company, June 15, 1994.
9. Kirkpatrick JB. 2003. A 90-day oral (diet) toxicity study of MON 5775 in rats. WIL Research Laboratories, Ashland, OH.
10. California Environmental Protection Agency. 1997. Public Health Goal for alachlor in drinking water. Office of Environmental Health Hazard Assessment, December 1997.
11. Kraus LJ, Hopkins WE, Kinnett ML and Wilson AGE. 1995. Elimination, absorption, tissue distribution and metabolism of alachlor ethane sulfonate (MON 5775) in Long-Evans rats following oral administration. Monsanto study number ML-95-066.
12. Hotz K. 1995. Effect of MON 5775 on cell proliferation in the nasal tissue of male F-344 rats. Monsanto Report #ML-95-070.
13. Iatropoulos MJ and Wang CX. 1995. Evaluation of cell proliferation and measurement of mucosal thickness in gastric fundi of rats from study SB-92-383. Monsanto study number AH-95-071.
14. Cifone MA. 2000. L51787 TK+/1 mouse lymphoma forward mutation assay with a confirmatory assay with MON 5775. Monsanto study number CV-2000-97.
15. Murli H. 2000. Chromosomal aberrations in cultured human peripheral blood lymphocytes with MON 5775. Monsanto study number CV-2000-100.
16. Aga DS and Thurman EM. 2001. Formation and transport of the sulfonic acid metabolites of alachlor and metolachlor in soil. *Environ Sci Tech* 35: 2455-2460.
17. Aga, DS. 2001. Personal communication.
18. Wisconsin Department of Agriculture, Trade and Consumer Protection. 2004. Bureau of Laboratory Services. Analytical Method 1002.
19. U.S. Environmental Protection Agency. 2006. Drinking Water Standards and Health Advisories, August, 2006. Office of Water. EPA-822-R-02-038.
20. U.S. Environmental Protection Agency. 2006. Cumulative risk from chloroacetanilide pesticides. Office of Pesticide Programs, Health Effects Division.