Report of the Food Quality Protection Act (FQPA) Tolerance Reassessment Progress and Risk Management Decision (TRED) for Acetochlor

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Approved By:

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Date

I. Regulatory Determination

The Federal Food, Drug and Cosmetic Act (FFDCA), as amended by FQPA, requires EPA to reassess all the tolerances for registered chemicals in effect on the day before enactment of the FQPA on August 3, 1996. In reassessing these tolerances, the Agency must consider, among other things, aggregate risks from non-occupational sources of pesticide exposure, whether there is increased susceptibility to infants and children, and the cumulative effects of pesticides with a common mechanism of toxicity. When a safety finding has been made that aggregate risks are not of concern, the tolerances are considered reassessed. Existing tolerances associated with acetochlor must be reassessed in accordance with FFDCA, as amended by FQPA. Ecological and occupational assessments were originally conducted when acetochlor was first registered in 1994. Therefore, no further ecological or occupational assessments were conducted as part of this Report of the FQPA Tolerance Reassessment Progress and Risk Management Decision for Acetochlor (also referred to as a TRED).

Acetochlor, 2-chloro-N-(ethoxymethyl)-N-(2-ethyl-6-methylphenyl)acetamide, is a chloroacetanilide herbicide used for preemergence control of weeds. It is registered for use on field corn and popcorn, although no tolerances currently exist for popcorn. Corn fields treated with acetochlor may later be rotated to grain sorghum (milo), soybeans, wheat, and tobacco, according to the currently registered use pattern. Residues in/on corn, popcorn and the rotational crops listed above were considered in the acetochlor dietary risk assessment supporting the acetochlor tolerance reassessment.

The Agency's human health and drinking water findings for the pesticide acetochlor are summarized in the following risk assessments: *Acetochlor. Revised HED Chapter of the Tolerance Reassessment Eligibility Decision (TRED) Document* dated March 1, 2006, and *Drinking Water Exposure Assessment for Acetochlor* dated February 16, 2006. For further details, please refer to these risk assessments and other technical documents pertaining to the acetochlor TRED, which are available on the internet at http://www.regulations.gov and in the public docket.

EPA has determined that acetochlor is a member of the chloroacetanilides group and that the chloroacetanilides share a common mechanism of toxicity due to their ability to cause nasal turbinate tumors. The chloroacetanilides group also includes alachlor and butachlor; however, butachlor was not incorporated into the cumulative assessment because there are no U.S. registrations or established tolerances. A chloroacetanilide cumulative assessment was, therefore, conducted for acetochlor and alachlor exposures based on a common mechanism of toxicity. The Agency concludes in the assessment that chloroacetanilide cumulative risks are below the Agency's level of concern. For more information please refer to the document: *Cumulative Risk from Chloroacetanilide Pesticides* dated March 8, 2006, which is also available on the internet at http://www.regulations.gov and in the public docket.

The Agency has evaluated the human health risks associated with all currently registered uses of acetochlor and has determined that there is a reasonable certainty that no harm will result from aggregate non-occupational exposure to the pesticide chemical residue. In making this determination, EPA has considered dietary exposure from food and drinking water and all other

non-occupational sources of pesticide exposure for which there is reliable information. In addition, the Agency has concluded that the cumulative risks associated with chloroacetanilide pesticides, including acetochlor, are below the Agency's level of concern. Therefore, the twelve (12) tolerances established for residues of acetochlor in/on raw agricultural commodities are now considered reassessed as safe under section 408(q) of FFDCA, as amended by FQPA.

The Agency is issuing this TRED document for acetochlor as announced in a Notice of Availability published in the ***Federal Register***. The Agency previously released the EPA's human health risk assessment and related documents for acetochlor for public comment on November 23, 2005. The Agency considered all submitted comments in preparing this TRED. Responses to these comments are also available on the internet at http://www.regulations.gov and in the public docket.

II. Tolerance Reassessment

A. FQPA Assessment Supporting Tolerance Reassessment Decision

The Agency has conducted risk assessments to ensure that the acetochlor tolerances meet the safety standards established by FFDCA, as amended by FQPA. These recent risk assessments for acetochlor include evaluation of potential susceptibility to infants and children; and dietary, drinking water, and aggregate risk from these various exposure pathways. EPA also considered potential cumulative risks for acetochlor and other substances sharing a common mechanism of toxicity. See also Section II.B of this document.

EPA has determined that risk from exposure to acetochlor, as well as cumulative risk from total exposure to chloroacetanilides pesticides, are within their own applicable "risk cups". In other words, EPA is able to conclude that the tolerances for acetochlor meet the FQPA safety standards. In reaching this determination, the Agency has considered the available information on the potential sensitivity of infants and children, as well as the chronic and acute food exposure. There are no residential uses of acetochlor nor are there residential post application exposures expected from currently registered uses. Therefore, an aggregate assessment was conducted for exposures through food and drinking water only. Results of this aggregate risk assessment indicate that the human health risks from these combined exposures are within acceptable levels; that is, combined risks from all exposures to acetochlor "fit" within the individual risk cup for this chemical. In addition, the Agency has concluded that the cumulative risks associated with chloroacetanilide pesticides, including acetochlor, are below the Agency's level of concern. The Agency's risk assessment conclusions are summarized below.

FQPA Safety Factor Considerations. The FFDCA, as amended by the FQPA, directs the Agency to use an additional tenfold (10X) safety factor to take into account potential pre- and post-natal toxicity and completeness of the data with respect to exposure and toxicity to infants and children. FFDCA authorizes the Agency to modify the tenfold safety factor only if reliable data demonstrate that the resulting level of exposure would be safe for infants and children.

Available developmental toxicity studies in two species and three two-generation reproductive toxicity studies in the rat did not show evidence of increased susceptibility of the offspring. There are low concerns and no residual uncertainties with regard to pre- and/or post-natal toxicity. However based on evidence of neurotoxicity, which was observed in studies in the dog and in the rat including frank neuropathology in a chronic dog study, the Agency is requiring that a developmental neurotoxicity (DNT) study be submitted by the registrant. Pending submission and Agency review of this study, an FQPA safety factor of 10X was retained for deriving the acute dietary reference dose for acetochlor to account for the absence of the DNT study. A 10X FQPA safety factor was not used in calculation of the chronic dietary reference dose because the results of the DNT are not expected to affect this risk assessment.

Dietary Risks from Food and Drinking Water. Acute, chronic, and cancer dietary (food and drinking water) risk assessments were conducted that considered all registered acetochlor uses (corn and rotational crops) using the Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID), which uses food consumption data from the USDA's Continuing Surveys of Food Intakes by Individuals (CSFII) from 1994-1996 and 1998. Although there is no existing tolerance for popcorn, a dietary risk assessment that included popcorn was completed since it is a registered use. Field corn field trial data were translated to popcorn for this assessment. The acute, chronic, and cancer dietary (food) exposure assessment incorporated tolerance or proposed tolerance level residues for all crops and percent crop treated data provided by the Acetochlor Registration Partnership (ARP). Processing data were available for numerous commodities and incorporated into the assessment. See also *Acetochlor. Acute, Chronic, and Cancer Dietary Exposure Assessments for the Tolerance Reassessment Eligibility Decision (TRED) Document* dated June 30, 2005 for detailed information.

The dietary risk assessment included residues of the parent, acetochlor, and the metabolites 2-ethyl-6-methylaniline (EMA) and 2-hydroxyethyl-6-methylaniline (HEMA) in/on the primary crops, corn and popcorn. In addition to EMA and HEMA, the dietary risk assessment also included residues of the metabolite hydroxymethyl ethyl aniline (HMEA) in/on rotational crops (i.e., crops grown in fields previously treated with acetochlor). These metabolites, EMA, HEMA, HMEA, are only found in plants, thus, they were not included in the drinking water assessment. Refer to the *Environmental Degradates* section below for additional information about metabolites found in drinking water.

EPA obtained drinking water residues from the Acetochlor Registration Partnership (ARP) acetochlor water monitoring program. The ARP monitored a total of 175 Community Water Supplies (CWSs) in nine mid-western and three Mid-Atlantic States for the acetochlor surface water monitoring program. The selection process was designed to include a wide array of CWSs with watersheds in areas of corn production, with an emphasis on including worst-case watersheds i.e., smaller watersheds (not on the Great Lakes and continental rivers) in areas of high corn production. Residues of acetochlor from this monitoring program were incorporated directly into the DEEM-FCID model. EPA considers both acute (one day) and chronic (lifetime) drinking water risks and exposure to pesticides through contamination of surface and ground water sources. The acetochlor risk estimates for acute, chronic, and cancer dietary exposure reflect combined food and drinking water exposure. For detailed information see the document

titled, *Revised Drinking Water Exposure Assessment for Acetochlor* dated February 16, 2006.

The population adjusted dose (PAD) is the dose predicted to result in no unreasonable adverse effects to any human subpopulation, including sensitive members of such subpopulation. Estimated dietary risks less than 100% of the PAD are not of concern to the Agency. The acute dietary risk assessment showed that for all registered commodities, the acute dietary risk estimates (food and drinking water) do not exceed the Agency's level of concern at the 99.9th percentile of exposure for all populations. The general U.S. population comprises 2% of the acute population adjusted dose (aPAD), with the highest exposed population subgroup being infants less than 1 year old at 6% of the aPAD. The aPAD is the dose at which a person could be exposed on any given day with no adverse health effects, and was derived from an acute rat neurotoxicity study in which decreased motor activity in females was observed.

EPA's chronic dietary risk assessment indicates that dietary risk from acetochlor residues in food and drinking water are low and also not of concern. The resulting chronic dietary exposure estimates using the DEEM-FCID model were less than 1% of the chronic population adjusted (cPAD) for the U.S. general population and all population subgroups including the most highly exposed population subgroup, all infants (<1 years old). The cPAD is the dose at which a person could be exposed over the course of a lifetime with no adverse health effects, and was derived from a chronic oral toxicity study in beagle dogs in which increased salivation and histopathology in the testes, kidney and liver were observed.

The Agency classified acetochlor as "likely to be carcinogenic to humans" based on increased incidence of lung tumors in male and female mice, histiocytic sarcoma in female mice and nasal epithelial tumors, and thyroid follicular cell adenomas in male and female rats. A nonmutagenic (with threshold) mode of action was established for the nasal and thyroid tumors; however, no mode of action was established for the other observed tumors. In the absence of supporting mechanistic data for the formation of lung tumors and histiocytic sarcomas in mice, a linear low-dose extrapolation was used to estimate cancer risk for those tumors. The cancer dietary exposure assessment incorporated tolerance or proposed tolerance level residues for all crops and percent crop treated data provided by the ARP, assuming consumption of those foods over a 70 year lifetime. Processing data were available for all commodities and incorporated into the assessment. The assessment also included the overall multi-year time weighted annualized mean surface water concentration generated from the ARP acetochlor water monitoring program. The chronic exposure value was multiplied by a linear low-dose response factor (Q_1*) of 3.27 x 10^{-2} based on animal studies to determine the lifetime cancer risk estimate. The estimated dietary (food and drinking water) cancer risk for the general U.S. population was 8.40 x 10^{-7}, and was below the Agency's level of concern (1 x 10^{-6}). Therefore, no mitigation measures are necessary to address dietary risks from food and drinking water.

Residential Risks. Currently there are no registered residential uses nor potential residential post-application exposures for acetochlor, thus no residential exposure assessment was conducted.

Aggregate Risk. In examining aggregate exposure, EPA takes into account the available

and reliable information concerning exposures from pesticide residues in food and other exposures including drinking water and non-occupational exposures, e.g., exposure to pesticides used in and around the home (residential). Risk assessments for aggregate exposure consider short-, intermediate- and long-term (chronic) exposure scenarios considering the toxic effects which would likely be associated with each exposure duration. Since there are no residential uses of acetochlor, the considerations for aggregate exposure are those from food and drinking water only. As discussed above, the results of the acute, chronic and cancer aggregate assessments indicate that the combined exposure to acetochlor from food and drinking water is below the Agency's level of concern. Therefore, no mitigation measures are necessary to address aggregate risks.

Environmental Degradates. The drinking water assessment was conducted using the parent acetochlor as the residue of concern. However, there are two degradates of acetochlor which may be found in drinking water. These degradates, acetochlor sulfonic acid (ESA) and acetochlor oxanilic acid (OXA), were not included in the water risk assessment based on comparison of the available toxicity data for acetochlor and the ESA and OXA degradates and structure-activity relationships which showed that neither ESA nor OXA degradates are likely to be carcinogenic and that both are significantly less toxic than the parent acetochlor.

However, extensive surface and ground water monitoring data for acetochlor and its two degradates have been collected as required by the Agency under the conditional registration of acetochlor. These monitoring studies showed that both the ESA and OXA degradates have been detected in water samples (both groundwater and surface water). Concentrations of the degradates in surface water were in the same order of magnitude as acetochlor while groundwater concentrations of the degradates were significantly higher than those of the parent. Given the potential for relatively high levels of degradates in drinking water, worst-case margin-of-exposure (MOE) calculations were conducted to estimate potential drinking water risks for the two degradates. MOEs ranged from >21,000 to 122,000 for ESA and 45,000 to 264,000 for OXA and, therefore, were below the Agency's level of concern.

B. Cumulative Assessment

As previously stated, acetochlor is a member of the chloroacetanilides group which shares a common mechanism of toxicity due to the members' ability to cause nasal turbinate tumors. The chloroacetanilide group also includes the chemicals alachlor and butachlor. This determination can be found in the chloroacetanilides common mechanism group (CMG) decision document published in 2001 entitled "The Grouping of a Series of Chloroacetanilide Pesticides Based on a Common Mechanism of Toxicity" (http://www.epa.gov/oppfead1/cb/csb_page/updates/commechs.htm). Butachlor, however, has no registered uses or tolerances and has been excluded from the risk assessment. Thus, the Common Assessment Group (CAG), on which the risk assessment was conducted, consists of acetochlor and alachlor only.

Development of nasal olfactory epithelium tumors in rats has been attributed to a non-linear, non-mutagenic mode of action. Thus, as per the 2005 EPA Cancer Guidelines, the Agency used a margin-of-exposure (MOE) calculation for the cumulative risk assessment as one would do

for a threshold noncancer toxicity risk assessment. Because the threshold approach was used for assessing the risks, uncertainty factors (UFs) of 10x (interspecies) and 10x (intraspecies) were used. Further, since there is no evidence of potential pre- and post-natal susceptibility, the FQPA safety factor was reduced to 1x. Therefore, MOEs above 100 were considered to be below the Agency's level of concern (LOC).

The chloroacetanilide cumulative risk assessment involved only two pathways of exposure (food and drinking water) via the oral route of exposure. Because the nasal olfactory epithelium tumors are a systemic chronic endpoint, only a chronic dietary analysis was conducted using the Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID^{TM}, Version 2.03). Results of the DEEM-FCID^{TM} analysis produced cumulated MOEs greater than 13,000 for all populations. Therefore, the cumulated MOE values estimated for the subject CAG are below the Agency's level of concern. Because these cumulative MOE values were obtained using high-end exposures, they are considered to be protective. More detailed information related to the chloroacetanilide cumulative risk assessment can be found in the document: *Cumulative Risks from Chloroacetanilide Pesticides* dated March 8, 2006, which is available on the internet at http://www.regulations.gov and in the public docket.

C. Endocrine Disruptor Effects

EPA is required under the FFDCA, as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following recommendations of its Endocrine Disruptor and Testing Advisory Committee (EDSTAC), EPA determined that there was a scientific basis for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

Studies in the rat evaluating thyroid and liver effects following dietary administration of acetochlor at various dose levels indicate that acetochlor may disrupt thyroid-pituitary homeostasis via increased hepatic UDPGH-mediated increased clearance of the thyroid hormone thyroxine (T4). Slightly increased incidence of thyroid follicular cell tumors have been observed in rat two-year bioassay studies at higher dose levels. Although thyroid follicular cell tumors were considered to be related to treatment, they were not considered as part of the cancer quantification, due to relatively low incidence and evidence for disruption of thyroid hormonal homeostasis as the mode of action. Structure-activity relationship data on the related chloroacetanilide herbicides alachlor and butachlor support this conclusion. The available data do not indicate that acetochlor disrupts androgen or estrogen hormone systems.

When additional appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, acetochlor may be subjected to further screening and/or testing to better characterize effects related to endocrine disruption.

D. Tolerance Summary

The current tolerance expression for residues of acetochlor resulting from direct application to primary crops is adequate. The Agency has determined that the tolerance expression for residues in/on corn, popcorn, and rotational crop commodities should include only acetochlor and its metabolites containing the 2-ethyl-6-methylaniline (EMA) and 2-hydroxyethyl-6-methylaniline (HEMA) moiety, expressed in acetochlor equivalents. A summary of acetochlor tolerance reassessments is presented in Table 1.

Tolerances Listed Under 40 CFR §180.470:

Adequate residue data have been submitted to reassess the established tolerances for corn commodities. The available field trial data indicate that the current tolerances on corn grain and stover are adequate, but the tolerance on corn forage should be increased to 3.0 ppm based on data from the early postemergence use. Adequate field rotational crop trials are also available to support the currently established tolerances on commodities of rotational sorghum, and wheat. The tolerance on soybean grain should be increased to 0.1 ppm based on the submitted rotational crop data.

As the tolerances on field corn commodities are for the direct application to a primary crop, these general tolerances on corn will be reassigned to 40 CFR §180.470(a). Likewise, tolerances on sorghum, soybeans, and wheat commodities are for inadvertent residues on rotational crops; therefore, these tolerances will be reassigned to 40 CFR §180.470(d).

The 40CFR §180.470 should be revised and separated into subparts (a) through (d). Subpart (a) should contain tolerances resulting from the direct application of acetochlor to a primary crop; (b) Section 18 emergency exemptions, (c) tolerances with regional registrations, and (d) tolerances resulting from indirect or inadvertent residues.

Based on the residue data for currently registered uses and rotational crops, tolerances for livestock commodities are not required at the present time.

Tolerances Needed Under 40 CFR §180.470(a):

Acetochlor is registered for use on popcorn; however, there are no existing tolerances associated with this use. Adequate data submitted by the ARP are available and a dietary assessment was conducted which included the use of acetochlor on popcorn. Information is being reviewed to determine whether the tolerance can be established, and the Agency will address this issue when it considers pending new use petitions.

Tolerances Needed Under 40 CFR §180.470(d):

The available rotational crop field trial data on wheat forage and straw indicate that residues are also likely to occur on wheat hay. A tolerance for wheat hay can be set using the residue data for wheat forage and adjusting for the differences in dry weight between the two commodities. Based on maximum residues of 0.457 ppm in/on wheat forage (25% dry wt.), maximum expected residues in/on wheat hay (88% dry wt.) would be 1.61 ppm. Therefore, a permanent tolerance of 2.0 ppm needs to be established for wheat hay. The addition of this tolerance will not change the current calculated maximum dietary burden for cattle.

Table 1. Tolerance Reassessment Summary for Acetochlor

Commodity	Current Tolerance (ppm)	Range of Residues (ppm)	Tolerance Reassessment (ppm)	Comment/*[Correct Commodity Definition]*
Tolerances Listed Under 40 CFR §180.470				
Corn, field, forage	1.0	<0.05-2.52	3.0	Tolerances on corn commodities should be reassigned to §180.470(a) as these tolerances are for the direct use on corn.
Corn, field, grain	0.05	<0.05	0.05	
Corn, field, stover	1.5	<0.05-1.08	1.5	
Sorghum, forage	0.1	<0.02-0.093	0.1	Tolerances on sorghum, soybean, and wheat commodities should be reassigned to §180.470(d) as these are tolerances for inadvertent residues in/on rotational crops. The correct commodity definition for Sorghum, grain is *Sorghum, grain, grain* and for Soybean, grain is *Soybean, seed*.
Sorghum, grain	0.02	<0.02	0.02	
Sorghum, grain, stover	0.1	<0.02-0.068	0.1	
Soybean, forage	0.7	<0.2-0.648	0.7	
Soybean, grain	0.02	<0.02-0.101	0.1	
Soybean, hay	1.0	<0.024-1.064	1.0	
Wheat, forage	0.5	<0.02-0.457	0.5	
Wheat, grain	0.02	<0.02	0.02	
Wheat, straw	0.1	<0.02-0.104	0.1	
Tolerances Needed under 40 CFR §180.470(a)				
Corn, pop, grain	0.5	<0.05	0.05	A permanent tolerance should be set at 0.05 ppm based on maximum residues in field corn grain.
	1.5	<0.05-1.08	1.5	A permanent tolerance should be set at 0.05 ppm based on maximum

Table 1. Tolerance Reassessment Summary for Acetochlor				
Commodity	Current Tolerance (ppm)	Range of Residues (ppm)	Tolerance Reassessment (ppm)	Comment/*[Correct Commodity Definition]*
Corn, pop, stover				residues in field corn stover.
Tolerances Needed under 40 CFR §**180.470(d)**				
Wheat, hay	None	1.61[1]	2.0	A permanent tolerance should be set at 2.0 ppm based on maximum residues in wheat forage corrected for moisture content.

1. Maximum expected residues in wheat hay (88% dry wt.), based on maximum residues of 0.457 ppm in wheat forage (25% dry wt.).

III. Data Requirements

There are data that must be submitted to support the continuing registration of acetochlor. These data are not expected to change the regulatory conclusions for acetochlor described in this document. A generic data call-in (DCI) will be issued and will require development and submission of these listed data:

Toxicology

870.6300 A developmental neurotoxicity study is required.

870.6200 Validation studies (positive controls) are required for the rat neurotoxicity studies.