Overview of Sodium Acifluorfen Risk Assessment June 7, 2001

Introduction

This document summarizes EPA's human health and ecological risk findings for the herbicide sodium acifluorfen, as presented fully in the documents: *Sodium Acifluorfen: HED Chapter for the Reregistration Eligibility Document,* dated April 27, 2001 and the Environmental Fate and Effects Division risk assessment *Reregistration of Sodium Acifluorfen for use on soybeans, peanuts, and rice* dated June 8, 2000. The purpose of this summary is to assist the reader by identifying the key features and findings of the risk assessments in order to better understand the conclusions reached in the assessments. This summary was developed in response to comments and requests from the public which indicated that the risk assessments were difficult to understand, that they were too lengthy, and that it was not easy to compare the assessments for different chemicals due to the use of different formats.

The Food Quality Protection Act (FQPA) requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity." Sodium acifluorfen is a member of the diphenyl ether group of herbicides, which includes lactofen, oxyfluorfen, nitrofen, and fomefasen. The acifluorfen anion is also a degradate of lactofen. The Agency has evidence that these compounds induce similar toxic effects but has not yet determined whether these compounds exhibit a common mechanism of toxicity. The Agency defers the cumulative risk assessment of acifluorfen and the other diphenyl ethers to a later date. For the purposes of tolerance reassessment, EPA is assuming no common mechanism. However, EPA is conducting an aggregate assessment for sodium acifluorfen and lactofen because acifluorfen is an environmental degradate of lactofen. To date, EPA has only identified two classes of chemicals that share a common mechanism of action and are being considered together for purposes of a cumulative assessment (e.g., the organophosphates and some carbamates.) In addition, EPA is in the process of developing methodology to conduct a cumulative assessment.

The risk assessments for sodium acifluorfen are available on the Internet and in the Pesticide Docket for public viewing. Meetings with stakeholders (i.e., growers, environmental groups, commodity groups, and other government offices) are planned to discuss the identified risks and to solicit input on risk mitigation strategies. This feedback will be used to complete the Reregistration Eligibility Decision (RED) document, which will include the resultant risk management decisions. Before issuing its reregistration decision, the Agency plans to conduct a closure conference call with interested stakeholders to describe the regulatory decisions presented in the RED.

Use Profile

Broad Spectrum Herbicide registered for use on soybeans, peanuts, and rice for post-emergent weed control. Also registered as a spot treatment for residential use.

Formulations: Sodium acifluorfen is sold in the United States under the trade names Blazer® and Status®. It is also sold as a co-pack or premix with other herbicides under the trade names Galaxy® (premix with bentazon), Manifest® (co-pack with bentazon and sethoxydim), Storm (premix with bentazon), Conclude® (co-pack with bentazon), and Scepter OT® (co-pack with imaziquin). Sodium acifluorfen is formulated as technical grade manufacturing product (39% active ingredient), soluble concentrate/liquid (6.8 to 21.4% active ingredient), and a liquid ready to use product (0.12% ai). When active ingredient is expressed in terms of weight per volume, sodium acifluorfen formulations range from 0.67 to 2.0 lb active ingredient per gallon.

Methods of Application: Sodium acifluorfen is applied with spray adjuvants using aerial or groundboom equipment.

Use Rates: Depending on the crop and formulation, sodium acifluorfen rates range from 0.125 to 0.375 lb ai/acre.

Annual Poundage: Approximately 1.5 million pounds of sodium acifluorfen active ingredient are applied annually.

Use Sites: Soybeans, peanuts, and rice. Residential driveways, sidewalks, and patios.

Registrants: BASF, Bonide

Acute Toxicity

- Sodium acifluorfen has low acute toxicity via the oral, dermal, and inhalation routes of exposure, but causes severe eye irritation and moderate skin irritation.

- Sodium acifluorfen has been placed in Acute Toxicity Category I for acute eye irritation and in Category II for acute dermal irritation.

Human Health Risk Assessment

Acute Dietary (Food) Risk

Acute dietary risk is calculated considering what is eaten in one day. A risk estimate that is less than 100% of the acute Population Adjusted Dose (aPAD) (the dose at which an individual

could be exposed on any given day with no expected adverse health effects) does not exceed the Agency's level of concern. The aPAD is the reference dose (RfD) adjusted for the FQPA Safety Factor.

An acute dietary analysis was conducted, which utilized average residue values from field trial studies, concentration factors from processing studies, and percent crop treated information. The dietary risk assessment was based only on residues of acifluorfen because metabolites are not expected to be present at significant levels. The only acute toxicology endpoint effect identified was for developmental toxicity, which is relevant only to women of childbearing age. Because no relevant effects following a single exposure of sodium acifluorfen were identified for the U.S. general population, an acute dietary risk assessment for the entire U.S. population was not conducted. The acute dietary assessment applied only to the subpopulation of "females 13+ years old" because EPA is concerned that developmental effects could occur after a single dietary exposure.

The acute dietary exposure analysis is a Tier 2 assessment based on the Dietary Exposure Evaluation Model (DEEM™). The DEEM™ analysis evaluated the individual food consumption as reported by respondents in the USDA 1989-92 Continuing Surveys for Food Intake by Individuals (CSFII) and accumulated exposure to the chemical for each commodity.

- The acute dietary (food) risk estimate is not of concern. Acute dietary exposure comprises < 1% of the aPAD.

- For "females 13+ years," a NOAEL of 20 mg/kg/day was established based on effects of decreased fetal weight and increased incidence of dilated lateral ventricles of the brain observed in a rat developmental toxicity study. Both the decreased fetal weight and the brain malformations are presumed to occur after a single exposure (dose), and thus, are appropriate for this acute risk assessment.

- The uncertainty factor (UF) is 100 to account for inter-species extrapolation (10X) and intra-species variation (10X).

- The FQPA safety factor of 10X was retained for acute dietary exposures for females age 13+ based on the following:

  - data gap for developmental neurotoxicity study and
  - increased susceptibility following *in utero* exposure to rats.

- The acute PAD for females 13+ is 0.02 mg/kg/day. No acute PAD has been established for the general population.

Chronic Dietary (Food) Risk

For the chronic (non-cancer) dietary risk assessment, an average of consumption values for each sub-population is combined with average residue values in/on commodities over a 70-year lifetime to determine average exposure. A risk estimate that is less than 100% of the chronic PAD (the dose at which an individual could be exposed over the course of a lifetime and no adverse health effects would be expected) does not exceed the Agency's level of concern.

The chronic dietary analysis utilized anticipated residue values based on field trial studies, concentration factors from processing studies, and percent crop treated information.

- The chronic dietary (food) risk estimate is not of concern. Chronic dietary exposure comprises <1% of the cPAD for the U.S. population and all subpopulations.

- The NOAEL used in the chronic dietary assessment is 1.25 mg/kg/day, based on kidney lesions, and is derived from a 2-generation reproductive toxicity study in rats.

- The uncertainty factor (UF) is 100 to account for inter-species extrapolation (10X) and intra-species variation (10X).

- The FQPA safety factor of 3X was retained for chronic dietary exposures for females age 13+, infants, and children based on the data gap for the developmental neurotoxicity study. This study provides important information about the susceptibility of infants, children, and women of childbearing age to potential neurotoxic effects of a chemical. EPA retains a 3X safety factor when a data gap is identified for this study. EPA has determined that the increased susceptibility seen in the rat developmental toxicity study has no bearing on chronic exposure.

- The chronic PAD is 0.013 mg/kg/day for the general population and 0.004 mg/kg/day for infants, children, and females 13+. The chronic PAD for infants, children, and females 13+ reflects the additional 3X FQPA safety factor while the chronic PAD for the general population does not.

Cancer Dietary (Food) Risk

Chronic (cancer) dietary risk is also calculated by using the average consumption values for food and average residue values for those foods over a 70-year lifetime. The chronic exposure value is combined with a linear low-dose (Q_1*) approach to determine the lifetime (cancer) risk estimate. The Agency generally considers risks greater than 1×10^{-6} (1 in 1 million) to exceed its level of concern for cancer dietary exposure.

- Sodium acifluorfen is currently classified as a B2 chemical carcinogen (likely human carcinogen), based on the appearance of liver tumors (adenomas and carcinomas) and stomach tumors (papillomas) in mice.

- A linear low-dose (Q_1*) approach was used to characterize human health risk. The unit risk, or Q_1*, is based on liver tumors (adenoma and carcinoma) seen in a chronic cancer study in mice. The Q_1* is 5.30 X 10^{-2} $(mg/kg/day)^{-1}$ in human equivalents, based on the 3/4 scaling factor and the time-to-tumor Weibull statistical model.

- The results of EPA's current risk analysis show that the cancer dietary risk from food alone is 2.2 X 10^{-8} for the general U.S. population, which is below the Agency's level of concern.

- The registrant has voluntarily submitted two new toxicity studies for sodium acifluorfen. The Registrant contends that sodium acifluorfen is carcinogenic by a threshold mechanism based on peroxisome proliferation.

- In 1996 and 1999, EPA proposed new cancer risk assessment guidelines which stated that nonmutagenic carcinogens known to cause cancer via a threshold mechanism could be assessed using a nonlinear margin of exposure (MOE) approach rather than the Q_1* method.

- EPA is currently reviewing the new studies to determine whether the data demonstrate a threshold mechanism for acifluorfen.

Drinking Water Dietary Risk

Drinking water exposure to pesticides can occur through groundwater and surface water contamination. EPA considers acute (one day) and chronic (lifetime) drinking water risks and uses either modeling or actual monitoring data, if available, to estimate those risks. To determine the maximum allowable contribution from water allowed in the diet, EPA first looks at how much of the overall allowable risk is contributed by food and then determines a "drinking water level of comparison" (DWLOC) to determine whether modeled or monitoring estimated environmental concentration (EEC) levels exceed this level. EECs that are above the corresponding DWLOC exceed the Agency's level of concern. Modeling is generally considered to be an unrefined assessment that provides high-end estimates.

For the sodium acifluorfen drinking water assessment, the Agency considered both sodium acifluorfen and lactofen, a related pesticide. Lactofen degrades to acifluorfen in the environment at a rate of approximately 52%. Therefore, EPA estimated total acifluorfen residues, from both acifluorfen and lactofen, and compared the estimates of total residues with the appropriate DWLOC.

- **Acute drinking water concentrations** for surface water (modeled with GENEEC) and groundwater (modeled with SCI-GROW) were less than the acute DWLOCs of 600 ppb for females age 13+; therefore, acute dietary risk from food and drinking water are not of concern. The acute surface water EEC for total acifluorfen (from both acifluorfen and lactofen) is 18.9 ppb, and the acute groundwater EEC for total acifluorfen is 15.7 ppb.
- **Chronic drinking water concentrations** for surface water and groundwater were less than the chronic DWLOCs of 455 ppb for the general U.S. population, 120 ppb for females

13+, and 40 ppb for infants and children. Therefore, chronic dietary risk from food and drinking water are not of concern. The average chronic surface water EEC for total acifluorfen is 4 ppb and the chronic groundwater EEC is 15.7 ppb.

- However, **chronic drinking water concentrations for surface water and ground water exceeded the cancer DWLOC of 0.7 ppb**. Both the modeled concentration of 1.7 ppb total acifluorfen in surface water and 15.7 ppb total acifluorfen in groundwater exceeded the cancer DWLOC of 0.7 ppb. Total acifluorfen includes acifluorfen derived from both sodium acifluorfen and lactofen.

- **Acifluorfen was detected in several water monitoring studies.** Acifluorfen was detected in 56 out of 283 ground water samples with concentrations ranging from 1 to 46 ppb. The overall mean for the 56 detections was 8.36 ppb. The Pesticides in Ground Water Database (PGWDB, USEPA, 1992) reported residues in 4 of 1185 wells sampled with concentrations ranging from 0.003 to 0.025 ppb. The only surface water monitoring for acifluorfen is that from the USGS National Water Quality Assessment (NAWQA). The NAWQA study reports a single acifluorfen detection of 0.17 ppb out of 965 samples collected from major aquifers and 1 detection (0.07 ppb) out of 314 samples collected from shallow urban ground water.

Residential Risk

- The only scenario for residential exposure is a short-term spot treatment exposure scenario to kill weeds on driveways, sidewalks, and patios.

- A margin of exposure (MOE) of 1,000 or greater is not of concern for residential exposure scenarios. The FQPA safety factor of 10X was retained for short term residential exposures for females age 13+ for the reasons given above. The MOE for residential exposure is 4300 and is not of concern.

- A cancer risk of less than 1×10^{-6} does not exceed the Agency's level of concern for residential exposure. For this scenario there was a cancer risk of 8.3×10^{-7} which is not of concern.

- In the residential handler cancer risk assessment, EPA assumed that a one gallon container of product would be used by an applicator for spot treatments in one year and that applicators would be potentially exposed for 50 years over a 70 year lifespan.

- EPA does not anticipate post-application dermal exposures for adults or children due to the frequency, duration and location of residential spot treatment applications.

Aggregate Risk

Aggregate risk considers the combined risk from exposure through food, drinking water, and, if appropriate, residential uses. Generally, all risks from these exposures must be less than 100% of the aPAD and cPAD (*non-cancer*) and cancer risks must be less than 1 X 10^{-6}. For sodium acifluorfen, the aggregate risks would include food, drinking water, and residential exposure. However, aggregate risk assessment considered residential exposure only for short-term exposure because chronic residential exposure is not expected with sodium acifluorfen.

- As stated previously, both the acute and chronic dietary risks (food and water only) from acifluorfen are not of concern. Residential exposure is considered to be short term rather than acute exposure. As stated above, short term residential risk is not of concern for sodium acifluorfen. The short term DWLOC for females 13+ was 462 ppb, which is far greater than the modeled water concentrations of 0.34 to 10.3 ppb. Therefore, EPA has no concern for short-term aggregate exposure.

- For cancer, aggregate risk is of concern. A cancer DWLOC of 0.7 ppb was calculated. This value represents the concentration of acifluorfen in drinking water as part of the aggregate exposure from food and water that results in a negligible cancer risk. The modeled surface and groundwater concentrations (1.7 ppb and 15.7 ppb, respectively) exceed the DWLOC; therefore the Agency has a concern for aggregate cancer risk from acifluorfen.

Occupational Risk

Workers can be exposed to a pesticide through mixing, loading, or applying the pesticide, and re-entering a treated site. Worker risk is measured by a Margin of Exposure (MOE), which determines how close the occupational exposure comes to the No Observed Adverse Effect Level (NOAEL) taken from animal studies. For sodium acifluorfen, dermal MOEs that are greater than 100 do not exceed the Agency's level of concern. A dermal absorption factor of 20% was used to account for differences in absorption between the oral and dermal routes. Oral and inhalation absorption were assumed to be equivalent.

For workers entering a treated site, restricted entry intervals (REIs) are generally calculated to determine the minimum length of time required before workers or others are allowed to enter.

Summary of Toxicological Information

- **Short- and Intermediate Term:** The dermal NOAEL is 20 mg/kg/day, based on decreased fetal weight and increased incidence of dilated lateral ventricles of the brain in an oral rat developmental toxicity study. The inhalation NOAEL was also 20 mg/kg/day, from the same rat developmental toxicity study.

- **Long-term:** No toxicological endpoint was selected because long term occupational exposure to sodium acifluorfen is not expected based on the currently registered uses.

- **The cancer Q_1*** is 5.30 X 10^{-2} $(mg/kg/day)^{-1}$ based on liver tumors in mice. A 3/4 scaling factor was used to extrapolate from animals to humans.

Mixer/Loader/Applicator Risk

Short and Intermediate-Term Risk:

- The registrant conducted a worker exposure and biomonitoring study on sodium acifluorfen. This study monitored dermal and inhalation exposure to workers who mixed, loaded, and applied acifluorfen to soybean fields for weed control. Dermal and inhalation exposure from this study were used in the worker exposure assessment. Surrogate data from the Pesticide Handlers Exposure Database (PHED), version 1.1, were also used to assess potential exposures resulting from mixing, loading, or applying sodium acifluorfen.

- Most short and intermediate combined MOEs for mixers and loaders are of concern at baseline (MOEs < 100). Applicators and flaggers are the only scenarios with MOEs not of concern at baseline. When personal protective equipment is used, MOEs for all scenarios are > 100 and not of concern.

Cancer Risk:

- For most scenarios, cancer risks are not of concern at baseline. The only two scenarios with risks of concern are mixing/loading liquids for aerial and groundboom application; cancer risks for these scenarios exceed 1 X 10^{-4} at baseline. With personal protective equipment, cancer risks range from 2.6 X 10^{-6} to 9.6X 10^{-8}. With engineering controls, cancer risks are in the range of 10^{-7} to 10^{-9} and are not of concern.

Post-Application Risk:

- The post-application risk assessment estimated potential exposures for workers entering treated fields for specific tasks. Chemical-specific foliar dislodgeable residue data for sodium acifluorfen were used in this postapplication assessment. The restricted entry interval (REI) is set at the day after treatment that the MOE is 100 or greater and the day that the cancer risk is greater than 1 X 10^{-4}. For sodium acifluorfen, all post-application MOEs are > 100 and all cancer risk estimates are < 4 X 10^{-5} on the day of application. Cancer risks are < 1 X 10^{-6} on day 2 to 8 after application, depending on the scenario and data source.

- The current REI for sodium acifluorfen is 48 hours based on the acute toxicity. The REI will likely remain 48 hours based on the acute toxicity.

Incident Data

- No poisoning incidents from exposure to sodium acifluorfen have been reported to the OPP Incident Data System, Poison Control Centers nationwide, or the California Department of Food and Agriculture. Further, the National Pesticide Telecommunications Network (NPTN) has received no reports of human poisonings from sodium acifluorfen.

Ecological Risk Assessment

To estimate potential ecological risk, EPA integrates the results of exposure and ecological toxicity studies using the quotient method. Risk quotients (RQs) are calculated by dividing exposure estimates by ecological toxicity values, both acute and chronic, for various species. The higher the RQ the greater the concern. Risk characterization provides further information on the likelihood of adverse effects occurring by considering the fate of the chemical in the environment, communities and species potentially at risk, their spatial and temporal distributions, and the nature of the effects observed in studies.

Fate and Transport

- Sodium acifluorfen is persistent on soils and in aquatic environments and relatively mobile. Acifluorfen is stable to hydrolysis and does not break down in sunlight. Initial off-target transport is expected to be through drift, leaching, and later through erosion and runoff.

- Sodium acifluorfen exists in the anion (negatively charged) form in most agricultural soils. Several factors, including soil pH, soil organic carbon content, and soil iron content determine the extent to which acifluorfen adsorbs to soil particles. Therefore, the persistence and mobility of acifluorfen vary with different soil conditions.

- Because acifluorfen's fate properties showed that it might leach to groundwater, EPA required a small scale prospective ground water monitoring study, which was conducted on soybeans in the central sands of Wisconsin. Acifluorfen and two degradates were monitored, parent only was detected at concentrations ranging from 1 to 46 ppb (average 7.33 ppb) in 56 out of 283 samples.

- EPA recommends that additional fate studies be conducted for sodium acifluorfen to better understand the fate processes that control its movement in soil under different environmental conditions. Desirable studies include OPP Guidelines 163-1 (Soil Partition Coefficient), 162-1 (Aerobic Soil Metabolism), 162-2 (Anaerobic Soil Metabolism), 162-3 (Anaerobic Aquatic Metabolism), 162-4 (Aerobic Aquatic Metabolism), 164-1 (Terrestrial Field Dissipation), and 164-2 (Aquatic Dissipation).

- EPA's water quality assessment for sodium acifluorfen also considers the herbicide lactofen, which degrades to acifluorfen.

Ecological Risk

- EPA does not have acute risk concerns for terrestrial animals, freshwater and estuarine animals, or aquatic plants.

- The Agency has chronic risk concerns for plant and insect eating birds, but not for mammals, when acifluorfen is used at a rate of 0.25 lb ai/A.

- The Agency is uncertain about risks to freshwater and estuarine animals. The acute toxicity data do not suggest a risk concern. However, EPA does not have sufficient information to assess chronic risk. A no effect level could not be determined in a chronic fish toxicity study because the lowest dose level resulted in an effect (reduced larvae weight). A comparison of the maximum peak concentration of acifluorfen in water is 100 fold lower than the LC50 for rainbow trout or bluegill sunfish. Because acifluorfen is persistent in water, the Agency is concerned about the potential for chronic risk.

- The Agency is uncertain about risks to terrestrial plants. EPA could not conduct a risk assessment for terrestrial plants due to lack of adequate data. Since sodium acifluorfen is an herbicide, EPA assumes that there is a risk to nontarget plants, although the magnitude of the potential risk is unknown.

Potential Alternatives

As part of the reregistration process, EPA has conducted a preliminary analysis of potential alternatives to sodium acifluorfen. These alternatives are summarized in the table below. EPA is seeking comments on the viability of these alternatives, as well as information on additional alternatives that are not listed below.

Crops, Weeds, and Alternatives

Crop	Major Weeds	Registered Alternatives
Peanuts	Cocklebur	2,4-DB, bentazon, chlorimuron, imazapic, imazethapyr, paraquat, pyridate
	Morning glory	2,4-DB, bentazon, chlorimuron, glyphosate, imazapic, imazethapyr, paraquat,
	Ragweed	2,4-DB, bentazon, chlorimuron, glyphosate, imazethapyr, paraquat,
	Sesbania, Hemp	2,4-D amine, bensulfuron, bentazon, MCPA, propanil, quinclorac, triclopyr
Soybeans	Cocklebur	2,4-DB, bentazon, cloransulam-methyl, chlorimuron, flumetsulam, **fomesafen**, **glyphosate**, imazamox, imazaquin, imazethapyr, **lactofen**, metribuzin, sulfentrazone, thifensulfuron, trifluralin
	Lambsquarters	2,4-DB, bentazon, clomazone, flumetsulam, **fomesafen**, **glyphosate**, imazamox, imazaquin, imazethapyr, **lactofen**, linuron, metolachlor, metribuzin, pendimethalin, sulfentrazone, trifluralin.

Crop	Major Weeds	Registered Alternatives
	Morning glory	2,4-DB, bentazon, chlorimuron, clorasulam-methyl, flumetsulam, **fomesafen**, **glyphosate**, imazaquin, imazethapyr, **lactofen**, sulfentrazone.
	Pigweed, Redroot	2,4-DB, bentazon, chlorimuron, flumetsulam, **fomesafen**, **glyphosate**, imazamox, imazaquin, imazethapyr, **lactofen**, metolachlor, metribuzin, pendimethalin, sulfentrazone, thifensulfuron, trifluralin
	Ragweed	2,4-DB, bentazon, chlorimuron, clorasulam-methyl, **fomesafen**, **glyphosate**, imazamox, imazaquin, imazethapyr, **lactofen**, linuron, metribuzin.
	Velvetleaf	2,4-DB, bentazon, chlorimuron, clomazone, clorasulam-methyl, flumetsulam, **fomesafen**, **glyphosate**, imazamox, imazaquin, imazethapyr, **lactofen**, metribuzin, thifensulfuron
	Waterhemp, Common	2,4-D, bentazon, chlorimuron, clorasulam-methyl, **fomesafen**, **glyphosate**, imazaquin, imazethapyr, **lactofen**, metribuzin, sulfentrazone, thifensulfuron.

(Alternatives in bold were suggested by Registrant at the Acifluorfen Smart Meeting of March 11, 1999)

Data Needs

The preliminary risk assessment for sodium acifluorfen could be refined with additional information. Several areas of the occupational and non-occupational risk assessment would improve with more information and data. Areas of information and data needs include:

- The Hazard Identification Assessment Review Committee recommended a developmental neurotoxicity study in rats be conducted (870.6300). This study is required because of neurotoxicity which occurred in a developmental toxicity study in rats (increased incidence of dilated lateral ventricles of the fetal brain, MRID 00122743).

- The following product and residue chemistry requirements are needed: UV/visible absorption data (830.7050) and additional plant analytical methodology data (radio validation and a lower LOQ for rice straw).

- There are data gaps for Tier II terrestrial plant test data: FIFRA Guidelines 123-1(a) Seed Germination/Seedling Emergence and 123-1(b) Vegetative Vigor.

- EPA also needs information to clarify the persistence of acifluorfen in different types of soil and its mobility to groundwater. This information might be provided through new laboratory studies, literature studies, or unpublished data not previously submitted to EPA.