OVERVIEW OF LINDANE RISK ASSESSMENT

January 30, 2002

Introduction

This document provides an overview of EPA's human health, environmental fate and transport, and ecological risk findings for the pesticide lindane as presented fully in the documents, "*Revised HED* [Health Effects Division] *Risk Assessment for Lindane*," dated January 9, 2002 and "*Revised EFED* [Environmental Fate and Effects Division] *RED Chapter for Lindane*," dated December 20, 2001. The purpose of this overview is to assist the reader by identifying the key features and findings of these risk assessments in order to better understand the conclusions reached in the assessments. This overview format was developed in response to comments and requests from the public which indicated that Agency 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 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." The reason EPA considers other substances is due to the possibility that low-level exposures to multiple chemical substances that cause a common toxic effect by a common mechanism could lead to the same adverse health effect as would a higher level of exposure to any of the other substances individually. The Agency has not performed a cumulative risk assessment as part of this reregistration review of lindane because it has not determined there are any other chemical substances that have a common mechanism of toxicity. If the Agency identifies other substances that share a common mechanism of toxicity with lindane, then a cumulative risk assessment will be conducted that includes lindane once the final framework the Agency will use for conducting cumulative risk assessments is available. Further, the Agency is in the process of developing criteria for characterizing and testing endocrine disrupting chemicals, in accordance with FQPA. EPA plans to implement an Endocrine Disruptor Screening Program at a later date; lindane will be reevaluated at that time and additional testing may be required.

The risk assessments for lindane and additional supporting documents are posted on EPA's Internet website (http://www.epa.gov/pesticides/lindane.htm) and are available in the Pesticide Docket for public viewing. The Agency plans to discuss the risk assessments, identify risks of concern, and solicit input on risk mitigation strategies (if needed) with stakeholders (growers, extension offices, states, tribes, commodity groups, the general public, and other Federal agencies). This feedback will be used to complete the Reregistration Eligibility Decision (RED) document, which describes the Agency's risk management decisions for lindane. Prior to finalizing the reregistration decision, the Agency will conduct a close-out conference call with interested stakeholders to describe the regulatory decisions that will be presented in the RED.

Use Profile

- **Manufacturer/Technical Registrant**: INQUINOSA Internacional, S.A. (Industries Quimica de Nordouesta SA). Sole member of the Centre Internationale d'Etudes du Lindane (CIEL, the Lindane task force).

- **Type of Pesticide:** Insecticide.

- **Target pests:** Seed corn beetles, seed corn maggots, white grubs, and wireworms.

- **Crops/use sites:** The technical registrant is supporting six crops/sites: for pre-plant seed treatment of barley, corn, oats, rye, sorghum, and wheat. Other existing uses/crops/sites will be voluntarily cancelled. The risk assessments are also considering the pending registration on canola (seed treatment only).

- **Formulations:** Dust, Emulsifiable concentrate, Flowable concentrate, Liquid-ready to use, and Wettable powder.

- **Methods of Application:** Liquid seed treater; Planter/seed box; Seed treater; Slurry-type seed treater.

- **Use Rates:** 0.031 to 0.125 lbs ai/100 lbs of seed. (The registrant has applied for a new use on canola. If approved, the maximum application rate on canola would be 1.5 lbs ai/100 lbs seed.)

- **Annual Poundage:** Up to 200,000 lbs/year.

- **Other Registrants:** Agriliance LLC, Agsco Inc., Amvac Chemical Corp., Drexel Chemical Co., Gustafason LLC, Prentiss Inc., Pursell Industries, Inc., Gustafason LLC, Platt Chemical Co. Inc., Tomen Agro Inc., Trace Chemicals LLC, Uniroyal Chemical Co. Inc., and Wilbur-Ellis Co.

- **Classification:** General use.

- **Timing**: Used as a pre-plant seed treatment only.

Human Health Risk Assessment

Acute Toxicity

- Lindane has been placed in Acute Toxicity Category II for exposures by the oral and dermal routes and in Acute Toxicity Category III for eye irritation.

Acute Dietary (Food) Risk

Acute dietary risk is calculated considering what is eaten in one day. Dietary exposure 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 that would not be expected to result in adverse health effects) does not exceed the Agency's risk concern. The aPAD is the acute Reference Dose (RfD) adjusted for the FQPA Safety Factor.

An acute dietary analysis was conducted using anticipated residues for all commodities supported for reregistration including a proposed new use on canola. The dietary assessment, which is a Tier 3 probabilistic assessment based on the Dietary Exposure Evaluation Model (DEEM™), was conducted using percent crop treated and total radioactive residues (TRRs) from plant metabolism studies and from poultry and ruminant metabolism studies. A processing study for canola found no detectable lindane residues in canola oil, therefore, one half the limit of quantitation (½ LOQ) was used as the DEEM™ adjustment factor. DEEM™ default adjustment factors were used for all other concentration factors.

- The acute dietary (food) risk estimate is not of concern for any population subgroup at the 99.9th percentile. The highest dietary risk estimate is 17 % of the aPAD for the population subgroup All Infants. For the U.S. population, the estimate is 7% of the aPAD.

- The acute dietary endpoint was derived from an acute neurotoxicity study in rats. The No Observable Adverse Effect Level (NOAEL) for neurotoxic effects was 6 mg/kg for females and the Lowest Observable Adverse Effect Level (LOAEL) was 20 mg/kg based on increased forelimb grip strength and decreased grooming behavior and motor activity.

- An uncertainty factor (UF) of 300 was applied to account for inter-species extrapolation (10X), intra-species variation (10X), and the FQPA safety factor (3X).

- An FQPA safety factor of 3X is required for lindane since there is evidence of increased susceptibility of the young demonstrated in both the developmental neurotoxicity study (quantitative) and the 2-generation reproduction study in rats (qualitative).

- The FQPA safety factor was reduced to 3x because: 1) the toxicology data base is complete; 2) the available data provide no indication of increased susceptibility in rats from *in utero* exposure to lindane in the prenatal developmental study; 3) although the developmental toxicity study in rabbits was classified unacceptable, the HIARC concluded that a new study is not required; 4) the offspring effects seen in the developmental neurotoxicity study were the same as those seen in the two-generation reproduction study (no additional functional or morphological hazards to the nervous system were noted); 5) adequate actual data, surrogate data, and/or modeling outputs are available to satisfactorily assess food exposure and to provide a screening level drinking water exposure assessment; and 6) there are currently no residential uses.

- Therefore, the aPAD is 0.02 mg/kg/day. (NOAEL of 6 mg/kg/day divided by 300 (Uncertainty Factor of 100 and FQPA safety factor of 3).

Chronic Dietary (Food) Risk

Chronic dietary risk is calculated by using the average consumption value for food and average residue values on those foods over a 70-year lifetime[1]. A risk estimate that is less than 100% of the chronic Population Adjusted Dose (cPAD) does not exceed the Agency's level of concern. The cPAD is the chronic Reference Dose (cRfD) adjusted for the FQPA Safety Factor. The RfD is the dose at which an individual could be exposed over the course of a lifetime with no adverse health effects.

The chronic dietary analysis was conducted using anticipated residues for all commodities supported for reregistration including a proposed new use on canola. The chronic dietary assessment was based on the Dietary Exposure Evaluation Model (DEEM™) using percent crop treated and TRRs from plant metabolism studies beginning with seed treatment and from poultry and ruminant metabolism studies. A processing study for canola found no detectable lindane residues in canola oil, therefore, ½ LOQ was used as the DEEM™ adjustment factor. DEEM™ default adjustment factors were used for all other concentration factors.

- Chronic dietary risk from food is not of concern. For the most highly exposed sub-population, children 1-6 years, exposure is 11% of the cPAD; while the exposure for the U.S. population is 3% of the cPAD.

- The chronic dietary endpoint is derived from a chronic toxicity/oncogenicity study in rats. The systemic toxicity NOAEL is 0.47 mg/kg/day based on adverse liver histopathology, increased liver and spleen weights and decreased platelets. The LOAEL is 4.81 mg/kg/day.

[1]For an infant the chronic risk is calculated over 1 year, for a child (ages 1-6) over 6 years, for females of child bearing age (ages 13 - 50) 37 years.

- An uncertainty factor (UF) of 300 was applied to account for inter-species extrapolation (10X), intra-species variation (10X), and the FQPA safety factor (3X).

- The FQPA safety factor of 3X was retained for chronic dietary exposures for the reasons described above in the acute dietary discussion.

- Therefore, the cPAD was determined to be 0.0016 mg/kg/day [NOAEL of 0.47 mg/kg/day divided by 300 (UF of 100 multiplied by the FQPA safety factor of 3).]

Subpopulation Dietary Assessment

Lindane does not occur naturally in the environment. Once released into the environment, lindane can partition into all environmental media. Because of long-range atmospheric transport, lindane has been detected in air, surface water, groundwater, sediment, soil, ice, snowpack, fish, wildlife, and humans. The Arctic is considered a "sink" for persistent organic pollutants such as lindane. Once in the Arctic, lindane bioaccumulates in the food chain due to its high lipid solubility. Lindane is bioconcentrated rapidly in microorganisms, invertebrates, fish, birds and mammals. However, biotransformation and elimination are relatively rapid when exposure is discontinued.

The indigenous people of the US Arctic region (Alaska) rely heavily on game for their food source. Because lindane concentrates in game, the Agency performed a supplementary chronic dietary exposure and risk assessment to determine risk to indigenous Alaskan people from worldwide use and manufacture of lindane. An acute dietary assessment is not possible at this time because the Agency does not have the information on a typical day's diet of indigenous people. Nevertheless, based on limited residue data, the Agency believes acute dietary risks are unlikely to be of concern because indigenous adults and children would have to consume more than 50 and 10 lbs of game, respectively in a single day to exceed the aPAD.

Chronic dietary risks based on traditional foods are generally not of concern. For the most highly exposed sub-population, children 1-6 years, the subsistence diet results in lindane exposures that range from 13 - 138 % of the cPAD; while for the adult population the subsistence diet is 3 - 44% of the cPAD. Only one dietary intake scenario (in one community where EPA assumed that children ate 1.3 lbs of predominantly whale per day) showed children above 100% of the cPAD; all other scenarios were 65% or less of the cPAD.

The Agency believes this assessment is conservative and probably over estimates dietary risk because: (1) this assessment is based on data **obtained from the Alaska Department of Fish and Game Division of Subsistence** from three highest exposed communities of approximately 180 Alaskan communities with the highest harvest amounts of seal, whale, and walrus; (2) maximum detected residues in any game tissue were used to assess chronic exposure; (3) whale, walrus and seal blubber residues were used to assess all meat residues, which are expected to have much lower lindane residues than blubber, and (4) it was assumed that harvest was equal to intake (i.e, adults consume up to 2.4 lbs and children up to 1.3 lbs of meat per day).

Cancer Dietary (Food) Risk

The Agency reviewed a newly submitted carcinogenicity study in CD-1 mice along with other data. In accordance with the EPA Draft Guidelines for Carcinogen Risk Assessment (July, 1999), lindane is categorized as "Suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential" based on an increased incidence of benign lung tumors in female mice only. Therefore, quantification of human cancer risk is not required.

Drinking Water Dietary Risk

Drinking water exposure to pesticides can occur through groundwater and surface water contamination. EPA considers both 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 of lindane in drinking water allowed in the diet, EPA first looks at how much of the overall allowable risk is contributed by food, then determines a "drinking water level of comparison" (DWLOC) to determine whether modeled or monitoring concentrations exceed this level. DWLOCs were calculated based on the dietary exposure and default body weights and water consumption figures.

The Agency uses the DWLOC as a surrogate to capture risk associated with exposure from pesticides in drinking water. The DWLOC is the concentration of a chemical in drinking water that would be acceptable as an upper limit considering total aggregate exposure to that chemical from food, water, and residential sources. Risks from drinking water are assessed by comparing the DWLOCs to the estimated environmental concentrations (EECs) in surface water and groundwater. Drinking water modeling is considered to be an unrefined assessment and provides high-end or conservative estimates so modeling tends to overestimate risk.

Surface water EECs resulting from lindane seed treatment use were predicted with the Tier 1 assessment model, GENEEC. Groundwater EECs were estimated using SCI-GROW.

Acute Drinking Water. The highest EECs for lindane in surface water (0.67 ppb, from GENEEC) and in groundwater (0.011 ppb, from SCI-GROW) are less than the acute DWLOCs for all sub-populations (lowest acute DWLOC = 170 ppb) indicating that acute aggregate exposure to lindane in food and water does not exceed the Agency's level of concern.

Chronic Drinking Water. The chronic EECs for lindane in surface water (0.16 ppb, from GENEEC) and in groundwater (0.011 ppb, from SCI-GROW) are less than the lowest chronic DWLOC (14 ppb), indicating that chronic exposure to lindane in food and water is less than the Agency's level of concern.

For the indigenous people of the arctic, the Agency has insufficient information on lindane concentrations in Alaskan drinking water sources to determine if chronic exposure to lindane in food and water is below the Agency's level of concern. The available EECs are not appropriate for assessing potential exposures in Alaska, because they are specific to seed

treatment uses, and are not representative of background environmental levels. In addition, drinking water monitoring data are not readily available for Alaska. Nevertheless, the Agency estimates that lindane drinking water concentrations below 6 ppb for children, and 31 ppb for adults would result in food and water exposures below the Agency's level of concern for most Alaskan communities. These estimates are based on very conservative estimates of lindane exposure from game discussed previously in the Subpopulation Dietary Assessment section.

Residential Risk

There are no residential or other non-occupational (e.g., golf course) pesticidal uses of lindane regulated by EPA. However, there is a pharmaceutical use of lindane for head lice and scabies treatment, which is not included in this risk assessment at this time.

Aggregate Risk

The aggregate risk assessment for lindane examines the combined risk from exposure through food and drinking water only since there are no residential or other non-occupational uses of lindane. Therefore, the DWLOC was calculated based only on dietary exposures. As noted above the acute and chronic EECs for surface and groundwater do not exceed the Agency's level of concern.

Occupational Risk

The Agency assessed 5 worker exposure scenarios. Workers can be exposed to lindane through: (1) mixing/loading/planting dry formulations for on farm seed treatment; (2) mixing/loading/applying of liquid formulation for commercial seed treatment at small/medium and large facilities; (3) handling treated seed for commercial use at small/medium and large facilities; (4) loading treated seed for planting; and (5) planting treated seed. Worker risk is measured by a Margin of Exposure (MOE) which determines how close the occupational exposure comes to a NOAEL taken from animal studies. Generally, MOEs greater than 100 do not exceed the Agency's level of concern.

- The Agency assumed that on-farm workers could be exposed to lindane for short-term (1 - 30 days) durations, while commercial workers could be exposed for both short- and intermediate-term (1 - 6 months) durations.

- The short term and intermediate dermal endpoints are derived from a rat oral developmental neurotoxicity study. A NOAEL of 1.2 mg/kg/day and LOAEL of 5.6 mg/kg/day were established based on reduced pup survival, decreased body weight and body weight gains during lactation, increased motor activity, and decreased motor activity habituation. A 10% dermal absorption factor was used to account for differences in absorption between the oral and dermal routes. Therefore, the effective dermal NOAEL is 12 mg/kg/day.

- The short- and intermediate-term inhalation endpoints are derived from a 90-day rat inhalation study. The inhalation NOAEL of 0.13 mg/kg/day and LOAEL of 1.3 mg/kg/day were based on clinical signs (diarrhea, piloerection), increased kidney weights, and bone marrow effects.

- Because the endpoints for dermal and inhalation are different, exposures from different routes are not combined and separate MOEs are calculated.

- An uncertainty factor of 100 was applied (10X for inter-species extrapolation and 10X for intra-species variation) to calculate risks for exposure from both the inhalation and dermal routes. An MOE of 100 or greater is not of concern.

- For the worker risk assessment, EPA assumes that "on farm" workers wear a single layer of clothing (long pants and long sleeve shirt) and gloves. EPA assumes that commercial seed treatment workers wear an additional, second layer of clothing (coveralls) and gloves.

- *Existing seed treatment uses*. There is one short-term on-farm dermal MOE of 19 for mixing/loading/planting activities that exceeds the Agency's level of concern. EPA estimates that this scenario would still be of concern with additional personal protective equipment (PPE). All other short- and intermediate-term dermal and inhalation MOEs range from 98 to 43,000, and do not exceed the Agency's level of concern.

- *Canola Use*. The canola seed treatment rate (1.5 lbs. ai/100 lbs of seed) would be approximately 40 times greater than other seed treatment uses of lindane assessed by the Agency. A total of four worker scenarios exceed the Agency's level of concern, including: on-farm mixing/loading/planting activities (scenario 1), mixing, loading, and application of the liquid formulation for commercial seed treatment (scenario 2) at large facilities (MOEs range from 2.6 to 5.3) and small/medium facilities (MOEs range from 20 to 40), and commercial treated seed handler exposures (scenario 3) at large facilities (inhalation MOE is 20).

- The commercial seed treatment occupational exposures for both current crops and canola are based on a chemical-specific (lindane) study that provided useful information but did not meet current guideline requirements. The worker risks may change based on recently received studies that were included in Canada's Pesticide Management Regulatory Agency (PMRA) risk assessment of lindane. These studies are currently under review and information from these studies will be included in the final RED.

Post-Application Occupational Risk

The Agency has determined that once seeds treated with lindane have been planted in the ground, any potential post planting exposure or risk to individuals is negligible.

Ecological Risk

To estimate potential ecological risk, EPA integrates the results of exposure and ecotoxicity studies using the quotient method. Risk quotients (RQs) are calculated by dividing exposure estimates by ecotoxicity values, both acute and chronic, for various wildlife species. RQs are then compared to levels of concern (LOCs). Generally, the higher the RQ, the greater the potential risk. An RQ 0.5 is of concern for acute risks, while an RQ 1 is of concern for chronic risks. For endangered species, an RQ 0.1 for terrestrial organisms, and an RQ 0.05 for aquatic organisms are of concern.

Environmental Fate and Transport

Lindane is persistent and moderately mobile. It is resistant to photolysis and hydrolysis (except at high pH), and degrades very slowly by microbial actions. Lindane bioconcentrates, but in the absence of additional sources of lindane, it purges rapidly.

Lindane is transported through the environment by both hydrologic and atmospheric means. Lindane has often been detected in surface and ground water, and lindane and its isomers have been detected in areas of non use (e.g., the Arctic), indicating global atmospheric transport may occur. The source of these lindane detections is unclear but may be the result of a combination of lindane's past widespread use and its extreme persistence. Currently, U.S. uses of lindane are restricted to (agricultural) seed treatments at relatively low application rates.

Nontarget Terrestrial Risk

- Both current and proposed seed treatment uses present acute and chronic risk to birds and mammals. RQ's range from 0.21-5.48 for acute risks and from 3.9-83.3 for chronic risks. These assessments assume the entire animal's diet consists of lindane-treated seeds, which were treated at the maximum label application rate.

- There is a possibility of acute risk to small mammals with high metabolic rates that dig and cache seeds. Chronic risk to these species may be greater during breeding season due to high seed consumption and the persistence of the compound in soil.

- There is acute risk to songbirds and other similar seed eating avian species (RQ's range from 0.21-5.48); however, some studies have shown that birds, when given a choice of seeds, will preferentially eat seeds not treated with lindane.

- Lindane is highly toxic (0.2 to 0.56 ug/bee) to honeybees. However, because of the nature of the seed treatment use, EPA assumes low risk to flying insects. Beneficial soil dwelling insects may be at some risk.

- Lindane is a potential endocrine disruptor in birds and mammals, and the chronic avian and mammalian endpoints are based on adverse effects on reproduction. Adverse effects include disruption in male reproductive behavior and functioning in mammals, eggshell thinning, and estradiol insufficiency in female birds, which may cause a drastic reduction in clutch size.

Nontarget Aquatic Risk

Aquatic risk estimates are highly conservative because they are based on the assumption that 100% of the lindane from the seed treatment migrates to surface water after planting. However, some lindane from seed treatment is expected to remain with the seed/plant, or in the soil or volatilize. This assessment could be refined with a seed leaching study.

- At current application rates used on major crops, acute high risk and restricted use levels of concern are exceeded for both freshwater and estuarine/marine organisms. The RQ's range from 0.03 to 8.7.

- No chronic LOC's are exceeded for freshwater fish and invertebrates while chronic risk to estuarine/marine fish could not be assessed due to a lack of toxicity data.

Risks to Endangered Species

Endangered birds and especially small mammals that eat a large daily proportion of seeds may be at risk from the current and proposed seed treatment uses. Endangered freshwater fish and invertebrates may also be at acute risk. Also, exposed endangered birds, mammals and possibly fish may be jeopardized due to the endocrine disrupting properties of lindane combined with already limited population sizes and/or losses in critical habitat.

Summary of Pending Data

- The commercial seed treatment occupational exposures for both current crops and canola are based on a chemical-specific (lindane) study that provided useful information but did not meet current guideline requirements. The worker risks may change based on recently received studies that were included in Canada's PMRA risk assessment of lindane.

International Considerations

There are several bilateral and multilateral agreements and treaties that either list lindane among other pollutants, or may list lindane in the future. These may impact the ultimate reregistration decision on lindane. These include:

- The Great Lakes Binational Toxics Strategy, a voluntary agreement between the U.S. and Canada. Lindane is listed as a Level II substance. Website: http://www.epa.gov/glnpo/bns/

- The POPs (Persistent Organochlorine Pollutants) Protocol to the Convention on Long-Range Transboundry Air Pollution (LRTAP) treaty, a legally-binding regional treaty. Lindane is listed as an annex II substance. Website: http://www.unece.org/env/lrtap/

- The Rotterdam Convention on Prior Informed Consent (PIC), a procedure for certain hazardous chemicals and pesticides in international trade, a legally-binding global treaty. Lindane is a chemical subject to the PIC procedure. Website: http://www.fao.org/waicent/FaoInfo/Agricult/AGP/AGPP/Pesticid/PIC/pichome.htm

- The North American Free Trade Agreement (NAFTA). As a component of NAFTA and efforts to harmonize pesticide product registration, the U.S. and Canada are sharing information in re-evaluating lindane in both countries (Website: http://www.epa.gov/oppfead1/international/naftatwg/). Also, under the NAFTA environmental side agreement, the U.S., Canada, and Mexico are considering to proceed with a North American Regional Action Plan (NARAP) on lindane beginning in June 2002. Website: http://www.cec.org/programs_projects/pollutants_health/smoc/

Summary of Public Comments

The Agency received more than 1300 comments on its lindane risk assessment. In addition to comments received on specific areas of the Agency's human health and environmental risk assessments, three general issues were raised:

Well over 1,000 commentors expressed concern for direct application of lindane (pharmaceutical) products during lice and scabies treatments. They either encouraged EPA to include these pharmaceutical uses (regulated by FDA) in its human health risk assessment based on FQPA, and/or work with FDA to jointly assess these risks, and incorporate them into EPA's current (FIFRA-based) risk assessment.

A small number of the foregoing commentors also asked EPA to include the (pharmaceutical) pediculicide (head lice treatment) uses into its environmental risk assessment because lindane-containing pediculicide is usually disposed of into municipal wastewater treatment systems that are not able remove the lindane before discharge to surface waters.

About 200 Canadian canola growers and small commercial seed treaters encouraged the Agency to register lindane for the use on canola in the U.S. They described lindane products as a cost effective treatment for the control of flea beetles.