UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

MEMORANDUM

Date: August 15, 2012

TXR No.: 0056398

SUBJECT: **Norflurazon:** Summary of Hazard and Science Policy Council (HASPOC) Meetings of July 12, 2012: Recommendations on the requirement of a subchronic inhalation study and the neurotoxicity screening battery for norflurazon.

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TO: Linda Taylor, Ph.D.
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MEETING ATTENDEES:

HASPOC Members: Elizabeth Mendez, Jeff Evans, Jess Rowland, Jonathan Chen, Marquea King (for Elissa Reaves), Michael Metzger

Presenter: Linda Taylor

Other Attendees: Ana Rivera-Lupianez, Julie Van Alstine, Kristin Rury, Will Donovan

I. PURPOSE OF MEETING:

Risk Assessment Branches V and VII (RAB V & VII) are preparing a Registration Review human health scoping document for norflurazon, a pyridazinone herbicide. Based on the current 40 CFR Part 158 data requirements, acute and subchronic neurotoxicity studies are required for norflurazon. Based on current policies, a repeated dose inhalation toxicity study in rats is required due to the potential for repeated inhalation exposure to aerosolized formulations of norfulurazon. The Hazard and Science Policy Council (HASPOC) met on July 12, 2012 to discuss the need for a neurotoxicity screening battery and a 28-day inhalation study in rats to support the registered uses of norflurazon.

II. SUMMARY OF USE PROFILE & PREVIOUS RISK ASSESSMENT:

Norflurazon is a pyridazinone herbicide that controls germinating grasses and broadleaf weeds. Norflurazon is currently registered for use on the following agricultural commodities: alfalfa; asparagus; caneberries; citrus; cotton; cranberries; grapes; hops; nursery stock; pome fruits; soybeans; stone fruits; tree nuts; and non-crop areas such as outdoor industrial/construction areas, non agricultural rights-of-way, fence rows, hedgerows, and uncultivated areas/soils. There are no registered products containing norflurazon that are intended for homeowner use. A single application (i.e., one application per year) on nursery stock is permitted prior to emergence on weeds.

Norflurazon is available as liquid, granular and dry flowable formulations and may be applied using aerial, chemigation, and ground equipment, and also may be impregnated onto dry bulk fertilizers.

There is potential for short- and intermediate-term occupational exposure to norflurazon during handling (mixing, loading, and applying), or re-entry into previously treated areas. Based on the use pattern, long-term exposures (greater than 6 months) are not anticipated.

In the most recent risk assessment (M. Metzger, D282851, 05/06/2002) an oral point of departure (POD) was used for assessing risk via short-term inhalation exposure. The POD (10 mg/kg/day) is based on increased incidence of skeletal variations in the rabbit fetuses seen at the lowest observed adverse effect level (LOAEL = 30 mg/kg/day) in the rabbit developmental toxicity study. The POD for assessing chronic dietary risk and intermediate-term inhalation exposure is based on increased liver weights (absolute and relative), increased thyroid weights, and increased cholesterol in both sexes seen at the LOAEL of 4.77 mg/kg/day in the 6-month dog feeding study (NOAEL = 1.5 mg/kg/day). An acute POD was not selected for the general population because there were no observed effects attributable to a single dose. However, the POD for assessing acute dietary exposure of females 13-49 was based on increased incidence (on both a fetal and litter basis) of skeletal variations seen at the LOAEL (30 mg/kg/day) seen in the rabbit developmental toxicity study (NOAEL = 10 mg/kg/day). The uncertainty factors for risk assessment will be revisited during Registration Review of norflurazon.

The estimated acute dietary (food only) exposure estimate for female 13-49 years old resulted in a risk estimate that utilized 10% of the acute population adjusted dose (aPAD) at the 95th

percentile of the exposure distribution. The estimated chronic dietary (food only) exposure estimates resulted in a risk estimate that utilized 4% of the chronic population adjusted dose (cPAD) for the U.S. general population, and 11% of the cPAD for children (1-6 years old), the most highly exposed population subgroup. Drinking water levels of comparison (DWLOCs) were calculated and compared to estimated environmental concentrations (EECs) provided by EFED. However, the chronic surface water EEC exceeded the DWLOCs for all infants and the children population subgroups, indicating that risk levels exceed HED's level of concern (LOC) for the chronic dietary exposure scenario.

In support of the Registration Review of norflurazon, a re-assessment of worst-case occupational exposure scenarios was performed to obtain current MOEs (LOC = 100). Some occupational handler inhalation MOEs are of concern for the registered uses of norflurazon. Mixing/loading dry flowable norflurazon for chemigation application to citrus results in the highest short-term occupational inhalation exposure (MOE = 28) and highest intermediate-term occupational inhalation exposure (MOE = 5) and are of concern to HED. Short-term inhalation MOE estimates range from 28-900 and intermediate-term inhalation MOE estimates range from 5-135 for norflurazon.

III. STUDY WAIVER REQUESTS

a. Inhalation Study

Previously, the Office of Pesticide Programs (OPP) used a set of criteria to determine whether or not an inhalation study could be waived. These criteria considered the scientific information available for the chemical, including its: (1) degree of irritation and corrosivity; 2) volatility; 3) aerosol particle size; and 4) Acute Toxicity Category and extrapolated MOEs (e.g., MOEs 10 times higher than the target). In 2009, OPP developed an issue paper on risk assessment approaches for semi-volatile pesticides. As part of that issue paper, an analytical comparison was conducted of oral and inhalation experimental toxicology studies. In general, this analysis showed that the degree to which oral PODs were protective of potential inhalation toxicity varied. In many cases the oral POD was protective, but in some cases the inhalation PODs were significantly more sensitive. Currently, OPP uses a weight of the evidence (WOE) approach that builds upon OPP's experience using the criteria listed above and conclusions from the 2009 SAP. As approaches for route-to-route extrapolation continue to evolve and improve, OPP may incorporate additional considerations into the WOE analysis.

Inhalation exposure can be to vapors, droplets, and/or particles/dusts. The form of inhalation exposure is determined by a number of factors including physical-chemical properties, use pattern, and exposure scenarios. OPP's interim WOE approach considers:

1. **Physical-chemical properties:** Vapor pressure and Henry's law constant are key considerations with respect to the volatilization after sprays have settled. Norflurazon has a vapor pressure of $<1 \times 10^{-5}$ mmHg 25 °C. The Henry's law constant is 3.50×10^{-05} Pa $\cdot m^3 \cdot mol^{-1}$ at 25 °C. However, low vapor pressure and/or Henry's law constant does not preclude exposure to aerosolized droplets or particles/dusts.

2. **Use pattern & exposure scenarios:** Any application scenario that leads to inhalation exposure to droplets needs to be considered in the WOE analysis for an inhalation toxicology study waiver request. It is, however, acknowledged that airblast and aerial applications are more likely to lead to higher occupational handler inhalation exposure, particularly to droplets, and may contribute to spray drift. All occupational uses for norflurazon are either through handheld, aerial, or ground applications. Mixing/loading norflurazon for chemigation application to citrus results in the highest inhalation exposure to norflurazon.

3. **Margins of Exposure (MOEs):** The MOE estimates for inhalation scenarios were calculated using an oral toxicity study and should be considered in the WOE analysis for an inhalation toxicology study waiver request. In the past, OPP has used MOEs of approximately 10 times higher than the level of concern as a benchmark for granting waiver requests. The 2009 analysis suggests this approach is appropriate for most pesticides but not all. Using this interim WOE approach, MOEs from 10-100 times greater than the level of concern will be considered in combination with other factors discussed here. Occupational exposure estimates from norflurazon use result in several inhalation MOEs less than 100 and do not meet the waiver criterion. Mixing/loading dry flowable norflurazon for chemigation application to citrus results in the highest short-term occupational inhalation exposure (MOE = 28) and highest intermediate-term occupational inhalation exposure (MOE = 5), and are of concern to HED.

4. **Toxicity:** Norflurazon exhibits low acute toxicity via all routes of administration. Norflurazon is not an eye irritant and produces mild acute inhalation toxicity (Toxicity Category IV). Following an acute (4 hour) inhalation exposure (nose only), only secretory (excessive salivation, chromdacryorrhea, red nasal dischange, dried red or brown material on facial area) and respiratory (labored breathing and moist rales) effects were seen during or immediately after exposure; all of the effects abated thereafter. All rats were free of treatment-related signs after 3 days, and all survived until sacrifice.

   In rats, norflurazon was rapidly absorbed and eliminated via the urine (18.5%-28.4%) and feces (65.3%-79.5%) within 4 days post dose. The major target organs of repeated oral exposure to norflurazon are the liver, thyroid, and kidney. The POD (10 mg/kg/day) selected to estimate short-term inhalation exposure risks is based on increased incidence of skeletal variations in the rabbit fetuses seen at the LOAEL (30 mg/kg/day) in the rabbit developmental toxicity study. The skeletal variations were seen at doses lower than doses that produced maternal toxicity. The POD (1.5 mg/kg/day) selected to estimate intermediate-term inhalation exposure risks is based on increased absolute and relative liver weights in dogs of both sexes seen at the LOAEL (4.77 mg/kg/day) in the 6-month dog feeding study. There was an increased incidence of congestion/hemorrhage/dark macroscopic lesions in the lung in male rats was seen at 1025 ppm (51 mg/kg/day) following 104 weeks of dietary exposure in the chronic toxicity/carcinogenicity study.

   In considering the need for an inhalation toxicity study, the Agency will evaluate other pesticides that share the same Mode of Action (MOA) and/or are in the same class. These pesticides can provide important information with respect to potential inhalation toxicity. Specifically, if other similar pesticides show inhalation toxicity studies to be more sensitive, an inhalation toxicity study may be required regardless of MOE, depending on the exposure profile. Norflurazon

belongs to a class of pyridazinone herbicides that inhibit carotenoid synthesis. It also causes a progressive deterioration of the lamellae in chloroplasts and an almost complete prevention of the accumulation of the green chlorophyll pigment.

Acute inhalation toxicity data, but not subchronic inhalation toxicity data, were found on two other pyridazinone herbicides; flufenpyr-ethyl and pyrazon/chloridazon. In the flufenpyr-ethyl acute inhalation study, rales were seen in one male on day 0, in 2 males and 3 females on day 1, and in 2 males and 4 females on day 2. Decreased body weight was seen in 2 females during the first 3 days of the study, however all females gained weight thereafter. One rat per sex had dark red lungs. All rats survived until sacrifice on day 14. (LC = >5 mg/L; Toxicity Category IV). In the pyrazon/chloridazon acute inhalation study, irregular respiration was seen at 2-4 hours; respiration was accelerated in all rats from 15 minutes through 1 hour, then in half of the rats at 2 hours; and eyelid closure was seen in all rats from 1 hour to 4 hours. All rats survived until sacrifice on day 14. (LC = $\geq$5.4 mg/L; Toxicity Category IV).

The HASPOC concludes, based on a weight of evidence (WOE) approach, that a 28-day inhalation toxicity study is required at this time. This approach considered all of the available hazard and exposure information for norflurazon, including: (1) the physical/chemical properties of norflurazon, including its potential to volatilize (<1 x 10^{-5} mmHg 25 °C vapor pressure); and (2) that many of the occupational handler inhalation scenarios result in risks of concern to HED using an ~~conservative,~~ oral endpoint. Therefore, a subchronic inhalation toxicity study is required for norflurazon to refine the risk estimates for occupational inhalation exposure.

b. Neurotoxicity Studies

Acute and subchronic neurotoxicity studies are required in the 2007 revised 40 CFR Part 158 Toxicology Data Requirements because they provide important scientific information on potential nervous system effects from pesticide exposure. These studies can provide data on a wide range of functional tests for evaluating neurotoxicity including sensory effects, neuromuscular effects, learning and memory and histopathology of the nervous system. The Agency acknowledges that there are no clear signs of neurotoxicity following acute, subchronic or chronic dosing in multiple species in the norflurazon database. However, the Agency also notes that the existing guideline studies are inadequate in their assessment of behavioral effects and do not use optimal methods to evaluate the potential toxicity to the nervous tissue structure and function.

With respect to considering whether the acute and subchronic neurotoxicity studies should be required as part of registration review, the HASPOC used a WOE approach:

- **Evidence for neurotoxicity in the norflurazon database of toxicology studies:** There are no clear signs of neurotoxicity following subchronic or chronic dosing in multiple species in the norflurazon database. The toxicity profile of norflurazon shows that the principal toxic effects are changes in the liver, thyroid, and kidney following repeated oral dosing. Liver, developmental, and body weight effects provide the basis for the PODs used for overall risk assessment (NOAELs of 1.5-10 mg/kg/day for repeat exposures). The dog was the most sensitive species with respect to liver effects following norflurazon exposure. In the 2-

generation reproduction study in rats, clinical signs possibly suggestive of a neurotoxic effect were observed in F0 males only: lethargy (1 F0 male), ataxia (2 F0 males), prostration (1 F0 male), and hyperreflexia (4 F0 males at 1500 ppm and 750 ppm).

- **Evidence for neurotoxicity in the database of toxicology studies for other pyridazinone herbicide pesticides:** Acute neurotoxicity studies were not available for flufenpyr or pyrazon/chloridazon; and no neurotoxic effects were noted in either chemical's database. Thus, the totality of available information indicated that there is low concern for neurotoxicity for this class of chemicals.

- **Risk assessment considerations:** The available data indicate that neurotoxicity is not the most sensitive endpoint for norflurazon, and the POD used for overall risk assessments would be protective of any potential neurotoxicity.

Therefore, based on a WOE approach considering all the available hazard and exposure information for norflurazon, the HASPOC concludes that acute and subchronic neurotoxicity studies are not required at this time. This approach considered all of the available hazard and exposure information for norflurazon, including: (1) the lack of neurotoxicity and neurobehavioral effects seen in the norflurazon toxicity database; (2) the liver, thyroid, and kidneys are the primary target organs of norflurazon toxicity, and liver, developmental, and body weight effects provide the basis for the most sensitive PODs for risk assessment; and (3) because of the low acute dietary exposure, unacceptable dietary risks would result only if the acute neurotoxicity study results in an acute dietary POD significantly lower than 1.0 mg/kg/day that would be used for the most highly exposed subpopulation, children 1-6. However, the toxicity profile of norflurazon does not indicate that the acute neurotoxicity would yield such a low POD (<1 mg/kg/day) because in order to elicit adverse neurotoxicity high dose levels will be tested in the acute neurotoxicity.

IV. HASPOC RECOMMENDATIONS:

Based on a WOE approach considering all the available norflurazon hazard and exposure information, the HASPOC concludes that a 28-day day inhalation study is required. However, acute and subchronic neurotoxicity studies are not required for norflurazon at this time.