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

OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

MEMORANDUM

Date: May 12, 2015

SUBJECT: Chlorimuron-ethyl: Tier I Review of Human Incidents for Draft Risk Assessment

PC Code: 128901
Decision No.: 502175
Petition No.: NA
Risk Assessment Type: NA
TXR No.: NA
MRID No.: NA

DP Barcode: D426223
Registration No.: NA
Regulatory Action: NA
Case No.: NA
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Summary and Conclusions

Chlorimuron-ethyl was previously reviewed in 2010 (K. Middleton et al., 08/19/2010, D380339). At the time, there were no incidents reported for the single chemical chlorimuron-ethyl only in Main IDS and three incidents reported to Aggregate IDS from January 1, 2000 to May 25, 2010. In addition, there two cases reported for chlorimuron-ethyl to NIOSH SENSOR-Pesticides from 1998 to 2007. Upon review of these incidents, it was concluded that "Based on the low frequency and severity of incident cases, there does not appear to be a concern at this time that would warrant further investigation."

The current IDS analysis from January 1, 2010 through March 10, 2015, shows one incident reported involving chlorimuron-ethyl in Main IDS involving multiple chemicals and six incidents reported to Aggregate IDS. There were no single chemical incidents reported to IDS. The query of SENSOR-Pesticides 1998-2011 identifies the same two cases, both involving multiple active ingredients, that were previously identified in 2010.

Based on the low frequency and mostly low severity of incident cases reported for chlorimuron-ethyl in both IDS and NIOSH SENSOR-Pesticides, there does not appear to be a concern at this time that would warrant further investigation. Several initial investigations within the AHS have made an epidemiological risk estimate of the association between chlorimuron ethyl and various anatomical cancer endpoints; however, these cancer sites were either not related to use of chlorimuron ethyl (prostate or lung cancers, NHL, and cutaneous melanoma), or the association measured was non-statistically significantly modest in size (<1.5) (breast, colorectal, pancreatic cancers). The Agency will continue to monitor the incident information and if a concern is triggered, additional analysis will be conducted.

Detailed Review

I. ACTION REQUESTED

Chlorimuron-ethyl are being considered under the FQPA-mandated Registration Review program established to review, on a 15 year cycle, pesticides for which a Re-registration Eligibility Decision has been made. One component of the Agency's Registration Review Program is consideration of human incident data. In conjunction with a human health risk assessment based on other data sources, such human incident data can assist the Agency in better defining and characterizing the risk of pesticides/pesticide products.

Reports of adverse health effects allegedly due to a specific pesticide exposure (*i.e.*, an "incident") are largely self-reported and therefore, generally speaking, neither exposure to a pesticide or reported symptom (or the connection between the two) is validated or otherwise confirmed. Typically, causation cannot be determined based on incident data. However, incident information can be an important source of feedback to the Agency: incidents of severe outcome, or a suggested pattern or trend among less severe incidents, can signal the Agency to further investigate a particular chemical or product. Observational epidemiology studies relate the risk of disease, *e.g.*, cancer, and exposure to an agent such as a pesticide product in the general population or specific sub-groups like pesticide applicators.

II. BACKGROUND

Chlorimuron-ethyl is a sulfonylurea class herbicide with a mode of action of inhibiting acetolactate synthatase. Chlorimuron-ethyl controls grasses and broadleaf weeds. Chlorimuron-ethyl is registered for use on soybeans, field corn, peanuts, low growing berries and non-crop areas such as fence rows and roadsides. Soybean is the predominant agricultural usage. There are no registered residential uses for chlorimuron-ethyl methyl.

For this evaluation, both OPP Incident Data System (IDS) and the Centers for Disease Control and Prevention/National Institute for Occupational Safety and Health (CDC/NIOSH) Sentinel Event Notification System for Occupational Risk-Pesticides (SENSOR) databases were consulted for pesticide incident data on the active ingredient chlorimuron-ethyl (PC Code: 128901). The purpose of the database search is to identify potential patterns in the frequency and severity of the health effects attributed to chlorimuron-ethyl exposure.

In addition, findings from the Agricultural Health Study (AHS) were reviewed. The AHS is a high quality, prospective epidemiology study evaluating the link between pesticide use and various health outcomes including cancer. Chlorimuron-ethyl is included in the AHS and the findings are summarized in this report.

III. RESULTS/DISCUSSION

a. IDS (Incident Data System)

OPP's IDS includes reports of alleged human health incidents from various sources, including mandatory Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) Section 6(a)(2) reports from registrants, other federal and state health and environmental agencies, and individual consumers. Since 1992, OPP has compiled these reports in IDS. IDS contains reports from across the U.S. and most incidents have all relevant product information recorded. Reports submitted to the IDS represent anecdotal reports or allegations only, unless otherwise stated in the report.

IDS records incidents in one of two modules: Main IDS and Aggregate IDS:

- Main IDS contains incidents resulting in higher severity outcomes and provides more detail with regard to case specific. This system stores incident data for death, major and moderate incidents, and it includes information about the location, date and nature of the incident. Main IDS incidents involving only one pesticide are considered to provide more certain information about the potential effects of exposure from the pesticide.

- Aggregate IDS contains incidents resulting in less severe human incidents (minor, unknown, or no effects outcomes). These are reported by registrants only as counts in what are aggregate summaries.

From January 1, 2010 to March 18, 2015, there were no incidents reported to Main IDS involving the single active ingredient, chlorimuron-ethyl. There was one incident reported to Main IDS, involving multiple active ingredients including chlorimuron-ethyl, thifensulfuron-methyl, flumioxazin, s-metolachlor, and sodium salt of fomesafen. This incident involved a 54 year male who died five days following inhalation exposure to two products (Registration numbers 100-1268 and 352-756). He was loading the products into a truck and it blew back into his face. His initial symptoms included fever, no appetite, body aches, and difficulty walking which were followed by renal failure, and hypovolemic shock. The patient required intubation, but eventually died. The radiologist's reading of the case's chest x-ray indicated "suspicious for multi-lobular pneumonia." No autopsy was conducted and causation cannot be determined based on the incident data provided.

From January 1, 2010 to March 18, 2015, there were six incidents reported to Aggregate IDS involving chlorimuron-ethyl. These incidents were classified as minor severity. Overall there were few incidents reported to IDS involving chlorimuron-ethyl.

b. SENSOR-Pesticides

The SENSOR-Pesticides database covers 12 states from 1998-2011, although reporting varies from state to state. Cases of pesticide-related illnesses are ascertained from a variety of sources, including: reports from local Poison Control Centers, state Department of Labor workers' compensation claims when reported by physicians, reports from State Departments of Agriculture, and physician reports to state Departments of Health. Although both occupational and non-occupational incidents are included in the database, SENSOR focuses on occupational pesticide incidents, and is of particular value in providing that information. A state SENSOR contact specialist attempts to follow-up with cases and obtains medical records to verify symptoms, circumstances surrounding the exposure, severity, and outcome. Using standardized protocol and case definitions derived from poison center reporting, SENSOR coordinators at State Departments of Health enter the incident interview description provided by the case, medical report, physician and patient into the SENSOR data system. The SENSOR data system is accessible to participating states and EPA.

A query of SENSOR-Pesticides from 1998-2011 identifies a total of two cases involving chlorimuron (pc code 128901); no single ai cases were identified. Both cases were low in severity. One case experienced dermal irritation and redness and the other case was a bystander in his car who saw and was sprayed by an aerial application and reported cough and headache.

c. Agricultural Health Study (AHS)

The AHS is a high quality, prospective epidemiology study evaluating the link between pesticide use and various health outcomes including cancer. The AHS includes private and commercial pesticide applicators and their spouses. If there are AHS findings relevant to a particular pesticide going through registration review, the Agency will ensure they are considered in the problem formulation/scoping phase of the process and, if appropriate, fully reviewed in the risk assessment phase of the process. The AHS includes information on use of 50 different pesticide active ingredients commonly used in agriculture.

Authors with the AHS have reported risk estimates regarding the association between chlorimuron-ethyl and several specific anatomical cancer sites. In nested case control analyses of breast, colorectal and pancreatic cancer, authors estimated the association between chlorimuron ethyl and cancer. Regarding breast cancer, among 30,434 wives of AHS applicators there were 309 cases. Chlorimuron-ethyl use modestly non-statistically significantly increased the odds of breast cancer by 30% (1.3 (95% confidence interval (95% CI) 0.6, 2.8), among only 7 chlorimuron-ethyl exposed cases (Engel et al., 2005). In a study of pancreatic cancer risks, ever use of chlorimuron-ethyl was related to a 40% increased odds of pancreatic cancer (1.4 (95% CI 0.7, 3.0), among 11 exposed cancer cases (Andreotti et al., 2009). Among 56, 813 AHS applicators, there were 305 cases of colorectal cancer; however, use of chlorimuron-ethyl was not related to this cancer (0.80 (95% CI 0.6, 1.2)) (Lee et al., 2007). Overall, from these preliminary, hypothesis generating studies within the AHS, chlorimuron-ethyl is not strongly linked to these anatomical cancer sites. For other anatomical cancer sites evaluated within the AHS including prostate, lung, non-Hodgkin lymphoma and cutaneous melanoma, authors did not present an epidemiological risk estimate for chlorimuron-ethyl because a risk estimate with this compound was not calculated (too few exposed cases) or not presented (Alavanja et al., 2004; Alavanja et al., 2014; Alavanja et al., 2003; Dennis, Lynch, Sandler, & Alavanja, 2010; Koutros et al., 2013).

Hoppin et al. (2002) evaluated the association between agricultural pesticide use and wheeze among 20,468 applicators within the AHS. Using self-reported information concerning pesticide use and physician diagnosis of wheeze, authors reported a significantly increased odds of wheeze among chlorimuron-ethyl users (1.14 (95% CI 1.02, 1.29), p for trend 0.01 across four exposure categories. Several other pesticides were also related to this outcome; however the plausibility for a role of this chemical in adverse respiratory outcomes remains unclear.

IV. CONCLUSION

Based on the low frequency and mostly low severity of incident cases reported for chlorimuron-ethyl in both IDS and NIOSH SENSOR-Pesticides, there does not appear to be a concern at this time that would warrant further investigation. Several initial investigations within the AHS have made an epidemiological risk estimate of the association between chlorimuron ethyl and various anatomical cancer endpoints; however, these cancer sites were either not related to use of chlorimuron ethyl (prostate or lung cancers, NHL, and cutaneous melanoma), or the association measured was non-statistically significantly modest in size (<1.5) (breast, colorectal, pancreatic cancers). The Agency will continue to monitor the incident information and if a concern is triggered, additional analysis will be conducted.

Citations:

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