September 6, 2011

Cynthia Oshita
California Environmental Protection Agency
Office of Environmental Health Hazard Assessment
1001 I Street
Sacramento, California 95814

RE: Nichino America, Inc. Comments on Pyraflufen-Ethyl in regards to
Prioritization: Chemicals for Consultation by the Carcinogen Identification
Committee [7/22/11]

Dear Ms. Oshita:

Nichino America, Inc. appreciates the opportunity to provide comments with respect to the chemical pyraflufen-ethyl and its consideration and review by the Proposition 65 Carcinogen Identification Committee (CIC). Nichino believes that pyraflufen-ethyl should not be prioritized as a chemical for further review by OEHHA for possible preparation of hazard identification materials for the reasons that are listed below. Pyraflufen-ethyl is an herbicide used for broadleaf weed control of glyphosate and ALS-resistant weeds in corn, soybeans, and wheat and as a defoliant/desiccant on cotton. Pyraflufen-ethyl is an excellent tool used in agriculture in the state of California.

Nichino proposes that pyraflufen-ethyl not be prioritized for OEHHA action based on the following considerations:

1. Very Limited Worker/Consumer Exposure
   - Very low application rate and very low total use of the chemical in California based on California use-reporting data.
   - The maximum single application rate for pyraflufen-ethyl for weed control is 0.0053 lb. active ingredient per acre with a seasonal maximum of 0.009 lb. active ingredient per acre.
   - Very low amount (lbs.) used in all of California

   o Listed below are the pounds of pyraflufen-ethyl applied in California for the last 5 reported years (Pesticide Use Report Data Indexed by Chemical) as well as the total acres treated.

<table>
<thead>
<tr>
<th>Year</th>
<th>Lbs.</th>
<th>Acres</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td>728</td>
<td>142,845</td>
</tr>
<tr>
<td>2008</td>
<td>847</td>
<td>212,506</td>
</tr>
<tr>
<td>2007</td>
<td>1,026</td>
<td>292,443</td>
</tr>
<tr>
<td>2006</td>
<td>1,428</td>
<td>362,964</td>
</tr>
<tr>
<td>2005</td>
<td>4,624</td>
<td>332,511</td>
</tr>
</tbody>
</table>

   - Virtually no residential exposure to pyraflufen-ethyl in California. In 2009, the last year the Pesticide Use Report Data was provided, only 1.86 pounds of
pyraflufen-ethyl was used for landscape maintenance. Thus, turf use of pyraflufen-ethyl is not a concern in California.

2. Quick Degradation of pyraflufen-ethyl in the environment, with low likelihood of mobility or persistence
   - Half-life in soil is less than 1 day
   - No evidence of mobility in field soil dissipation studies
   - No detects in groundwater

3. Mammalian toxicity
   - Carcinogenicity (discussed in more detail below)
     - Evidence of carcinogenicity is limited to the mouse, with liver toxicity at the LOAEL of 98 mg/kg/day.
     - No evidence of tumors in the rat
     - EPA classified pyraflufen-ethyl as a likely human carcinogen based on increased incidence of hepatocellular tumors (benign adenomas) in male and female mice.
     - There are no metabolites that have carcinogenic activity
     - Not mutagenic or genotoxic
     - Preliminary evidence of peroxisome proliferation resulting in benign liver tumors.
   - Acute
     - Low acute toxicity
     - No acute dietary exposure assessment conducted by EPA since there is no single acutely toxic dose with relatively low toxicity following single, oral, dermal, and inhalation exposure
   - Endocrine
     - No hormonal disruption activity in subchronic or chronic carcinogenicity studies
   - Neurotoxicity
     - No concerns for neurotoxicity or developmental neurotoxicity, since the chemical is not an organophosphate or carbamate. No evidence of neurotoxicity in any of the studies conducted for registration.
   - Children
     - No increased evidence of increased susceptibility following pre-natal exposures to rats and rabbits and pre- and post-natal exposure to rats

4. Rat and Mouse Oncogenicity
   - Rat
     - Pyraflufen-ethyl was administered in the diet to groups of 70 CR:CD rats/sex/dose at dose levels of 0, 80, 400, 2000, and 10,000 ppm (3.4, 17.2, 86.7, 468.1 mg/kg/day for males and 0, 4.4, 21.8, 111.5, and 578.5 mg/kg/day for females for 24 months.

     - The NOEL was 2,000 ppm (86.7 and 111.5 mg/kg make and female, respectively) with a LOAEL of 10,000 ppm (468.1 and 578.5 mg/kg male and female, respectively) based on reduced body weight with liver and kidney toxicity.
The US EPA Carcinogen Assessment Review Committee (CARC) stated there were no treatment-related increases in any tumors in male or female rats.

- **Mouse**
  - Pyraflufen-ethyl was administered in the diet to groups of 60 (SPF) ICR (Crl:CD-1) mice/sex/dose at dose levels of 0, 200, 1000, or 5000 ppm (0, 20.99, 109.7 and 546.8 mg/kg/day for males and 0, 19.58, 98.3 and 523.7 mg/kg/day for females for 18 months.
  - The CARC concluded that there were statistically significant increases in hepatocellular adenomas in male mice at 1000 (non-statistical but above historical control value) and 5000 ppm and in females at 5000 ppm. Although there was an increase in combined adenomas and carcinomas, there were no treatment-related increases in hepatocellular carcinomas.
  - Incidence table

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Control</th>
<th>200 ppm</th>
<th>1000 ppm</th>
<th>5000 ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Male</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenomas</td>
<td>16/47 (34%)</td>
<td>12/48 (25%)</td>
<td>24/44 (55%)</td>
<td>31/47 (66%)</td>
</tr>
<tr>
<td>Carcinomas</td>
<td>1/47 (2%)</td>
<td>1/48 (2)</td>
<td>2/44 (5%)</td>
<td>1/47 (2%)</td>
</tr>
<tr>
<td>Hepatoblastoma</td>
<td>0/47 (0%)</td>
<td>0/48 (0%)</td>
<td>1/44 (2%)</td>
<td>1/47 (3%)</td>
</tr>
<tr>
<td>Combined</td>
<td>17/47 (36%)</td>
<td>12/48 (25%)</td>
<td>25.44 (57%)</td>
<td>33/47 (70%)</td>
</tr>
<tr>
<td>Laboratory</td>
<td>Adenoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>historical</td>
<td>Mean 28.6%</td>
<td>Carcinoma</td>
<td>Mean 6.9%</td>
<td>Huntingdon; 9</td>
</tr>
<tr>
<td></td>
<td>Range 13.5 -</td>
<td></td>
<td>Range 0-21.2%</td>
<td>studies from 1991 - 1995</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenomas</td>
<td>1/48 (2%)</td>
<td>0/46 (0%)</td>
<td>1/41 (2%)</td>
<td>16/48 (33%)</td>
</tr>
<tr>
<td>Carcinomas</td>
<td>0/48 (0%)</td>
<td>0/46 (0%)</td>
<td>0/41 (0%)</td>
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<td>Laboratory</td>
<td>Adenoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>historical</td>
<td>Mean 2%</td>
<td>Carcinoma</td>
<td>Mean 0%</td>
<td>Huntingdon; 9</td>
</tr>
<tr>
<td></td>
<td>Range 0-6.5%</td>
<td></td>
<td>Range 0-0%</td>
<td>studies from 1991 - 1995</td>
</tr>
</tbody>
</table>

- All tumors that were treatment-related were benign hepatoadenomas.
- There is a clear threshold in both male and female mice of 200 ppm.
o Mouse hepatocellular adenoma is a very common tumor with a high background incidence. Mouse liver tumors are also very commonly treatment induced.

o No other treatment-related tumors in any other tissue were observed.

- Mechanistic data
  - Non-Genotoxic: CARC concluded pyraflufen-ethyl was non-genotoxic in all studies conducted (reverse gene mutation assay in bacteria, mammalian cell gene mutation assay in mouse lymphoma cells, mammalian cell cytogenetics assay in human lymphocytes, mouse bone marrow micronucleus assay and unscheduled DNA synthesis (UDS) assay.
  - Mode of action studies
    i. Mice fed 0, 200, 1000, 5000, and 10,000 ppm for 7 days showed an increase in B-oxidation and a decrease in catalase activity in the liver that contributed to the increase in lipid peroxide. This coincided with the induction of hepatocellular necrosis in mice fed 5000 ppm of pyraflufen-ethyl in the diet.
    ii. A study on hepatic drug-metabolizing enzymes showed liver enlargement did not involve induction of hepatic drug-metabolizing enzymes by a single dose but following 28-day exposure showed inhibition. With some enzymes inhibited possibly due to the inhibition of heme synthesis that was the result of diminished heme incorporation into cytochrome P-450.
    iii. Hepatocyte proliferative activity was measured by immunohistochemical (PCNA) staining in the 18 month oncogenicity study. Hepatocyte proliferation (mean PCNA labeling cells) in males at 1000 ppm increased by about 317% and 1250% of control after 13 and 78 weeks, respectively. In females the proliferation was about 490% and 780% of controls at 13 and 78 weeks, respectively. In animals receiving 5000 ppm the PCNA was 475% and 1900% of the male control group and 1150% and 1810% of the female control group at 13 and 78 weeks, respectively. The CARC concluded increased hepatocyte proliferation as a result of treatment-related liver toxicity was suggested as the likely mechanism for the increased induction of hepatocellular adenomas in the mid- and high-dose males and in high-dose females.
    iv. A study evaluating serum AST and ALT liver activity showed no correlation between hepatocellular necrosis or cell proliferation.
    v. The CARC discussed the mechanism of liver tumor induction by pyraflufen-ethyl and felt that although peroxisome proliferation could be part of the mechanism for liver tumor formation, such a mechanism has not been proven directly, but only indirectly.

In conclusion, only benign liver tumors were observed in mice and were not seen in rats. Pyraflufen-ethyl is non-genotoxic suggesting a non-genotoxic mechanism. Preliminary data suggests that liver necrosis followed by proliferation induction was linked to peroxisome proliferation. All EPA cancer risk assessments demonstrated acceptable levels of cancer risk. No residential or bystander exposure is anticipated in California. Pyraflufen-ethyl does not present a
carcinogenic hazard at the low exposure levels estimated by the low usage of the chemical in California.

Based on the provided information, Nichino appreciates the Committee considering pyraflufen-ethyl not being prioritized as a chemical for further review by OEHHA for possible preparation of hazard identification materials.

If you have any questions on this matter, I can be reached by telephone at (302) 636-9001 x229 or by email at tformella@nichino.net.

Sincerely,

Timothy M. Formella
Senior Manager, Regulatory Affairs

CC: Jay Schreider, CDPR, Medical Toxicology Branch