Dear Ms. Oshita;

Dow AgroSciences is pleased to submit comments to the Proposition 65 Cancer Identification Committee (CIC) on whether a high priority for preparation of hazard identification materials and future consideration as a carcinogen is justified for ethalfluralin.

Although ethalfluralin is a dinitroanaline (DNA) compounds, we request that the CIC consider and prioritize these active ingredients separately rather than as a group. As required under federal law, the US EPA has evaluated whether to consider the carcinogenic potential of structurally similar compounds as cumulative (related). Accordingly, in recent decisions by the EPA where these potential cumulative impacts have been considered, the EPA has concluded that DNA compounds should be considered separately, not cumulatively, regarding their carcinogenic potential.

All the information available from animal research demonstrates that ethalfluralin has not been “...clearly shown through scientifically valid testing according to generally accepted principles to cause cancer” as stated by The Safe Drinking Water and Toxic Enforcement Act of 1986. There were no treatment related effects in long term male or female mouse studies or in male rats. Mammary tumors were seen only in female rats, were non invasive, spontaneous, strain and species specific, high control incidence with no biological significance to humans.

Ethalfluralin is not mutagenic. Therefore, ethalfluralin would not qualify for a high priority for future consideration of listing under Proposition 65.

Enclosed please find the following comments for ethalfluralin:

- Dow AgroSciences’ Comments on CIC’s Prioritization of Ethalfluralin for Listing Under Proposition 65 as a Carcinogen. S. Papineni. 20 September 2011. 3 pp.

Thank you for your consideration of these comments.

Brian L. Bret

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Summary: Dow AgroSciences, as the lead registrant for ethalfluralin, is pleased to provide the Carcinogen Identification Committee (CIC) with our comments to assist in your process of prioritizing these chemicals for future consideration under Proposition 65. Our comments are summarized as follows:

Ethalfluralin has a complete toxicology data set as required for pesticide registration of a molecule under 40 CFR Part 158. All the information available from animal research demonstrates that ethalfluralin has not been “…clearly shown through scientifically valid testing according to generally accepted principles to cause cancer” as stated in the CIC guidance criteria. Therefore, ethalfluralin would warrant a “low priority” for future consideration of listing under Proposition 65.

Carcinogenic potential of ethalfluralin:

Long term two year studies were conducted both in rats and mice evaluating the carcinogenic potential. No treatment related findings were observed in mouse long term study (1). Increase in benign mammary tumors was observed in Fischer rat study in female rats only (Table 1.) (2).

<table>
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<th>Dose %</th>
<th>0.0</th>
<th>0.01 (4.2 mg/kg/day)</th>
<th>0.025 (10.7 mg/kg/day)</th>
<th>0.075 (32.3 mg/kg/day)</th>
</tr>
</thead>
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<tr>
<td>Ratio</td>
<td>13/60</td>
<td>11/60</td>
<td>25/60</td>
<td>29/60</td>
</tr>
<tr>
<td>Percent</td>
<td>21.7</td>
<td>18.3</td>
<td>43.3</td>
<td>48.3</td>
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<tr>
<td>Z-statistic</td>
<td>--</td>
<td>-.46</td>
<td>+2.38</td>
<td>+3.12</td>
</tr>
</tbody>
</table>

USEPA: Reregistration Eligibility Decision(RED) (1995) and Memorandum (1994) (1,3):

US EPA, in their recent summary indicated ethalfluralin as low level of concern by concluding it as Group C, a “possible” human carcinogen, not “known”, “likely” or “probable” carcinogen and, accordingly, it has not been considered previously under Proposition 65.

USEPA also conducted a recent human health risk assessment in Nov 2007 and stated that the calculated cancer risk for ethalfluralin falls below the benchmark level, estimated cancer risk is considered to be below the level of concern.

Non-human relevance of Mammary fibroadenomas:

The apparently increased incidence of this very benign neoplasm, which is common in the Fischer 344 female with a wide variation in incidence reported in the literature, was probably of no biological significance for the following reasons:

- The mammary fibroadenoma is a commonly occurring “benign” neoplasm in the Fischer 344 rat.
- There was no difference in the morphologic appearance between the control and treated groups, and the “latency period was not affected”.
- The tumors were observed “only in females and not in males”.
- The incidence of malignant mammary neoplasms was not increased; and
- There was “no effect on the well-being or survival of the rats”.
- NTP spontaneous control incidences in this strain reported up to 60% (5, 6).
- The background incidence of this benign tumor has “wide variability” and increases quite rapidly in a lifetime study to 57% (6).
- Additionally, ethalfluralin has “no mutagenic potential” in a study of induction of DNA repair synthesis, in a modified Ames test, or in a dominant lethal study in the rat.

Conclusion:

In conclusion, the mammary fibroadenomas evaluated according to the generally accepted principles by CIC identifies them as non invasive, spontaneous, strain and species specific, high control incidence tumors observed only in female Fischer rats with no biological significance to humans. In addition, the doses at which these are observed are way beyond the exposure levels and therefore very unlikely to pose any cancer risk to humans. Based on all the weight of evidence available, ethalfluralin should be given a “low priority” for future consideration by CIC.

References


