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 benfluralin (benfyn).

Although benfluralin is a dinitroanaline (DNA) compound, we request that the CIC consider and prioritize the DNA compounds separately rather than as a group. As required under federal law, the US EPA evaluates 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.

There is overwhelming weight of evidence from animal studies combined with mechanistic data that clearly fail to support the listing of benfluralin under proposition 65 as a carcinogen. Studies were equivocal across species and sexes. Liver and thyroid follicular cell tumors in male F344 rats were observed only at the higher doses where there was a clear exceedance of the MTD. The results of the mechanistic study demonstrates that benfluralin acts through a mode of action that are not relevant to humans, do not pose a cancer risk to humans, and should not be proposed to be listed under proposition 65 as human carcinogen. Thus benfluralin would not qualify as a high priority for cancer assessment.

Enclosed please find the following comments for benfluralin:

- Dow AgroSciences’ Comments on CIC’s Prioritization of Benfluralin for Listing Under Proposition 65 as a Carcinogen. S. Papineni. 20 September 2011. 4 pp.

Thank you for your consideration of these comments.

Brian L. Bret

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Summary:

Dow AgroSciences, as the lead registrant for benfluralin, 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:

Benfluralin has a complete toxicology data set as required for a pesticide registration under 40 CFR Part 158. There is overwhelming evidence from animal research including mechanism of action studies to demonstrate that trifluralin 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.

Therefore, we believe that benfluralin takes a “low” priority for future consideration of listing under Proposition 65.

Carcinogenic potential of Benfluralin:

Two long-term studies were conducted in rodents to evaluate the carcinogenicity potential of benfluralin. Liver (males only) and thyroid tumors (females and males) were identified in the rat study (1) and a border line increase in liver tumors were observed in female mice only (2).

US EPA memo 2004 (3)

Benfluralin has been assessed extensively by CARC in 2004 and was classified into the category “suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential”. (emphasis added)

Thus, US EPA concurs that benfluralin is not “known to be” or “probable” carcinogenic in humans and indicated the compound to be a low level of concern, fully consistent with our summary, and consistent with all other authorities that have assessed the potential carcinogenicity of benfluralin.

EFSA provided its conclusion regarding the peer review of the pesticide risk assessment of the active substance benfluralin on 03 March, 2008 and indicating the following with regards to its carcinogenicity potential:

“Based on rats’ thyroid tumours and liver tumours observed in both rats and mice, a classification as category 3 carcinogen is proposed for benfluralin leading to the following symbol and risk phrase: Xn; R40 “limited evidence of a carcinogenic effect”.

Thus, EFSA concurs with the USEPA’s evaluation of benfluralin carcinogenicity by giving it a lowest level of cancer classification a molecule can obtain. Additional mode of action (MOA) data as discussed in detail above was generated after USEPA and EFSA’s review which clearly demonstrates the human non-relevance of the thyroid and liver tumors observed and thus was not a part of their assessment.

Scientific rationale combined with the mechanistic data to demonstrate the non-relevance of these tumors to humans as discussed below:

1) The liver and thyroid tumors in rat study were identified only at the two highest doses. However, these doses were considered excessive by Cancer Assessment Review Committee (CARC), the USEPA review committee and no tumors were observed at lower doses, which were considered adequate for cancer testing. As per the agency this study contributes little to the overall weight of evidence for a positive finding of carcinogenicity for benfluralin.

2) Female mice had a borderline statistically significant increase in liver tumors at doses that were adequate. No tumors were seen in the male mice. If there is an effect, it is marginal and only seen at the high-dose and accompanied by increased liver weight and hyperplasia, which are consistent with a phenobarbital-mediated MOA, which is a mechanism demonstrated as non-relevant to humans (5).

3) There was a lack of carcinogenic potential in rats, a lack of mutagenic potential in a battery of tests (2).

4) In addition Dow AgroSciences conducted a mechanistic study (6) which clearly demonstrates the non relevance of these tumors to humans as detailed in the following sections. The results of this mechanistic study demonstrate that benfluralin acts through a phenobarbital-like MOA CAR-mediated for the liver (6,7), and UGT-mediated for the thyroid (6,7). Identification of the early CAR-mediated and UGT-mediated key events at the carcinogenic dose, 5000 ppm, demonstrate that the liver and thyroid tumors seen in F344 rats after chronic exposure are not considered relevant to humans due to quantitative and qualitative differences. Detailed discussion is provided in the following sections.
Human Relevance Framework for the Mode of Action:

Liver Tumours: Phenobarbital (CAR) MOA (6,7):

The proposed MOA for the benfluralin-induced liver tumors in male F344 rats is phenobarbital-like (CAR) mediated. The data demonstrated that the carcinogenic dose of 5000 ppm triggered the key events for this MOA as follows:

- CAR activation as demonstrated by increased Cyp2b1 and Cyp2b3 expression
- increased PROD
- increased liver weight
- increased hypertrophy and increased cell proliferation
- preneoplastic hepatocytes and liver tumors reported in the chronic rat study (2).

Thyroid Tumours: UGT-Mediated Thyroid Tumor MOA (6,7):

The proposed MOA for the benfluralin-induced thyroid tumours in male F344 rats is UGT-mediated (4). The data demonstrated that the carcinogenic dose of 5000 ppm triggered the key events for this MOA. These key events occur readily in rats (especially males), but not in humans because of the presence of the thyroxine-binding globulin (TBG) protein (not present in rats) that prevents the excretion of thyroid hormones (8).

The responses observed in the study support CAR- and UGT-mediated MOAs for the observed benfluralin-induced liver and thyroid tumors, respectively, both of which have little to no relevance to humans.

Conclusion:

The existing database on the potential carcinogenicity of benfluralin, and its relevance to humans is robust. The mode of action of the thyroid tumors is rodent-specific and liver tumors is related to phenobarbital-like mode of action; and are not considered to be relevant to humans. Thus benfluralin should be of a “low priority” for future consideration and an evaluation by the CIC under Proposition 65’s clearly shown standard would come to the same conclusion.

References:


4 EFSA (2008): Conclusion regarding the peer review of the pesticide risk assessment of the active substance Benfluralin. EFSA Scientific report. 127,1-82,


6 Stagg et al., 2010. Evaluation of the mode of action (MOA) for liver and thyroid tumors in male F344/DuCrI rats with benfluralin. Poster presented at Society of Toxicology, Baltimore, WA, March 2010. (Published Abstract).
