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TO: Board Members
FROM: Lebelle Hicks PhD DABT
RE: Toxicity Review of Tribenuron Methyl Active Ingredient in DuPont's Express Herbicide (EPA# 352-632)

August 28, 2008

Following the August 1, 2008, Board meeting discussion regarding the request for a 24(c) supplemental label for control of bunchberry in low bush blueberry culture a request was made to DuPont for a summary toxicological data for this product. Specific toxicological issues raised at the Board meeting included:

- The potential for effects on foraging mammals and the dose level where these effects would occur. This is stated on the MSDS as severe weight loss and decreased food consumption (**see 1st note on MSDS**)
- Carcinogenic potential of tribenuron methyl (**see 2nd note on EPA's cancer classification criteria**)
- Potential effects on bees (**see 3rd note on EPA's bee hazard label requirements**)

Tribenuron methyl

The active ingredient in DuPont's Express Herbicide (EPA# 352-632) is tribenuron methyl. It is a sulfonylurea herbicide that works in the plant by inhibiting the synthesis of the branch chain amino acids (WSSA 2002). The toxicological summary supplied by DuPont was reviewed. There were no deaths in the single dose median lethal dose test; (oral LD₅₀ in rats) using the EPA limit dose of 5000 mg/kg and 5 animals per sex, indicating that the LD₅₀ is greater than 5000 mg/kg.. Over the 14 day observation period, there was no weight loss observed in the males and three of the five female rats had a reduction in body weight (10 to 13%) by day 11. At the end of the 14 day period the final body weights for the females surpassed their fasting weights. There were no gross pathological lesions at necropsy (DuPont 2004). These data would account for the statement on the MSDS relating to single doses resulting in weight loss (**see note 1. below on MSDS sheets**).

In the subchronic (28 to 90 day studies) tribenuron methyl administered via oral gavage or diet in rats, and by diet in mice and dogs the effects reported at the lowest observable adverse effect level (LOAEL) were decrease body weight and/or nutritional effects. In addition effects on clinical chemistry and organ weights were observed at the LOAEL and higher doses. The rat was the most sensitive species with a no observable adverse effect level (NOAEL) of 7 mg/kg/day (males) and 8 mg/kg/day (females) (DuPont 2004).

In the chronic studies rats (2 yrs), mice (18 months) and dogs (1 yr) received tribenuron methyl in their diets on a daily basis. The rat was the most sensitive species with NOAELs of 0.95 mg/kg/day in males and 1.2 mg/kg/day in females. Effects at doses greater than the NOAEL

included body deficits and nutritional effects. An increase in mammary tumors was observed at 1,250 ppm (76 mg/kg/day) exposure level (Dupont 2004).

Risk to Foraging Animals

Tribenuron methyl is rapidly and extensively metabolized in soil (Roberts 1998) and in plants (Pesticide Manual 2003). This would indicate that exposure to foraging mammals and birds would be a subchronic exposure. Using standard risk assessment methodology, the NOAEL of 7 mg/kg/day from the subchronic study is divided by an uncertainty factor (UF) of 10 for interspecies extrapolation, a safety factor of 10 for intraspecies extrapolation. The resulting subchronic reference dose (RfD) for tribenuron methyl is 0.07 mg/kg/day.

The tolerance for tribenuron methyl in wheat is 0.1 mg/kg (feed). Dietary exposure at this tolerance level would result in the daily consumption 0.005 mg/kg/day in small mammals and 0.007 mg/kg/day for bobwhite quail. This assessment uses the conservative assumption that all of the plant material in the diet is wheat and that the wheat all has levels of tribenuron methyl at the tolerance level. With these assumptions subchronic dietary exposure is below the RfD, indicating acceptable risks.

EPA classifies tribenuron methyl as a “C” possible carcinogen based on limited animal evidence. Given that the increase in tumors was seen only at the highest dose tested, EPA has not recommended a quantitative cancer risk assessment for this compound (**see note 2. below in EPA’s cancer classification system for 1986 [EPA 2006]**).

Potential Bee Effects

The potential for impacts on bees did not appear on the MSDS for Express (MSDS 2006) or the section 3 label for Express (Express Label 2007). EPA’s Label Review Manual specifies that bee hazard statement must be on the label if the product contains ingredients in bee toxicity categories I or II (**see note 3. below on bee precautionary statements**). Tribenuron methyl has acute LD₅₀ of > 100 mg/bee placing it in bee toxicity category III and the label does not have to have bee precautionary language. The bee toxicity and the associated EPA bee toxicity categories of several insecticides and herbicides are summarized in Table 1.

Table 1. Bee Toxicity Information for Selected Insecticides and Herbicides			
Compound	Type	Bee LD₅₀	EPA Toxicity Category Bees
carbaryl	carbamate insecticide	1 ug/bee	I
beta-cyfluthrin	pyrethroid insecticide	< 0.1 ug/bee	I
2,4-D	chlorophenoxy herbicide	> 10 ug/bee	II or III
metsulfuron-methyl	sulfonylurea herbicide	> 44.3 ug/bee	III
tribenuron-methyl	sulfonylurea herbicide	> 100 ug/bee	III

Note 1. Material Safety Data Sheets (MSDS)

Material Safety Data Sheets (MSDS) are compiled as a requirement of the federal Occupational Safety and Health Administration (OSHA). OSHA is the agency responsible for the content of MSDS. Their rules require that any hazardous materials present at greater than 1% and carcinogens (as determined by the National Toxicology Program (NTP), International Agency for Research on Cancer (IARC), the Association of Governmental Industrial Hygienist (ACGIH) or OSHA) present in the formulations at greater than 0.1 % be reported on the MSDS [OSHA 1910.1200 d (5) (ii)]. **EPA cancer classifications are not considered by OSHA.** Because MSDSs are meant for workers, they do not attempt to summarize environmental exposures and characterize risks associated with those exposures.

Note 2. EPA Cancer Classifications (EPA 2006)

On EPA's most current list of compounds ranked for carcinogenic potential the more recent scheme (likely, not likely etc). is also used. The criteria for those classifications are also readily available.

1986 CLASSIFICATION

The following cancer classification scheme was first introduced in 1986. It was used until 1996.

GROUP A: HUMAN CARCINOGEN. This group is used only when there is sufficient evidence from epidemiologic studies to support a causal association between exposure to the agents and cancer.

GROUP B: PROBABLE HUMAN CARCINOGEN. This group includes agents for which the weight of evidence of human carcinogenicity based on epidemiologic studies is limited and also includes agents for which the weight of evidence of carcinogenicity based on animal studies is sufficient. The group is divided into two subgroups. **Group B1** is reserved for agents for which there is limited evidence of carcinogenicity from epidemiologic studies. **Group B2** is used for Agents for which there is sufficient: evidence from animal studies and for which there is inadequate evidence or no data from epidemiologic studies.

GROUP C: POSSIBLE HUMAN CARCINOGEN. This group is used for agents with limited evidence of carcinogenicity in animals in the absence of human data.

GROUP D: NOT CLASSIFIABLE AS TO HUMAN CARCINOGENICITY. This group is generally used for agents with inadequate human and animal evidence of carcinogenicity or for which no data are available.

GROUP E: EVIDENCE OF NON-CARCINOGENICITY FOR HUMANS. This group is used for agents that show no evidence for carcinogenicity in at least two adequate animal tests in different species or in both adequate epidemiologic and animal studies.

Note 3. Bees

The following excerpt is from EPA’s Label Review Manual regarding precautionary bee toxicity language:

If a pesticide is used outdoors as a foliar application, especially to crops, and is toxic to pollinating insects, a Bee Hazard warning must be included in the Environmental Hazards. 40 CFR56.10 (h)(2)(ii)(E). The toxicity categories for bees and the need for a precautionary statement are:

- Toxicity Category I: acute LD₅₀ of < 2 mg/bee; **Precautionary statement required**
- Toxicity Category II: acute LD₅₀ of > 2 micrograms/bee but < 11 mg/bee; **Precautionary statements required**
- Toxicity Category III Acute LD₅₀ > 11 mg/bee; **No precautionary statement is required**

REFERENCES	
Cited as	Reference
24c Label	Express Herbicide Proposed 24c label for control of Bunchberries in lowbush Blueberry culture DuPont 2008
DuPont 2004	Belcher, L. A., O’Neal, F. O., Tilbury, L.F., Ryan, D.L., and Donner, E.M. (2004) <i>Tribenuron Methyl, Active Substance Annex IIA: Section 3: Mammalian Toxicology; Summaries and Assessment Tier II- Document M-II Revision IA</i>
EPA 2003	Label Review Manual
EPA 2006	Carcinogenicity Classification of Pesticides; EPA April 2006
Express Label 2007	Express Herbicide Section 3 label (EPA# 352-632) (DuPont 2007)
MSDS 2006	Material Safety Data Sheet for Express Herbicide (DuPont 2006)
Pesticide Manual 2003	Pesticide Manual, 13 th edition. British Crop Protection Council (2003)
Roberts 1998	Roberts, T.R. (1998) <i>editor</i> Metabolic Pathways of Agrochemicals, The Royal Society of Chemistry
WSSA 2002	Herbicide Handbook