Fluometuron

The mouse oncogenicity study

Proposal to the Health Effects Division, US EPA to maintain the 24-month CD-1 mouse oncogenicity study (Burdock 1982b) Supplementary, while reserving the requirement for a new study.

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Executive Summary

Makhteshim Agan of North America, Inc. requests that the Agency place the repeat oncogenicity study of fluometuron in mice on reserve while maintaining the current oncogenicity study as Supplementary.

A repeat study will likely not affect the Agency's risk characterization of fluometuron for the following reasons:

The resulting Q_1*, if tumors evident, would likely be lower (i.e., show less risk) than the current Q_1* of 1.80×10^{-2}.

A negative study would likely not reverse the Agency's stance that fluometuron is a possible human carcinogen, Category C.

Fluometuron is applied only to cotton and its use rate is much reduced due, in part, to the increasing role of Roundup Ready™ cotton.

The current risk assessment by the Agency is conservative in that water exposure estimates are considered high and the Q_1* is relatively high. Using these data, the Agency will ensure the public is protected in a conservative way.

Additionally, placing the repeat mouse oncogenicity study on reserve, while maintaining the current study as Supplementary will facilitate the completion of the RED, scheduled for September 2005.

Introduction

The Agency has noted that a data gap exists for the oncogenicity study in mice with fluometuron[1]. (Goodis 2004; Reaves 2004)

The basis of this request is the determination that the Hazleton Laboratories America mouse oncogenicity study (Burdock 1982b), previously submitted to the Agency, was found inadequate, based on the modest toxicity induced by the highest dose tested (HDT), 2000 ppm. HED judged that mice could tolerate higher dose levels of fluometuron (Reaves 2004, 2005). Since OPPTS 870.4200b guideline requires adequate signs of toxicity at the high dose[2], Burdock (1982)[3] does not satisfy the data requirement for oncogenicity testing, as it remains classified Supplementary rather than Core Minimum.

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[1] IUPAC Name: 1,1-dimethyl-3-(ααα-trifluoro-m-tolyl)urea
CAS Name: N,N-dimethyl-N'-(3-(trifluoromethyl)phenyl)urea
CAS Number: 2164-17-2
PC Code: 035503
DP Barcode: D300553
Case Number: 0049
Tolerances: 40 CFR §180.229

[2] The HDT needs to reflect the characteristics of a Maximum Tolerated Dose, MTD.

[3] MRIDs 00163854, 42413501, and 43506601.

The oncogenicity study was initially judged adequate for carcinogenicity testing by EPA (McMahon and Ioannou 1991), noting that the MTD was 2000 ppm, based on decreased body weight gain in male and female mice during weeks 0-52 and weeks 0-104. Subsequently, the Agency found this weight gain decrease insufficient to support the high dose as an MTD (Taylor and Rinde 1996), a view that was confirmed by EPA's RfD Committee (Spencer and Burnam 1995; Taylor *et al.* 1995). Final evaluation of the study was deferred to the Cancer Peer Review Committee which agreed, by consensus, that the highest dose was too low for fully assessing the carcinogenicity of fluometuron in both sexes, based on comparable body weight gains in treated versus control animals and only slight clinical changes observed in both sexes (Taylor and Rinde 1996).

During this review process the registrant at that time, Ciba-Geigy, submitted a rebuttal to the Agency outlining the basis for concluding the HDT was sufficient (Breckenridge 1994). The Agency reviewed the arguments set forth but found them less than compelling (Spencer and Burnam 1995). These arguments, as reported by the Agency, included:

1) The registrant referenced an IBT 28 day feeding study, which used five animals/sex/dose and indicated that the body weights were slightly decreased at 10,000 ppm and above.

2) Also referenced was a six-week feeding study in mice completed by Hazelton Laboratories, which showed cyanosis in both sexes at 3000 ppm and above at the week 6 completion.

3) A 90-Day subchronic study was reference as completed by the NCI as a preliminary to chronic feeding studies in B6C3F1 mice. The study showed inhibited body-weight gains at 4000 ppm and above in both sexes.

4) The registrant also referenced and NCI 2-year bioassay in B6C3F1 mice using 500 or 1000 ppm feeding levels, which showed no toxicity but was equivocally positive for tumor increases at the top dose.

The Reregistration Eligibility Decision (RED) for fluometuron is scheduled for completion in September 2005 (US EPA 1998). The status of this mouse oncogenicity study will likely be included in the fluometuron RED. Makhteshim Agan of North America, Inc. understands that a formal request for a replacement study would issue as a DCI pursuant to the RED if the Agency judges this study as sufficiently important.

We ask that the mouse oncogenicity study be retained as Supplementary and that the need to initiate a replacement study be deferred at this time.

The Human Cancer Risk Characterization of Fluometuron

The Health Effects Division has classified fluometuron as a Category C carcinogen (possible human carcinogen) and calculated a Q_1^* of 1.80×10^{-2} (US EPA 2005). The Q_1^* is based on "statistically significant increases in combined adenomas/carcinomas of the lungs in male mice at the highest dose tested and malignant lymphocytic lymphomas in female mice at all dose levels" (Reaves 2005). The Agency also noted that

genotoxicity studies with fluometuron were negative (Reaves 2005).

Fluometuron's Q_1* is relatively high, compared to other upper bound carcinogen dose response slopes. As a consequence, the calculated cancer risk, based on estimated exposure levels, exceeds the Agency's level of concern[4].

The driver for human cancer risk includes the estimated exposure due to water consumption (both surface and ground water) and results from the environmental fate characteristics of fluometuron that promote its leaching and transport in water (e.g., water solubility of 105 ppm at 20 ^{o}C) (Ary *et al.* 2004).

The Agency has calculated the following human cancer risks for fluometuron:

Cancer Risk[5]	Dietary component
9.14×10^{-5}	Ground water, parent + major metabolite[6]
7.36×10^{-6}	Surface water, parent + major metabolite
9.27×10^{-5}	Food + ground water, based on exposure of 0.005147 mg/kg/day
8.58×10^{-6}	Food + surface water, based on exposure of 0.000476 mg/kg/day
1.22×10^{-6}	Food exposure alone (no water)

The Agency has noted that the significant cancer risk contributors are identified as water (direct, all sources and indirect, all sources) wheat (flour), soybean (oil), and rice (white) (Reaves 2004).

The possible outcomes of a new oncogenicity study in mice.
A replacement oncogenicity study in mice that targets a maximum tolerated dose, based on a new preliminary 90-day study, may (A): confirm that fluometuron is associated with tumors, currently noted as "equivocal" or (B): show the absence of tumors.

(A): A new study shows an association of fluometuron with tumors in mice.
Since the dose levels for the repeat study will exceed 2000 ppm, with intermediate doses likely higher, the resulting Q_1*, if tumors do result, may well be calculated at a lower value than is currently being used (that is, Q_1* for the new study would likely be less than 1.80×10^{-2}).[7] The resulting calculated cancer risk would approach and may no longer exceed the Agency's level of concern.

By example, using the relationship of Risk, Q_1*, and Exposure:

$$\text{Risk} = Q_1^* \times \text{Exposure},$$

Q_1* is calculated as:

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[4] EPA's level of concern for carcinogens is 1.0×10^{-6}; that is, an incidence of one in a million.

[5] Population Subgroup: General U.S. Population.

[6] CAG-41686, the demethylated fluometuron: 1-methyl-3-(α,α,α,-trifluoro-m-tolyl)urea.

[7] This assumes a comparable tumor pattern underlying the present Q_1* and is speculative for this discussion.

Q_1^* = Risk ÷ Exposure.

By example, for Food + Ground Water, where Exposure is 0.005147 mg/kg/day,
Risk = 0.018 $(mg/kg/day)^{-1}$ x 0.005147 mg/kg/day = 0.0000926 = 9.2 x 10^{-5}.

By entering the Agency's level of concern, 1 x 10^{-6}, for Risk and using the highest exposure estimated for food plus ground water, the Q_1^* that would result in an acceptable risk is 1.9 x 10^{-4}.

$10^{-6} = Q_1^* \div 0.005147$ mg/kg/day
$Q_1^* = 10^{-6} \div 0.005147$ mg/kg/day = 1.9 x 10^{-4}

Since the Agency's estimate of exposure is conservative, it is likely that a larger Q_1^* would produce risks that are below the Agency's level of concern (Reaves 2004).[8]

The result of a new study, therefore, would likely be a reduced level of risk. The Agency's reliance on the current Q_1^* is thus consistent with its stated conservative approach to protecting public health.

(B): A new study shows an absence of tumors in mice.
A new oncogenicity study that is negative would not likely change the cancer classification of fluometuron. The Agency generally defaults to positive data (even if equivocal) when faced with studies that are both positive and negative.

This new negative study would, therefore, have little bearing on the Agency's overall risk characterization for fluometuron.

Fluometuron use pattern
The Agency notes that fluometuron is used only for cotton and that the annual consumption has declined markedly over recent years due, in part, to Roundup Ready™ cotton. We are not suggesting that the Agency ignore risks associated with agrochemicals that have low usage rates; however, when considering requests for new (or, in this case replacement) data, the relatively low (and declining) use patterns of a chemical such as fluometuron should be one of the considerations by the Agency, particularly if the resulting data would likely have little bearing on the overall risk characterization, as noted above.

Rat oncogenicity studies
The Agency analysis of the study conducted in Fischer 344 rats (Burdock 1982a), based on a histological re-read, showed no significant trends in male rats but a significant difference was observed in a pair-wise comparison of the 10 and 1000 ppm dose groups[9] with controls for pituitary adenomas ($p<0.05$), as well as a significant difference in the

[8] "The unrefined groundwater estimate provided by the Environmental Fate and Effects Division (EFED) was calculated using the SCI-GROW model and may have overestimated the chronic dietary risk of fluometuron."
[9] Dose groups: 0, 10, 300 and 1000 ppm

pair-wise comparison of the 300 ppm dose group with controls, $p<0.01$. There were no compound related tumors in female rats (Reaves 2004).

The incidences noted were all within the historical controls of the testing facility (Hazleton Laboratories) (Taylor and Rinde 1996).

In a NCI rat study at 125 and 250 ppm, no tumors were associated with treatment, although dose levels could have been higher (Taylor and Rinde 1996).

These data suggest fluometuron is not carcinogenic in rats and this situation should be considered when evaluating the overall need for a new mouse oncogenicity study.

The Agency Options

The Agency can reaffirm that a repeat mouse oncogenicity study with fluometuron is sufficiently critical to their overall human risk assessment that it is required at this time, pursuant to the RED-related DCI, or it can maintain the currently available study, classified as Supplementary, is sufficient to maintain this data gap as a reserve requirement.

We suggest that the Agency is able to complete its human risk characterization with a high degree of confidence (and conservativeness) with the current mouse oncogenicity study and the Q_1* of 1.80×10^{-2}. Placing the requested repeat mouse oncogenicity study on reserve will allow the RED, scheduled for September 2005, to be published with less unnecessary "loose ends" while maintaining integrity for its risk assessment.

Conclusion

Makhteshim-Agan of North America, Inc. requests that Health Effects division scientists review the collective data for fluometuron with the option of placing the identified gap for mouse oncogenicity on reserve. This reserve status would be reflected in the Data Call In, pursuant to issuance of the fluometuron RED.

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