D- 9006 / LINURON SR 4-22-87

Attachment A

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APR 22 1987

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Abbreviated Peer Review of Linuron

FROM: Esther Rinde, Ph.D. E. Rinde 4/1/87
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Toxicology Branch/HED (TS-769c)

TO: Robert Taylor
Product Manager #25
Registration Division (TS-767c)

The Toxicology Branch Peer Review Committee met on March 2, 1987 to discuss and evaluate the weight-of-evidence on Linuron with particular reference to its oncogenic potential.

1. Individuals in Attendance:

A. Peer Review Committee: (Signatures indicate concurrence with peer review unless otherwise stated.)

Theodore M. Farber	Theodore M. Farber
William L. Burnam	Wm L Burnam
Anne Barton/Gary Burin	Anne Barton Gary Burin
Reto Engler	Reto Engler
Louis Kasza	Louis Kasza
Richard Levy	Richard Levy (corrections attached)
Judith Hauswirth	Judith W Hauswirth
Jack Quest	John A. Quest
Esther Rinde	Esther Rinde

Attachment to D-9004A

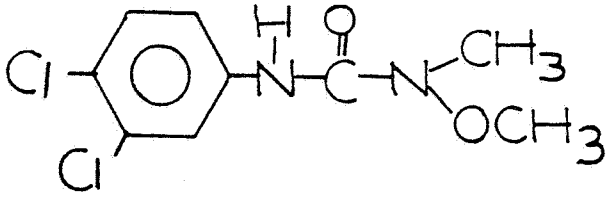
1. B. Reviewers: (Non-panel members responsible for data presentation; signatures indicate technical accuracy of panel report.)

James Rowe

Quang Bui

2. Background Information:

Linuron, currently in Special Review, was designated by the Carcinogen Assessment Group (CAG) as a class C oncogen and a risk assessment has been performed. Dupont recently submitted biochemical and histopathology data which purportedly indicates that the mechanism of action is mediated through the pituitary-testes (ovary) feed-back mechanism; based on this data, Dupont maintains that linuron should be considered as having a threshold for its oncogenic effect.



LINURON

3. Oncogenicity Studies:

The following 2 studies in the rat and in the mouse were reviewed by CAG ("Review of Rat and Mouse Data from the Dupont Chemical Company for the Carcinogenicity of Linuron" OHEA-C-117, April 30, 1984):

In the chronic rat study, conducted by DuPont, Charles River CD rats were fed linuron for two years at 0, 50, 125 or 625 ppm in the diet. Linuron produced a statistically significant increase in the incidence of interstitial-cell adenoma in the testes of male rats in mid and high-dose groups (controls, 4/68 or 5.9%; low dose, 9/56 or 16.1%; mid-dose, 19/64 or 29.7%; high-dose, 37/66 or 56.1%).

In the mouse study, conducted by Haskell Laboratory, Charles River CD-1 mice were fed linuron for 2 years at 0, 50, 150, or 1500 ppm in the diet. (The equivalent dose rates were reported as 0, 12, 35, and 455 mg/kg/day, respectively.) A statistically significant increase in the incidence of hepatocellular adenomas was observed at the highest dose group in female mice (controls, 5/79 or 6.3%; low dose, 6/79 or 7.6%; mid dose, 8/76 or 10.5%; high dose, 20/80 or 25% ($p=0.001$)), and in the lowest dose group (50 ppm) male mice (controls, 9.79 or 11.4%; low dose 18/80 or 22.5% ($p=0.048$); mid dose, 10/80 or 12.5%; high dose, 16/78 or 20,5%). Hepatocellular carcinomas were not significantly increased at any dose, in either sex.

The following 2 studies were reviewed by TOX Branch:
In a multi-generation rat reproduction study, also conducted by Dupont ("Special Review Submission on Hormonal Effects of Linuron" EPA I.D. #035506, Caswell # 528) Crl:CD strain rats were fed linuron at 0, 25, 125, or 625 ppm (estimated dose: 0.75-37 mg/kg body wt.) in the diet. Two uterine adenocarcinomas and one squamous cell carcinoma of the cervix were reported in the high dose group females*, however this incidence was not statistically significant when compared to concurrent controls. (Neither of these tumor types were seen in the chronic rat study, discussed above.) There was an increase in testicular interstitial-cell adenomas and hyperplasia in treated males of both generations, as compared to controls. The incidence of adenomas for the F_{1b} and F_{2b} groups combined was: controls, 1/19 or 5%; low dose, 0/25 or 0%; mid-dose, 6/25 or 24%; high-dose, 2/16 or 12%. In most instances, the adenomas were associated with hyperplasia.

Another study in Crl:CD(SD)BR rats was submitted by DuPont, in response to a data call-in ("Effects of linuron fed to aged male rats" study #394-86, 1986; MR No. 7351-001, Caswell 528). The estimated average age of the rats at the beginning of the study was 12 months. A statistically significant increase in testicular adenoma and hyperplasia was observed in male rats fed dietary linuron (625 ppm) for 12 months. Rats fed normal diet for 6 months, followed by 6 months of dietary linuron, had a non-statistically significant increase in testicular adenomas without elevation in testicular hyperplasia (see J.Rowe memo, 2/27/87 for details).

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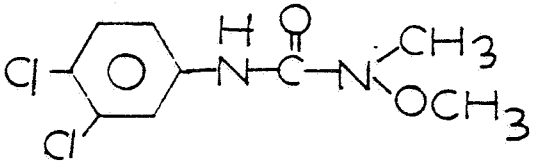
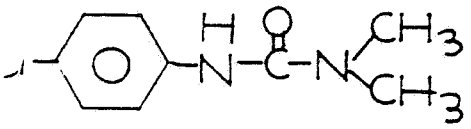
*A high degree (dose-related) of uterine endometrial hyperplasia was also observed in these female rats, which could be related to the testicular hyperplasia in males <L. Kasza>.

4. Ancillary Data for Weight of Evidence Determination:

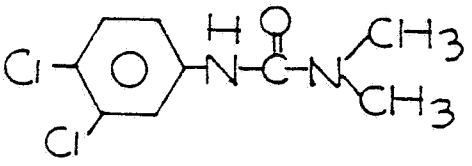
Linuron was negative in the following acceptable studies for mutagenicity: Ames Test, UDS, CHO-HGPRT gene mutation and in vivo bone marrow chromosomal aberration. No metabolism data were available for review. SAR: Monuron, a structural analog, was carcinogenic (kidney and liver) in the male (F344/N) rat; preliminary information suggests that diuron causes bladder tumors in Wistar rats; other analogs (propanil, and dimilin) were negative for oncogenicity in the mouse and rat (propanil was tested in the rat only).



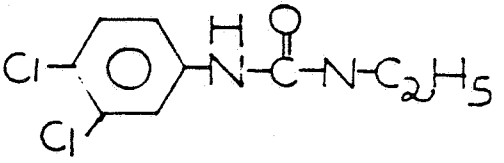
Linuron



Monuron



Diuron



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Biochemical and histopathological data were presented which suggest that linuron may affect testosterone metabolism in horse testicular microsomes for a range of dose levels (50-5000 uM = 11-1100 mg).

The Leydig cells of chronically dosed (625 ppm, high dose) male rats exhibited a hyperactive response to luteinizing hormone (LH) manifested by increased testosterone secretion. On the other hand, Leydig cells of rats exposed repeatedly (200 mg/kg per os for 3-7 days) or for 11 Or 19 months at intermediate dietary dose levels (125 ppm), apparently were hyporeactive to LH (decreased testosterone secretion).

In vitro secretion patterns of testosterone suggest that linuron effects on Leydig cells of rat testes are age and dose-related. Also, Husby (Cancer Res. (1981). 41:3172-3178) reported that prolonged LH hyperstimulation of Leydig cells in Fischer rats gives rise to hyperplasia and adenoma. (Leydig cell tumors occur spontaneously in older males of this strain).

5. Conclusion

The registrant (DuPont) maintains that these biochemical and pathological data (presented in section 4.) indicate that the mechanism of action for oncogenicity of linuron is mediated through a pituitary-testes (ovaries?) feedback mechanism and therefore linuron should be considered as having a threshold for this effect.

The Peer Review Committee concluded that these data are suggestive (but not definitive) of an hormone-mediated effect for oncogenicity; furthermore, whether or not this might be the only mechanism for oncogenicity could not be determined.
Linuron was classified by the Peer Review Committee as a Group C Carcinogen, in accordance with the 1986 Guidelines*, based on limited evidence in the rat and mouse (there was a statistically significant increase in the incidence of benign tumors only). The Committee also recommended that a quantitative risk assessment should be performed on the testicular tumors in the rat.

6. Additional Data Required for a Definitive WOE Determination

Two impurities found in linuron of potential toxicological concern are 3,3'(-) 4,4'-tetrachloroazobenzene (TCAB) and 3,3',4,4'-tetrachloroazoxybenzene (TCAOB), analogs of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), a potent carcinogen and acute toxicant. TCAB and TCAOB are contaminants of concern due to their structural similarity to TCDD, and recent preliminary reports of teratogenicity, chloracne, mutagenicity and binding potential to the apparent TCDD receptor site in the liver. In addition, it is known that TCDD and other dioxins strongly resist biodegradation and it is quite likely that TCAB and TCAOB would not be quickly degraded, as well. In order to properly compare the risks of use of two linuron product contaminants under consideration, a determination of the comparative maximal residues on food crops of TCAB and TCAOB has been requested from the Residue Chemistry Branch (RCB/OPP) based on the lb a.i./acre of each crop, that is, where it is possible to make such estimates. In addition, due to concern that these impurities are likely to be found in other pesticides of a similar chemical structure, RCB has also been requested to determine which compounds are known to contain TCDD-related impurities. If these appear significant in concentration, then OPP will evaluate whether or not bioassay data should be generated, possibly through the National Toxicology Testing Program (NTP) <J.Rowe>.

It was recommended that the DERs prepared by Dr. Rowe be sent to CAG for consideraton in their weight of evidence determination (CAG has received the DERs and is currently evaluating the OPP conclusions). It was also recommended that CAG should be asked for assistance in the future (e.g., in the preparation of Position Documents for the SAP) since the comprehensive review of linuron was performed by CAG.

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*EPA Guidelines for Carcinogen Risk Assessment, 1986 FR51: 33992-34003.