



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

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OFFICE OF  
PESTICIDES AND TOXIC SUBSTANCES

MAY 6 1981

MEMORANDUM

APR 30 1981

**DATE:**

**SUBJECT:** Review of a study entitled:  
The Effects of Dietary Administration of Diflubenzuron  
to male and female HC/CFLP Mice for 13 weeks

**FROM:** Salvatore F. Biscardi  
Review Section #1  
Toxicology Branch/HED (TS-769c) *Biscardi*

**TO:** Mr. Franklin Gee (PM-17)  
Registration Division (TS-767) *WFB*

**Purpose:** This study was undertaken to help in the design of the long term oncogenicity study and estimate the maximum tolerated dose

**Laboratory:** Huntingdon Research Centre  
Huntingdon, England

**Sponsor:** Philips - Duphar  
The Netherlands

**Chemical:** Diflubenzuron (Batch NO: FL55/906141)  
97.2% pure.

**Methodology:** Diflubenzuron was admixed with the diet and fed to HC/CFLP mice (male/female) for 13 weeks. There were six dose levels 0; 80; 400; 2,000; 10,000; and 50,000 ppm. Ninety-six males and ninety-six females were used as control animals. Fourty per sex per dose were assigned to the other dose levels. All mice had access to water. Observations were recorded for sign, clinical signs, mortality, food consumption, body weight changes, water consumption. Hematology and blood chemistries were also performed at 7 and 13 weeks. Gross and microscopic pathology were performed according to accepted procedures. Some tissues were prepared for electron microscopy. Data were analyzed statistically.

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Results:

The results observed in hematology are those expected from a chlorophenyl urea type compound. Methemoglobinemia and sulphhemoglobinemia are present along with an increase in Heinz bodies, reticulocyte counts, lower packed cell volume and red blood cell count. Bone marrow smears showed no effect on the ratio of myeloid to erythroid cells either at 7 weeks or at termination. An increase in platelets at 7 and 14 weeks was attributed to artifact. Increased levels of alkaline phosphatase were recorded at 50,000ppm in weeks 7 and 14 for males and females and at week 7 for females.

Increased levels of glutamic pyruvic transaminase were recorded in treated mice but also in control mice.

Blood cholesterol lowerings were noted in weeks 7 and 14 for males and females at 50,000 ppm, in females in weeks 7 at 10,000 and 2000ppm.

In the macroscopic pathology, dark discoloration and spleen enlargement go hand in hand with the hematological picture. The dark discoloration is expected to be due to hemosiderosis.

Spleen weights were increased with the exception of mice at the lowest dose level. Liver weights were increased again excepting for the animals at the two lowest dose levels.

Kidney weights were lower at the 2 highest dose levels as also seminal vesicle weights at the three highest dose levels.

Hepatocytic enlargement, hepatocytic cytoplasmic vacuolization, inflammatory foci and necrotic hepatocytes in varying degrees were found at the various dose levels along with splenic hemosiderosis.

A lymphosarcoma in lymph nodes and adrenals were found in one mouse at 50,000 ppm. Another reticulum cell sarcoma was reported in another mouse at 50,000 ppm and at 10,000 ppm a lymphosarcoma was found. Two control mice had reticulum cell sarcoma and lymphosarcoma respectively.

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Comment:

The final long term oncogenicity study is already in progress at Huntingdon Laboratories in England. This study furnished the data to individualize proper dose levels to be tested and to find the maximum tolerated dose. The dose levels for the long term study are 0; 16; 80; 400; 2,000 and 10,000 ppm. From the view of the data in this experiment, it would be proper to assume that the MTD requirement has been satisfied. Even if the animals die at the two highest dose levels, there will be three dose levels available for oncogenicity data.

Validation:

Core-Guideline

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