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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, DC 20460

APR 3 1990

OFFICE OF
PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Third Peer Review of Clofentezine (APOLLO™)

FROM: Roger Gardner, Acting Section Head
Review Section I
Toxicology Branch I (Insecticide/Rodenticide Support)
Health Effects Division (H7509C)

TO: Dennis Edwards
Product Manager #12
Registration Division (H7505C)

The Health Effects Division Peer Review Committee met on October 25, 1989 to reconsider and evaluate the weight-of-the-evidence on clofentezine with particular reference to its carcinogenic potential.

A. Individuals in Attendance:

1. Peer Review Committee: (Signatures indicates concurrence with the peer review unless otherwise stated.)

Penelope A. Fenner-Crisp	Penelope A. Fenner-Crisp
William L. Burnam	
Reto Engler	
Karl Baetcke	
Marion Copley	
Kerry Dearfield	
Julie Du	
Richard Levy	
John Quest	
Esther Rinde	
William Sette	
Yin-Tak Woo	

2. Reviewers: (Non-committee members responsible for d a t a presentation; signatures indicate technical accuracy of panel report.)

Roger Gardner (Reviewer) Roger Gardner 3-2-90

Bernice Fisher Bernice Fisher

3. Peer Review Members in Absentia: (Committee members who were unable to attend the discussion; signatures indicate concurrence with the overall conclusions of the Committee.)

Robert Beliles Robert J Beliles

George Ghali G. Ghali

Richard Hill —

Marcia Van Gemert Marcia van Gemert

4. Other Attendees: (Observers) Albin Kocialski, Hugh Pettigrew, and Henry Spencer.

B. Material Reviewed:

The material available for review consisted of a summary of the two previous Peer Reviews and special thyroid studies prepared by Roger Gardner and the Scientific Advisory Panel's report of its analysis. The material reviewed is attached to the file copy of this report.

C. Background Information:

After Peer Reviews held on September 16, 1987, May 18, 1988, and on February 21, 1990 and consideration by the Scientific Advisory Panel (SAP) on March 2, 1988, the Peer Review Committee concluded that clofentezine should be classified into Group C (Possible Human Carcinogen) on the basis of the increased incidence of male rats with thyroid follicular cell adenomas and carcinomas (see Table 1). Special thyroid studies were not considered sufficient to change the classification of the chemical. The Committee also concluded that, in addition to the short-term special studies, another chronic feeding study with a broader dose range (>400 ppm) and interim thyroid biochemical and necropsy observations is needed to define a mechanism for clofentezine's suggested induction of thyroid tumors in terms of the criteria described by the Agency in a draft document entitled Thyroid Follicular Cell Carcinogenesis: Mechanistic and Science Policy Considerations prepared by a Technical Panel of the Risk Assessment Forum (dated December 15, 1987).

Table 1

Incidence of Thyroid Follicular Lesions as Reported in the Chronic Feeding/Oncogenicity Study of Clofentezine in Rats

Observation	Dose (ppm) 0	10	40	400
Follicular cell tumors:				
Adenoma	1/70	1/70	1/70	3/70
Carcinoma	1/70	1/70	1/70	5/70
Combined adenoma/carcinoma	2/70 *	2/70	2/70	8/70 **

* Statistically significant linear trend; $P < 0.05$; Cochran-Armitage Test.

** Statistically significantly different from control; $P = 0.048$, Fisher's Exact Test.

D. Evaluation of Carcinogenicity Evidence for Clofentezine:

These studies have been summarized in previous Peer Review documents and Data Evaluation Records (DER).

E. Additional Toxicology Data on Thyroid Effects:

The special studies were considered with respect to the following criteria (from the proposed policy on the assessment of chemicals that potentially cause thyroid tumors):

1. Clofentezine may enhance the excretion of thyroid hormones.

2. The possibly enhanced excretion of thyroid hormones may lead to reduced circulating levels of T_3 and T_4 which could stimulate TSH levels to be increased as a result of the thyroid-pituitary hormone feedback mechanism.

3. The increased TSH may then cause thyroid follicular cell hypertrophy and hyperplasia.

4. During the course of a chronic feeding study, clofentezine may be associated with a progression from hypertrophy through hyperplasia to thyroid follicular cell tumors.

These criteria characterized the proposed mechanism for clofentezine's induction of thyroid follicular cell tumors in male rats.

The results of available thyroid studies suggested the following:

1. Hormone imbalances observed in clofentezine treated rats appear to be transient or reversible, even at dose levels much higher (up to 30,000 ppm) than the highest dose tested in the chronic feeding study (400 ppm) (see Table 2).

2. Although there are some changes in the extent to which thyroid hormones are metabolized in the liver and excreted in the bile, there is little indication that greater amounts of thyroid hormones and their metabolites are actually excreted from clofentezine treated rats than from untreated rats (see Table 3).

3. Clofentezine caused hypertrophy and hyperplasia which also appeared to be transient or reversible during the course of short-term feeding studies with doses equal to or greater than the chronic study's highest dose level (see Table 4).

4. Because of the possible adaptive responses in thyroids of treated rats, there are insufficient data to indicate a consistent progression from hypertrophy through hyperplasia to thyroid follicular cell neoplasia in the chronic feeding study or the short-term studies.

Based on the results of the available data, the Peer Review Committee concluded that there is insufficient evidence of a mechanism for thyroid follicular cell tumor induction by clofentezine in the male rat.

Table 2

Summary of Clofentezine's Effects
on Thyroid and Pituitary Hormone Levels in Rats

Dose (ppm)	Duration (weeks)	Observations
30,000	2	T_3 was decreased on days 2, 4, and 7 but was comparable to control levels at 14 days.
		T_4 was comparable to control levels throughout the 14-day study.
		TSH was increased on days 4, 7, and 14 and showed a trend toward decreasing to control levels; TSH never exceeded the highest value obtained for untreated rats.
	4	TSH was increased, but T_3 and T_4 values were comparable to control values.
	6	TSH, T_3, and T_4 values were all increased.
400	4	No statistically significant effects on TSH, T_3, or T_4 levels.
	6	T_4 statistically significantly increased.
		TSH and T_3 values were comparable to control values.
	119	T_4 was statistically significantly increased.
		TSH and T_3 were comparable to control values.

Table 3

Summary of the Effects of Clofentezine on the Clearance of Thyroid Hormones from the Rat

Dose (ppm)	Duration (weeks)	Liver Effects	Thyroid Effects
30,000	5	Shift in the total proportion of T_3/T_4 recovered in excreta to feces (40% of administered radio- recovered in 72 hrs. from treated rats and 26% recovered from control rats).	Total administered T_3/T_4 and metabolites recovered in urine and feces over 72 hrs. was the same for treat-ed and control rats.
	?	Bile flow rate was almost doubled in treated rats; the proportion of T_3/T_4 conjugates and metabolites recovered in the bile was increased; the concentration of T_3/T_4- and conjugate-associated radioactivity in bile of treated rats was 20 to 40% that of the control rats; 10.2% of administered radioactivity was recovered in bile collected over 4 hrs. in treated rats compared with 6.4% for control rats.	No thyroid functions or effects were examined.
	4	No liver effects were examined.	Clofentezine did not accumulate in thyroid tissue; iodine uptake by the thyroid was in-creased in treated rats: a statistically significant decrease in the half-life of T_3/T_4 in the blood of treated rats was not found.

Table 4

Summary of the Goitrogenic Effects of Clofentezine

Dose (ppm)	Duration (weeks)	Observations
30,000	4	Follicular cell hypertrophy in 20/20 animals, increased mitotic activity in 12/20 animals, hyperplasia in 8/20 animals. Thyroid gland weight was increased by 16.7% above that for untreated rats.
30,000	6	The area (mm^2) of thyroid sections from treated rats was increased along with the number of follicles and follicular cells per section.
3,000	4	Follicular cell hypertrophy in 19/20 rats, increased mitotic activity in 5/20 animals, and hyperplasia in 4/20. Thyroid weight was increased by 8% above that for untreated rats.
400	4	Follicular cell hypertrophy in 14/20 rats, increased mitotic activity was not observed in treated rats, and hyperplasia was not found in treated rats. Thyroid glands weighed approximately 8% less than those of untreated rats.
	119	Follicular cell hypertrophy in 32/67 treated rats compared to 16/70 untreated rats; hyperplasia in 7/69 treated rats vs. 3/70 untreated (statistically significant dose-related trend, but pair-wise comparison was not statistically significant). Thyroid weights were comparable for treated and untreated rats.

F. Weight of Evidence Considerations:

The Committee considered the following facts regarding the toxicology data on clofentezine to be of importance in a weight-of-the-evidence determination of carcinogenic potential.

1. An increased incidence of thyroid follicular cell adenomas and carcinomas combined was observed in male rats.

2. The tumor incidence was slightly greater than the upper limit of the historical control range (20% compared with 15%). (Data were adjusted by censoring animals dying prior to appearance of the first thyroid tumor.)

3. The tumor incidence was increased at a dose level well below a limit dose or Maximum Tolerated Dose (MTD) predicted by subchronic studies.

4. The tumor incidence was marginally increased only at the highest dose tested ($p = 0.048$, Fisher's Exact test on unadjusted data).

5. The tumor increase was observed only in male rats, and no increase in the incidence of tumors was observed in female rats or male and female mice.

6. Additional thyroid studies do not provide compelling evidence for the proposed mechanism of follicular cell tumor induction by clofentezine in treated rats.

7. Clofentezine did not cause genotoxicity in a battery of mutagenicity assays.

8. There is no available information on structure-activity relationships with respect to other known carcinogens.

The chronic study in rats is limited because the highest dose tested was well below a Limit Dose or a Maximum Tolerated Dose predicted by short-term studies.

G. Classification of Carcinogenic Potential:

Criteria contained in the EPA Guidelines [FR 51:33992-34003, 1986] for classifying a carcinogen were considered.

The Peer Review Committee reaffirmed its previous consensus to classify clofentezine as a Group C or Possible Human Carcinogen. Factors supporting this classification include:

1. An increased incidence of benign and malignant thyroid follicular cell tumors combined was observed in male rats.

2. The tumor incidence was greater than the upper limit of the historical control range.

3. The tumor incidence was increased at a dose level well below a limit dose or Maximum Tolerated Dose (MTD) predicted by subchronic studies.

After considering three new studies, the Peer Review Committee also reaffirmed its previous conclusion that all of the special thyroid studies were not sufficient to change the classification of clofentezine. The Committee also concluded that no quantification of risk would be done at the present time and that another long-term study using higher doses may be necessary to support appropriate characterization and quantification of potential risks associated with the uses of clofentezine. If the Registrant chooses to conduct such a study, the protocol should be discussed with the Agency prior to its initiation.