Apollo; CASRN 74115-24-5

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the IRIS assessment development process. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website.

STATUS OF DATA FOR Apollo

File First On-Line 01/31/1987

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	01/31/1987
Inhalation RfC (I.B.)	not evaluated	
Carcinogenicity Assessment (II.)	yes	06/01/1991

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — Apollo
CASRN — 74115-24-5
Last Revised — 01/31/1987

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg-day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of

substances that are also carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

I.A.1. Oral RfD Summary

Critical Effect	Experimental Doses*	UF	MF	RfD
Liver effects; organ weight changes **1-Year Feeding Dog Study** **BFC Chemicals, Inc., 1984**	NOEL: 50 ppm (1.25 mg/kg/day) LEL: 1000 ppm (25 mg/kg/day)	100	1	1.3E-2 mg/kg/day

*Conversion Factors: 1 ppm = 0.025 mg/kg/day (assumed dog food consumption)

I.A.2. Principal and Supporting Studies (Oral RfD)

BFC Chemicals, Inc. 1984. MRID No. 00149491, 00159080. Available from EPA. Write to FOI, EPA, Washington D.C. 20460.

Four groups of 6 male and 6 female dogs were given diets containing 0, 50, 1000, or 20,000 ppm Apollo for 1 year. All test animals were observed during the study for appearance of clinical signs or mortality, body weight, food consumption, ophthalmological observations, electrocardiograms, hematology, blood biochemistry, and urine analysis. At necropsy the tissues and organs were grossly examined and lesions were noted. Organ weights were determined and microscopic examinations were conducted on tissues. Apollo affected the liver of dogs given dietary levels of l000 and 20,000 ppm. The effects included hepatocyte enlargement with eosinophilic cytoplasm; increased liver, thyroid, and adrenal weights; and elevated serum cholesterol, triglycerides, and alkaline phosphatase.

I.A.3. Uncertainty and Modifying Factors (Oral RfD)

UF — An uncertainty factor of 100 was used to account for the inter- and intraspecies differences.

MF — None

I.A.4. Additional Studies/Comments (Oral RfD)

Final reports on long-term studies in rats and mice are pending. Interim reports for both studies (at 1 year for rats and mice and 18 months for rats) have been submitted and reviewed. From these reports it is considered that the dog appears to be the most sensitive species.

Data Considered for Establishing the RfD:

1) 1-Year Feeding - dog: Principal study (see description above); core grade minimum

2) 2-Year Feeding (oncogenic) - rat: NOEL=40 ppm (2 mg/kg/day); LEL=400 ppm (20 mg/kg/day) [increased liver weights and liver-to-body weight ratio (males); increased thyroxine levels; centrilobular hypertrophy and vacuolation of hepatocytes, focal cystic degeneration of hepatocytes, and diffuse distribution of fat deposits in liver (males)]; core grade minimum (Nor-Am Chemical Co., 1986)

3) 3-Generation Reproduction - rat: Reproductive NOEL=400 ppm (20 mg/kg/day) (HDT); Systemic NOEL=40 ppm (2 mg/kg/day); Systemic LEL=400 ppm (centrilobular hepatocyte hypertrophy, increased liver weight); core grade minimum (BCF Chemicals, 1984)

4) Teratology - rat: Teratogenic NOEL=3200 mg/kg/day; Fetotoxic NOEL=3200 mg/kg/day (HDT); Maternal NOEL=1280 mg/kg/day, Maternal LEL=3200 mg/kg/day (differential staining and slight enlargement of the centrilobular hepatocytes); core grade minimum (BCF Chemicals, 1982)

5) Teratology - rabbit: Teratogenic NOEL=3000 mg/kg/day (HDT); Fetotoxic NOEL=1000 mg/kg/day; Fetotoxic LEL=3000 mg/kg/day (bw reduction); Maternal NOEL=1000 mg/kg/day; Maternal LEL=3000 mg/kg/day (bw reduction, reduced food intake); core grade minimum (BCF Chemicals, 1983)

Other Data Reviewed:

1) 105-Week (oncogenic) - mice: Systemic NOEL=500 ppm (75 mg/kg/day); Systemic LEL=5000 ppm (750 mg/kg/day) [reversible decreases in body weight, decreased body weight gain (15 to 22%), increased incidence of eosinophalic areas or foci of hepatocytes in males; in females increased incidence of basophilic and/or eosinophilic foci or areas of hepatocytes, an increased mortality during weeks 78 to 105 with amyloidosis identified as a contributing factor to deaths]; core grade minimum (BCF Chemicals, 1983)

Data Gap(s): none

I.A.5. Confidence in the Oral RfD

Study --High
Database — High
RfD — High

The principal study appears to be of good quality and is given a high confidence rating. The additional studies are of fair to good quality, are comprehensive, and quantitatively support the choice of a NOEL; thus, the data base is given a high confidence rating. High confidence in the RfD follows.

I.A.6. EPA Documentation and Review of the Oral RfD

Pesticide Registration Files/ New Chemical

Agency Work Group Review — 04/22/1986, 09/16/1987

Verification Date — 04/22/1986

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfD for Apollo conducted in September 2002 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to the IRIS Hotline at hotline.iris@epa.gov or (202)566-1676.

I.A.7. EPA Contacts (Oral RfD)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name — Apollo
CASRN — 74115-24-5

Not available at this time.

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Apollo
CASRN — 74115-24-5
Last Revised — 06/01/1991

Section II provides information on three aspects of the carcinogenic assessment for the substance in question; the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in The Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

II.A. Evidence for Human Carcinogenicity

II.A.1. Weight-of-Evidence Characterization

Classification — C; possible human carcinogen

Basis — Based on an increase in thyroid gland follicular cell tumors in male rats and supportive findings in pituitary/thyroid hormone activity.

II.A.2. Human Carcinogenicity Data

None.

II.A.3. Animal Carcinogenicity Data

Limited. There was an increase in the incidence of a single tumor type in male rats. Charles River Sprague-Dawley rats (70/sex/group) were fed Apollo in the diet at 0, 10, 40 or 400 ppm for 27 months. Twenty animals/sex/dose were treated as satellite groups and killed at 12 months (FBC/Nor-Am Chemical Co., 1985a). In male rats there was a statistically significant dose-related trend in the incidence of both benign and malignant follicular cell tumors in the thyroid gland. There was also a statistically significant increase in the incidence of combined benign and malignant thyroid gland tumors in the male rats in the high-dose group; the incidences were 2/68, 2/65, 2/66 and 8/63 in the 0, 10, 40 and 400 ppm dose groups, respectively (Gardner, 1988). (Animals that died before week 52 were excluded because these animals are not at the same type of risk; the denominators reflect numbers of animals at risk.) Historical data for combined tumors from two studies conducted at the same laboratory ranged from 3/40 to 6/40, indicating that survival was not affected by the doses used in this study. Although both the Toxicology Branch Peer Review Committee and the FIFRA Scientific Advisory Panel concluded that the maximum tolerated dose (MTD) had not been achieved in this study, they decided that the study was not compromised. In a 90-day study in rats (BFC Chemicals, Inc., 1981) at dietary doses of 0, 40, 400 and 4000 ppm, Apollo produced liver changes (increased liver weight, morphologic changes, and increased clinical chemistry values) that were not life threatening and without body weight was not suppressed even at the highest dose tested.

Charles River CD-1 Swiss mice (52/sex/dose) were fed Apollo in the diet at levels of 0, 50, 500 and 5000 ppm for 105 weeks (FBC/Nor-Am Chemical Co., 1985b). Incidences of malignant and combined benign/malignanthepatocellular tumors were significantly increased in the 500 ppm males but not in high-dose males (no dose-response relationship). The incidences of malignant liver tumors in 0, 50, 500 and 5000 ppm males were 14/50, 16/46, 24/48 and 19/48, respectively; the incidence of combined benign and malignant tumors were 19/50, 20/46, 33/48 and 25/48, respectively (U.S. EPA, 1988a). No significant increase in these tumors was observed at any dose in the females (Peto prevalence procedures were employed in the tumor analysis of female mice). The male mice showed no change in survival with increased dose, while mortality increased with increased dose in the female mice. The dose selection for the male mice was indeed adequate based on body weight loss at the high dose. The doses administered to the females did not appear to reach the MTD respect to toxic effects, yet mortality was significantly increased at the high dose. The OPP Health Effects Division Peer Review Committee (Quest, 1988; Gardner, 1988) and the FIFRA Scientific Advisory Panel (U.S. EPA, 1988) agreed, based on the results of this study, that there were no compound- related effects on tumor incidence.

II.A.4. Supporting Data for Carcinogenicity

Several short-term studies in rats (reviewed in U.S. EPA, 1988a,b) have implicated the thyroid gland as the target organ for Apollo. Follicular hypertrophy, diminished colloid, and possible hyperplasia were characteristic of the histomorphological effects and were reversible when dosing stopped. Blood concentrations of thyroxine, tri-iodothyroxine, and thyroid-stimulating hormone (TSH) levels were increased; iodine uptake was also increased. The normal expectation for a goitrogenic material would be to have reduced thyroid hormone and increased TSH. Further studies revealed that Apollo increased bile flow rate and shifted the pattern of thyroxine excretion to the feces, suggesting that Apollo may enhance clearance of thyroid hormones.

The proposed mechanisms postulated that Apollo increased bile flow, causing an increase in metabolism and excretion of thyroxine. The reduced circulating thyroxine stimulated the pituitary gland through the hypothalamus to produce increased TSH. The elevated TSH stimulated the follicular cells and resulted in increased thyroxine and decreased colloid, follicular cell hyperplasia, hypertrophy and neoplasia in the male rat at the termination of the chronic study.

Apollo was negative in a Salmonella typhimurium mutagenicity test with or without hepatic homogenates. Results of a mutagenicity assay in a mouse lymphoma cell line with and without activation were equivocal. It was negative in a micronucleus test in mice at doses of up to 3200 mg/kg and did not produce gene conversion or mitotic recombination in Saccharomyces cerevisiae strain D7. At dietary doses of up to 400 ppm for 10 weeks, it did not produce dominant lethal effects in male rats (reviewed in U.S. EPA, 1988a).

Neither Apollo nor its urinary metabolites were found to be structurally related to any known carcinogen (reviewed in U.S. EPA, 1988a).

II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure

Not available.

II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

Not available.

II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)

II.D.1. EPA Documentation

Source Document — Gardner, 1988, 1990; Quest, 1988; U.S. EPA, 1988

The Office of Pesticide Programs (Health Effects Division, U.S. EPA) peer reviewed data pertaining to potential carcinogenicity of Apollo (Memorandum from R. Gardner to D. Edwards, Third Peer Review of Apollo 04/16/1990).

II.D.2. EPA Review (Carcinogenicity Assessment)

Agency Work Group Review — 11/09/1988, 02/08/1990

Verification Date — 02/08/1990

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the cancer assessment for Apollo conducted in September 2002 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to the IRIS Hotline at hotline.iris@epa.gov or (202)566-1676.

II.D.3. EPA Contacts (Carcinogenicity Assessment)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

III. [reserved]
IV. [reserved]
V. [reserved]

VI. Bibliography

Substance Name — Apollo
CASRN — 74115-24-5

VI.A. Oral RfD References

BFC Chemicals, Inc. 1982. MRID No. 00114270, 00159095. Available from EPA. Write to FOI, EPA, Washington DC 20460.

BFC Chemicals, Inc. 1983. MRID No. 00130761. Available from EPA. Write to FOI, EPA, Washington DC 20460.

BFC Chemicals, Inc. 1984a. MRID No. 00149491, 00159080. Available from EPA. Write to FOI, EPA, Washington DC 20460.

BFC Chemicals, Inc. 1984b. MRID No. 00147884, 00159070, 40289801. Available from EPA. Write to FOI, EPA, Washington DC 20460.

BFC Chemicals, Inc. 1985. MRID No. 00147885, 00159094, 40302001. Available from EPA. Write to FOI, EPA, Washington DC 20460.

Nor-Am Chemical Company. 1986. MRID No. 00147883, 00159081. Available from EPA. Write to FOI, EPA, Washington DC 20460.

VI.B. Inhalation RfC References

None

VI.C. Carcinogenicity Assessment References

BFC Chemicals, Inc. 1981. EPA Accession Nos. 070963, 071384, 071859. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

FBC/Nor-Am Chemical Company. 1985a. EPA Accession Nos. 262261, 262262. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

FBC/Nor-Am Chemical Company. 1985b. EPA Accession Nos. 262263, 262264. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Gardner, R. 1988. U.S. EPA, Washington, DC. Memorandum to D.H. Edwards, U.S. EPA, Washington, DC, July 27. Second Peer Review of Apollo (Clofentizine).

Gardner, R. 1990. U.S. EPA, Washington, DC. Memorandum to D.H. Edwards, U.S. EPA, Washington, DC, April 16. Third Peer Review of Apollo (Clofentizine).

Quest, J.A. 1988. U.S. EPA, Washington, DC. Memorandum to D.H. Edwards, U.S. EPA, Washington, DC., April 12. Peer Review of Apollo (Clofentizine).

U.S. EPA. 1988. Memorandum. Federal Insecticide, Fungicide, and Rodenticide Act. Scientific Advisory Panel Report. Stephen L. Johnson (Executive Secretary).

VII. Revision History

Substance Name — Apollo
CASRN — 74115-24-5

Date	Section	Description
06/01/1991	II.	Carcinogenicity assessment on-line
12/03/2002	I.A.6., II.D.2.	Screening-Level Literature Review Findings message has been added.

VIII. Synonyms

Substance Name — Apollo
CASRN — 74115-24-5
Last Revised — 01/31/1987

- 74115-24-5
- 88025-82-5
- Apollo
- Apollo 50W
- 3,6-Bis(2-chlorophenyl)-1,2,4,5-tetrazine
- Bisclofentezin
- Bisclofentezine
- Clofentezine
- NC 21314
- 1,2,4,5-Tetrazine, 3,6-bis(2-chlorophenyl)-