

2-27-84



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

003655

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Irgasan; Toxicology Data Requirements

TO: Arturo Castillo PM-32
Registration Division (TS-767)

FROM: *[Signature]* 1/30/84
Robert P. Zenzian Ph. D.
Toxicology Branch
HED (TS-769)

THROUGH: William Butler, Head *William Butler 2-27-84*
Review Section III

William Burnam, Chief
Toxicology Branch

Compound Irgasan® (triclosan, DP-300, FAT 80)
Registration# 100-502
Accession #s 251771-74
Tox Chem# 186A
Registrant Ciba-Gcigy

Irgasan is a disinfectant which is registered for a variety of uses. Due to a mixture of circumstances the toxicology data base of this compound is in disarray. The Registrant and the Agency are engaged in an effort to determine what toxicological studies are available and which of these can be used to satisfy the Agency's data requirements. The Registrant has submitted copies of all the reports of non-acute toxicity studies on Irgasan which they believe suitable for satisfying Agency requirements. These reports have been examined for their suitability in satisfying Agency data requirements and if not previously reviewed have been reviewed. Suitable studies have been compared against toxicology data needs for Irgasan, based on its registered uses, and a determination made of additional data requirements. The reported studies satisfy the Agency's requirements for subchronic oral studies, subchronic dermal studies and teratology studies. In addition data is on hand that satisfies

1 *[Signature]*

the Agency's requirements for mutagenicity studies. Agency requirements for a chronic oral study, two oncogenicity studies, a reproduction study and a metabolism study have not been satisfied. 003655

The registrant, under a cover letter dated Nov 7, 1983, submitted reports of 13 studies and subsequently submitted a 14th report. These studies are listed in Appendix A, Irgasan Data Requirements. Reviews of 9 of these studies were found in Toxicology Branch Files and the remaining 5 studies were reviewed (Appendix B, DEPs). The five newly reviewed studies are;

- 1) 90 Days Oral Toxicity Study in Sprague Dawley Rats with CH 3565. F. Leuscher, A. Leuscher, W. Schwerdtfeger & W. Dontenwill, Laboratorium fur Pharmakologie und Toxikologie July 27, 1970
- 2) 90 Days Oral Toxicity Study in Beagle Dogs with CH 3565 F. Leuschner, A. Leuschner, W. Schwerdtfeger & W. Dontenwill Laboratorium fur Pharmakologie und Toxikologie, July 10, 1970
- 3) 90 Days Oral Toxicity Study in New Zealand White Rabbits with CH 3565. F. Leuschner, A. Leuschner, W. Schwerdtfeger & W. Dontenwill. Laboratorium fur Pharmakologie und Toxikologie July 31, 1970
- 4) 1 Year Oral Toxicity Study in Baboons with compound FAT 80 023/A. J.C. Drake & A. Buxtorf Geigy Pharmaceuticals, Toxicology Department, Stamford Lodge, Wilmslow, Cheshire. Jun 28, 1976
- 5) 90-day Oral Toxicity Study in Rats with FAT 80'023/H, Final Report. L.A. Goldsmith & D.K. Craig, Litton Bionetics LBI Project No 22188, Oct 11, 1983

Appendix A lists all of the types of nonacute studies required for Irgasan and under each heading lists the studies which have been found to satisfy each particular requirement.

No usable chronic feeding (oral) or oncogenicity studies are available but the registrant has in progress a combined oral rat study which can satisfy the requirement for a combined chronic oral and oncogenicity study. A second oncogenicity study, in the mouse, is required.

No usable reproduction study is available and a reproduction study, in the rat, is required.

Three metabolism studies have been reviewed but these do not satisfy the requirement for a metabolism study. An oral metabolism study, in the rat, is required.

Numerous mutagenicity studies have been received and reviewed. They are uniformly negative. No further mutagenicity studies are required.

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Appendix A

-Irgasan Data Requirements-

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This entry lists the data requirements for Irgasan, based on its uses, and the studies submitted by the registrant which can fill specific portions of those requirements.

SUBCHRONIC ORAL TOXICITY (90-day, 13 week or 3-month)

✓ 1) 90-day rat minimum

90 Days Oral Toxicity Study in Sprague Dawley Rats with CH 3565. F. Leuscher, A. Leuscher, W. Schwerdtfeger & W. Dontenwill, Laboratorium fur Pharmakologie und Toxikologie July 27, 1970

doses 187, 375, 937 & 1875ppm
NOEL 1875ppm

no compound related effects observed

✓ 2) 13-week rat minimum

GP 41 353, 13-week Oral toxicity Study in Rats A. Buxtorf & R.A. Paterson Geigy, S.A. & Geigy U.K. Jan 22, 1968

doses 125, 250, 500 & 1000mg/kg/day
NOEL <125mg/kg/day

LEL 125mg/kg/day nephrosis, small infiltrations of mononuclear cells

✓ 3) 3-month rat minimum

Oral-Administration of Irgasan DP-300 to Albino Rats for Three Months. R.J. Fabian, M.R. Donikian, C.E. Hunt, K.A. Pittman and H.P. Drobeck. Sterling-Winthrop Research Institute PD.2-9028, March 16, 1973.

doses 50, 125 & 315mg/kg/day
NOEL 50mg/kg/day

LEL 125mg/kg/day increased liverweight

✓ 4) 90-day dog minimum

GP 41353 91-Day Oral Toxicity Study in Dogs A. Buxtorf & R.A. Paterson, Geigy S.A. & Geigy U.K. Dec 21, 1967

doses 25, 50, 100 & 200mg/kg/day
NOEL <25mg/kg/day

LEL 25mg/kg/day increased SAP, decreased hemoglobin and RBC

values, dose related jaundice, increased liver weight.

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5) 90-day dog minimum

90 Days Oral Toxicity Study in Beagle Dogs with CH 3565
F. Leuschner, A. Leuschner, W. Schwerdtfeger & W. Dontenwill
Laboratorium für Pharmakologie und Toxikologie, July 10, 1970

doses 125, 313 and 625ppm equal to 5, 12.5 & 25mg/kg/day
NOEL >25mg/kg/day

no compound related effects were observed.

✓ 6) 13-week rabbit minimum

GP 41 353, 13-week Oral Toxicity Study in Rabbits
A. Buxtorf & R.A. Paterson, Geigy S.A. & Geigy U.K.
March 31, 1969

doses 3, 30 and 150mg/kg/day
Noel 3mg/kg/day

LEL 30mg/kg/day neutrophilia, lymphopenia, pulmonary infection,
edema and lung necrosis

7) 90-day rabbit minimum

90 Days Oral Toxicity Study in New Zealand White Rabbits
with CH 3565. F. Leuschner, A. Leuschner, W. Schwerdtfeger &
W. Dontenwill. Laboratorium für Pharmakologie und Toxikologie
July 31, 1970

doses 250, 500, 1250 & 2500ppm
NOEL 2500ppm

no compound related effects observed

✓ 8) one year baboon minimum

1 Year Oral Toxicity Study in Baboons with compound
FAT 80 023/A. J.C. Drake & A. Buxtorf
Geigy Pharmaceuticals, Toxicology Department, Stamford Lodge,
Wilmslow, Cheshire. Jun 23, 1976

doses 30, 100 & 300mg/kg/day capsule
NOEL 30mg/kg/day

digestive effects, vomiting, failure to eat and diarrhoea at
100 & 300, mg/kg/day. Depression of RBCs at 300mg/kg/day.

9) 90-day rat minimum

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90-day Oral Toxicity Study in Rats with FAT 80'023/H,
Final Report. L.A. Goldsmith & D.K. Craig, Litton Bionetics
LBI Project No 22188, Oct 11, 1983

doses 1000, 3000 & 6000ppm
NOEL 1000ppm

nonspecific liver toxicity

SUBCHRONIC DERMAL (90-day

✓ 1) 90-day rabbit minimum

About the 90-Days-Dermal-Toxicity of CH 3565 in New
Zealand White Rabbits. F. Leuscher, A. Leuscher, W. Scherdtfeger
& H. Otto, Laboratoriu n fur Pharmakologie und Toxicologie
Sept, 7, 1970

doses 0.1, 0.5 & 1.0ml/kg/day of 3% CH 3565
NOEL dermal 0.1ml/kg/day
systemic >1.0ml/.kg/day

erythema, edema ranging to eschar and rhagades at the high
dose full recovery by 14th day of dosing.

CHRONIC FEEDING AND ONCOGENIC

No acceptable studies are listed in the Toxicology Branch
"one-liners" or found reviewed in the Branch files.

No studies were submitted by the registrant in their
submission of November 7, 1983. The registrant has indicated
that a new chronic-oncogenic rat study is in progress.

TERATOLOGY

✓ 1) mouse minimum

Effect of GP 41'353 on Pregnancy in the Mouse. A.K. Palmer &
G.M. Scales, Huntingdon Research Center, 2373/68/251
August 26, 1968

doses 10, 50 & 100mg/kg/day
NOEL teratogenic, not teratogenic at 100mg/kg/day
fetotoxic, not fetotoxic at 100mg/kg/day

maternal toxicity at 50 & 100mg/kg/day

no teratogenic effect observed, maternal toxicity included
deaths, decreased pregnancy rate and early parturition.

2) rabbit minimum

Effect of GP 41'353 on Pregnancy of the New Zealand White Rabbit. A.K. Palmer & M.A. Readshaw, Huntingdon Research Centre. 2403/68/280, Sept 26, 1968

doses 10, 25 & 50mg/kg/day

NOEL teratogenic 50mg/kg/day
fetotoxic 25mg/kg/day

no teratogenic effect observed, fetotoxicity at 50mg/kg/day consisted of "increase in 13 rib groups"

REPRODUCTION STUDY

No usable reproduction studies are listed in Toxicology Branch files.

METABOLISM STUDY

Toxicology Branch files list three metabolism studies of Irgasan, Oral Pharmacokinetic-Monkey Ciba-Geigy 10/19/78, Intravenous and intravaginal Pharmacokinetic-Rat Siddigui and Buttan 1979 and Metabolism-Rat Sundstrom et al. 1979. The information in the files indicates that these studies will not satisfy the requirement for a metabolism study.

MUTAGENICITY

Numerous mutagenicity studies on irgasan have been received by the agency. The compound is not a mutagen. No further studies are required.

Data Evaluation Report

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Compound Irgasan®, DP-300, (Triclosan)

Citation

90 Days Oral Toxicity Study in Sprague Dawley Rats with
CH 3565. F. Leuscher, A. Leuscher, W. Schwerdtfeger &
W. Dontenwill, Laboratorium fur Pharmakologie und Toxikologie
July 27, 1970

Reviewed by

[Signature] 150 1324
Robert P Zendzian PhD
Pharmacologist

Core Classification Minimum

Tox Catagory N/A

Conclusion

No compound related abnormalities were observed during and at termination of the study. Hematology, clinical chemistry and urinalysis were normal in the high group. No histopathological abnormalities were observed in the high dose group. NOEL 1875ppm.

Materials

Test compound was CH 3565 which has been identified as a code for Irgasan technical. Source and purity not identified.

Male and female Sprague Dawley rats, 44 days of age and 111-128 gms weight at the start of the study, from S. Ivanovas, Kisslegg/Wurtt.

Methods

Animals were assigned to five groups of 15 males and 15 females each. CH 3565 was supplied in the diet at doses of group I 187ppm, II 375ppm, III 937ppm, IV 1875ppm and V control. Animals were fed for 13 weeks.

Animals were observed daily and food consumption measured. Body weight was determined weekly.

The following determinations were taken on blood and urine in the fifth, ninth and thirteenth weeks on all animals in the control and high dose groups.

Hematology

Hemoglobin
 RBC Count
 WBC Count
 WBC Differential
 Hematocrit
 Reticulocyte count
 Thrombocyte count
 Prothrombin Time
 Blood Clotting Time
 ESR (sed. rate)

Clinical Chemistry

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Paper Electrophoresis
 SGPT
 SGOT
 Glucose
 Sodium
 Potassium
 SAP

Urine

Volume
 Color
 Specific Gravity
 pH
 Protein
 Glucose
 Hemoglobin

Bilirubin
 Ketone Bodies
 Cells
 Casts
 Organisms
 Inorganic material

Auditory and ophthalmic tests were performed on the same schedule.

All animals were sacrificed by decapitation and exsanguination after 13 weeks. All animals were subject to gross necropsy and the following organs weighed; heart, liver, lungs, spleen, kidneys, adrenals, thymus, hypophysis, gonads, thyroid and brain.

Histopathology was performed on tissue from the following organs from the control and high dose groups.

heart	thymus	spinal cord
aorta	lymph node	rib junction
lungs	brain	pituitary gland
liver	trachea	esophagus
kidney	stomach	thyroid
spleen	small intestine	gonads
adrenal	large intestine	prostate or uterus
pancreas	parotic gland	urinary bladder
eye	peripheral nerve	seminal vesical
tongue	mammary gland	
gall bladder		

Frozen sections of heart, liver and adrenal were prepared and stained with Sudan Red. Liver and spleen sections were stained with Prussian Blue, brain sections with Cresyl Violet and bone marrow smears with Giensa stain.

Student-t-test was utilized for statistical analysis.

Results

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No compound related abnormalities were observed in the animals during the dosing period. Food consumption and growth were comparable to controls throughout the study. Mean compound consumption throughout the study was calculated as shown below.

Group #	Dose ppm	Calculated Dose mg/kg	
		male	female
I	187	16.2	17.3
II	375	35.0	35.6
III	937	82.9	85.5
IV	1875	161.5	175.3

No abnormalities were observed in hematology, clinical chemistry or urinalysis.

Auditory response and ophthalmic examination remained normal throughout the study.

Gross necropsy and histopathology were negative.

DATA EVALUATION REPORT

003655

Compound Irgasan®, DP-300, (Triclosan)

Citation

90 Days Oral Toxicity Study in New Zealand White Rabbits with CH 3565. F. Leuschner, A. Leuschner, W. Schwerdtfeger & W. *Dontenwill. Laboratorium für Pharmakologie und Toxikologie July 31, 1970

Reviewed By

 11/30/80
Robert P. Zendzian Ph D
Pharmacologist

Core Classification Minimum

Tox Category N/A

Conclusion

No compound related abnormalities were observed during and at termination of the study. Hematology, clinical chemistry and urinalysis were normal in the high group. No histopathological abnormalities were observed in the high dose group. This study satisfies the requirement for a nonrodent subchronic study. NOEL 2500ppm.

Materials

Test compound was CH 3565 which has been identified as a code for irgasan technical. Source and purity were not identified.

Male and female New Zealand White rabbits 2.4 to 3.0 Kg at the start of the study.

Methods

Six males and six females per group were treated with CH 3565 in the diet at doses of 250ppm (I), 500ppm (II), 1250ppm (III), 2500ppm (IV) and 0ppm (V). Animals were housed individually and dosed for 90 days.

General behavior, physical condition and food consumption were determined daily. Animals were weighed weekly.

The following determinations were taken on blood and urine in the fifth, ninth and thirteenth weeks on all animals in the control and high dose groups.

Hematology

Hemoglobin
 RBC Count
 WBC Count
 WBC Differential
 Hematocrit
 Reticulocyte count
 Thrombocyte count
 Prothrombin Time
 Blood Clotting Time
 ESR (reviewer could not determine

Clinical Chemistry

Paper Electrophoresis
 SGPT
 SGOT
 Glucose
 Sodium
 Potassium
 Total Protein
 TBA
 SAP
 meaning of this)

Urine

Volume
 Color
 Specific Gravity
 Ph
 Protein
 Glucose
 Hemoglobin
 Bilirubin

Ketone Bodies
 Blood cells
 Organisms
 Casts
 Inorganic Material

Auditory and ophthalmic tests were performed on the same schedule.

All animals were sacrificed by decapitation and exsanguination after 13 weeks. All animals were subject to gross necropsy and the following organs weighed; liver, lungs, spleen, kidneys, adrenals, thymus, pituitary-hypophysis, gonads, prostate/ uterus, thyroid and brain.

Histopatholgy was performed on tissue from the following organs from the control and high dose groups.

heart	thymus	spinal cord
aorta	lymph node	rib junction
lungs	brain	pituitary gland
liver	trachea	esophagus
kidney	stomach	thyroid
spleen	small intestine	gonads
adrenal	large intestine	prostate or uterus
pancreas	parotic gland	urinary bladder
eye	peripheral nerve	seminal vesical
tongue	mammary gland	
gall bladder		

Frozen sections of heart, liver and adrenal were prepared and stained with Sudan Red. Liver and spleen sections were stained with Prussian Blue, brain sections with Cresyl Violet and bone marrow smears with Giemsa stain.

Student-t-test was utilized for statistical analysis.

Results

No compound related abnormalities were observed in the animals during the dosing period. Food consumption and growth were comparable to controls throughout the study. Mean compound consumption throughout the study was calculated as shown below.

Group #	Dose ppm	Calculated Dose mg/kg	
		male	female
I	250	13.8	14.7
II	500	25.8	27.0
III	1250	69.9	66.1
IV	2500	138.5	138.4

No abnormalities were observed in hematology, clinical chemistry or urinalysis.

Auditory response and ophthalmic examination remained normal throughout the study.

Gross necropsy and histopathology were negative.

DATA EVALUATION REPORT

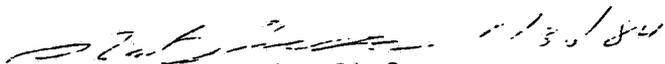
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Compound Irgasan®, DP-300, FAT 80 023/A

Citation

1 Year Oral Toxicity Study in Baboons with compound
FAT 80 023/A. J.C. Drake & A. Buxtorf
Geigy Pharmaceuticals, Toxicology Department, Stamford Lodge,
Wilmslow, Cheshire. Jun 28, 1976

Reviewed By


Robert P. Zendzian Ph.D.
Pharmacologist

Core Classification Minimum

Tox Category N/A

Conclusion

The subchronic oral toxicity of FAT 80 023/A in the baboon was characterized by effects on the digestive system, vomiting, failure to eat and diarrhoea at 100 and 300mg/kg/day, and depression of red blood cells at 300mg/kg. A NOEL was demonstrated at 30mg/kg/day. This study satisfies the requirement for a nonrodent subchronic study.

Materials

FAT 80 023/A, Irgasan®, DP 300, technical

Fifty-six baboons, 28 male and 28 female, with average body weights of 8.10 kg males and 6.54 kg females. Animals were maintained for at least seven months before the start of the study. All animals were negative for parasites and negative to tuberculin test.

Methods

Animals were assigned to one of four treatment groups of seven males and seven females and dosed with zero, 30, 100 or 300 mg/kg/day FAT 80 023/A orally by capsule for 52 weeks.

Clinical signs and food consumption were recorded daily and body weight weekly. Blood and urine samples were collected before test and on weeks 5, 9, 13, 20, 26, 39 and 52 and during week 56 from the recovery animals. Ophthalmic and hearing examinations were carried out before test and on weeks 5, 9, 16, 26, 40 and 52 and during week 56 from the recovery animals

Hematology

Hemoglobin
 Erythrocyte count
 Hematocrit
 Reticulocyte count
 Inclusion bodies
 Thrombocyte count
 Leucocyte count
 Leucocyte differential
 Prothrombin time
 ESR (sed. rate)
 Methhemoglobin

Clinical Chemistry

Sodium
 Chloride
 Glucose
 Urea
 SGOT
 SGPT
 SAP
 Total protein
 Electrophoresis
 Cholinesterase
 Cholesterol

Urine analysis

pH
 Specific Gravity
 Protein
 Glucose
 Bilirubin
 Ketones
 Blood
 Sediment

Two males and two female from each group were sacrificed at six months, three males and three females from each group were sacrificed at 52 weeks and the remaining animals after a six week recovery period.

Gross necropsy was performed on all animals at sacrifice and the following organs were weighed; adrenals, brain, gonads, heart, kidneys, liver, pituitary and thyroid.

The following tissues were were collected for histopathology:

Adrenals	Pancreas
Brain	Prostate or uterus
Gonads	Spinal cord
Kidneys	Thyroids
Lymph nodes, axillary & mesenteric	Bone marrow
Muscle	Eye and optic nerve
Pituitary	Heart
Spleen	Lungs
Thymus	Mammary gland
Aorta	Sciatic Nerve
Colon	Small intestine
Gross lesions	Urinary bladder
	Liver

Body weight and food consumption were analysed by the Profile Analysis Method and laboratory data by the Mann-Whitney U Test.

Results

Compound related signs of digestive tract effects were observed in groups three and four with the majority of effects in group four. Signs included vomiting, failure to eat and diarrhoea. Diarrhoea occurred 4-6 hours after dosing or during the night and was the most common toxic sign.

In the male animals, mean growth rate was decreased from week 32 through the end of dosing in groups 3 and 4 but there was no apparent difference between these two groups. In the female animals, mean growth rate was higher than controls from week 25 to the end of the study in groups 2 and 3 and lower than controls from week 25 to the end of the study in group 4.

No pattern of compound related effect on food consumption was observed. Consumption varied from week to week with some isolated depression at the high dose particularly in the males.

Depression of red blood cells at the high dose in both sexes was seen throughout the dosing period. No other changes in hematological parameters were observed.

A decrease in serum potassium and serum alkaline phosphatase was observed at the high dose, in both sexes, throughout the study. Decreased total protein was also observed at this dose but the effect was inconsistently present. No other effects were observed in clinical chemistry.

No compound related effects were observed in urine analysis.

At necropsy there was some indication of an effect on the lining of the stomach of the high dose animals at each sacrifice. Histopathology was slightly confirmatory of the stomach effect. No other compound related effects were observed in either gross necropsy or histopathology.

Data Evaluation Report

003655

Compound Irgasan® , CH 3565

Citation

90 Days Oral Toxicity Study in Beagle Dogs with CH 3565
F. Leuschner, A. Leuschner, W. Schwerdtfeger & W. Dantenwill
Laboratorium fur Pharmakologie und Toxikologie, July 10, 1970

Reviewed By

 1/30/84
Robert P. Zendzian Ph.D.
Pharmacologist

Core Classification Minimum

Tox Category N/A

Conclusion

No compound related abnormalities were observed during and at termination of the study. Hematology, clinical chemistry and urinalysis were normal in the high group. No histopathological abnormalities were observed. This study satisfies the requirement for a nonrodent subchronic study. NOEL 625ppm.

Materials

Test compound was CH 3565 which has been identified as a code for irgasan technical. Source and purity not identified.

Thirty two pure-bred beagle dogs (16 males and 16 females) from the laboratories breeding colony. The dogs were eight months of age at the start of the study.

Methods

The dogs were assigned (four males and four females) to one of four treatment groups which were dosed as follows; I 125ppm, II 313ppm, III 625ppm and IV untreated. These doses were equivalent to 5, 12.5, 25 and zero (control) mg/kg/day. Dogs were dosed for 90 days

Dogs were observed daily for signs of toxicity, food and water consumption, and fecal condition. Dogs were weighed on Monday, Wednesday and Friday throughout the study.

The following determinations were taken on blood and urine on the high dose and control dogs before dosing and on the fifth, ninth and thirteenth week of dosing.

Hematology

Hemoglobin
 RBC Count
 WBC Count
 WBC Differential
 Hematocrit
 Reticulocyte count
 Thrombocyte count
 Prothrombin Time
 Blood Clotting Time
 ESR (sed. rate)

Urine

Volume
 Color
 Specific Gravity
 pH
 Protein
 Glucose
 Hemoglobin

Clinical Chemistry

Paper Electrophoresis
 SGPT
 SGOT
 Glucose
 Sodium
 Potassium
 SAP
 Total Protein
 BUN

Bilirubin
 Ketone Bodies
 Cells
 Casts
 Organisms
 Inorganic material

Ophthalmic and auditory examinations were performed on all dogs prior to dosing and after 13 weeks of treatment.

Animals were sacrificed by a euthanasia solution and exsanguinated. All dogs were subject to gross necropsy. The following organs were weighed on all dogs; Liver, lungs, spleen, kidney, adrenals, thymus, pituitary, gonads, prostate/uterus, thyroid and brain.

Histopatholgy was performed on tissue from the following organs from all dogs.

heart	thymus	spinal cord
aorta	lymph node	sternum
lungs	brain	pituitary gland
liver	trachea	esophagus
kidney	stomach	thyroid
spleen	small intestine	gonads
adrenal	large intestine	prostate or uterus
pancreas	parotic gland	urinary bladder
eye	skin	seminal vesical
mammary gland	gall bladder	nerve with muscle

Frozen sections of heart, liver and adrenal were prepared and stained with Sudan Red. Liver and spleen sections were stained with Prussian Blue, brain sections with Cresyl Violet and bone marrow smears with Giensa stain.

Student-t-test was utilized for statistical analysis.

Results

There were no signs of compound related toxicity during the study. There was no effect on food or water consumption, or body weight. No abnormalities were observed in the hearing test or eye examination.

No abnormalities were observed in hematology, clinical chemistry or urinalysis.

Gross necropsy and histopathology were negative.

initials

Data Evaluation Report

003655

Compound FAT 80'023/H, Irgasan

Citation

90-day Oral Toxicity Study in Rats with FAT 80'023/H,
Final Report. L.A. Goldsmith & D.K. Craig, Litton Bionetics
LBI Project No 22188, Oct 11, 1983

Reviewed by


Robert P. Zendzian PhD
Pharmacologist

Core Classification Minimum

Tox Category N/A

Conclusion

The test compound caused a nonspecific dose-related liver toxicity at 3000 and 6000ppm. The low dose, 1000ppm, was a NOEL.

Materials

FAT 80'023/H, 2,4,4'-Trichloro-2'-Hydroxy Diphenyl Ether
Batch 5/0/0194/0 (Irgasan)

CRL:COBS CD(SD) BR strain rats from Charles River Breeding Laboratories.

Methods

Rats were assigned, randomly, to four groups of 25 males and 25 females. Groups were dosed with 0, 1000, 3000 or 6000ppm FAT 80 in the diet for 90 days. . .

Ophthalmological examinations ~~were~~ performed on all animals prior to dosing and during the 12th week of dosing.

Animals were observed twice daily for signs of toxicity and weighed and examined weekly. Food consumption was recorded weekly.

Clinical chemistry was performed on 10 rats/sex/dose at day 45. Hematology and clinical chemistry was performed on 15 rats/sex/dose at day 90. Urinalysis was performed on the control and 6000ppm rats at 90 days.

Clinical Chemistry

Day 45 & 90

alkaline phosphatase (SAP)
 alanine aminotransferase (SGPT)
 aspartate aminotransferase (SGOT)
 ornithine carbamyltransferase (OCT)
 gamma glutamyl transpeptidase (GGT)
 sorbital dehydrogenase (SDH)
 lactic dehydrogenase (LDH)

Day 90

Glucose
 BUN
 creatinine
 cholesterol
 triglyceride
 uric acid
 calcium
 phosphorus
 total protein
 albumin
 globulin
 A/G ratio
 potassium
 sodium
 chloride
 carbon dioxide
 total bilirubin
 direct bilirubin
 indirect bilirubin

Day 90

Hematology

RBC morphology
 hematocrit
 hemoglobin
 erythrocyte count
 total leukocyte count
 differential leukocyte count
 reticulocyte count
 platelet count

Day 90

Urinalysis

pH
 specific gravity
 protein
 glucose
 ketone
 occult blood
 microscopic examination of sediment
 color
 appearance
 bilirubin

Gross necropsy was performed on all animals that died on study and on all sacrificed animals. At day 45 10 rats/sex/group were sacrificed and the remaining rats were sacrificed at day 90. The following organs and tissues were preserved for histological examination.

brain	spleen
spinal cord (cervical, thoracic, lumbar)*	pancreal
pituitary	sciatic nerve
lungs with bronchi	stomach
kidneys	duodenum
adrenal glands	jejunum
liver	ileum
	cecum

colon
rectum
urinary bladder
ovaries
all gross lesions
seminal vesicle*
uterus (with fallopian tubes)
testes
epididymides
prostate*
heart
thymus
aorta
trachea
esophagus

salivary gland (submaxillary)*
lymph node (1 axillary and
1 mesenteric)
thyroid with parathyroid
skin*
mammary gland
skeletal muscle (thigh)*
eyes (with adenexes)*
exorbital lachrymal glands*
bone and marrow (sternum)
femur with articular surface*

The liver, kidney and lungs were examined in all animals sacrificed at 45 days and all non-asterisk tissues in the control and 6000ppm at final sacrifice.

Liver and kidneys were weighed at 45 days and brain, adrenals, gonads, heart, liver, kidneys and spleen at 90 days.

Appropriate numerical data was analyzed by Dunnett's t-test.

Results

No compound induced deaths occurred. Six animals died following terminal bleeding and before sacrifice. No compound related signs of clinical toxicity were observed. Terminal ophthalmoscopic examinations were negative.

Compound related depression in growth was observed at the high dose in both sexes and at the intermediate dose in females. Differences were statistically significant at the high dose in both sexes but not at the intermediate dose in females.

Due to food rejection and spillage by the high group animals the consumption values were distorted. Lower food consumption in the high dose groups appears to have occurred.

At 45 days there were no statistically significant differences in clinical chemistry in the treated males. However there were differences which appeared compound related; GGT increased all doses, LDH decreased intermediate and high dose and SGOT dose related decrease all doses. In the treated females, SDH decreased significantly at the intermediate and high doses and LDH increased at the same doses but not significantly.

At termination the following statistically significant changes were observed in clinical chemistry in the males; globulin decreased high dose, albumin/globulin ratio decreased high dose, triglycerides decreased intermediate and high dose, direct bilirubin decreased high dose, indirect bilirubin increased high dose and cholesterol decreased all doses dose related. LDH was decreased at all doses but significantly only at the low dose. In the females chloride was increased significantly at the low and intermediate dose. SGOT and SGPT decreased at all doses but not significantly. Triglycerides decreased at all doses, significantly at the intermediate dose. OCT increased significantly at the low and intermediate doses. Direct and total bilirubin decreased at the intermediate and high doses but not significantly. Creatinine increased at the intermediate and high doses, significantly at the latter dose.

In the hematology values taken at termination, for the males reticulocytes decreased at all doses but not significantly, white blood cells decreased at all doses significantly at the intermediate dose and red blood cells decreased at all doses significantly at the intermediate and high doses. For the females reticulocytes decreased at all doses but not significantly, white blood cells decreased at all doses but not significantly and red blood cells, hemoglobin and hematocrit decreased significantly at the high dose.

Urinalysis data from control and high dose taken at termination showed a doubling of the number of males with ketones in their urine.

Body, liver and kidney weights taken at the 45 day sacrifice showed, in the males decreased body weight at the high dose, increased liver weights at the intermediate and high doses and decreased kidney weights at the high dose. In the females there was decreased body and kidney weights at the high dose.

Body and organ weight taken at termination showed in the males, increased body weight not significant high dose, increased liver weight significant high dose and decreased spleen weight significant intermediate and high dose. In the females there was decreased heart weight significant at the intermediate and high dose.

Gross pathology at the 45 and 90 day sacrifices showed no compound related abnormalities.

Histopathology showed undifferentiated leukemia in one male in the high dose group sacrificed at 45 days. This was the only animal in the study showing "tumor".

The only compound-related lesion seen in histopathology was in the liver. Fatty metamorphosis was seen in 3 males in group 3 and 8 males in group 4. Cytomegaly was seen in one male in group 2, 10 females and 15 males in group 3 and 23 females and 21 males in group 4.

Discussion

Compound related toxicity was clearly demonstrated at the high dose of 6000ppm. Signs of toxicity included retarded growth, clinical chemistry abnormalities in the serum, ketones in the urine and histological abnormalities in the liver. The histological and clinical chemistry abnormalities were observed to a lesser degree in the intermediate dose, 3000ppm, animals.

The toxic effects noted appear to be a combination of unpalatable food and a nonspecific liver toxicity.

The low dose, 1000ppm, is a no observable effect level (NOEL).