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

JUL 6 1984

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Naphthalene Acetic Acid, Teratology in the Rabbit

TO: Robert Taylor (PM-25)
Registration Division (TS-767)

FROM: Robert P. Zendzian Ph. D. 6/18/84
Toxicology Branch
HED (TS-769)

THROUGH: William Butler, Head
Review Section III

William Burnam, Chief
Toxicology Branch 7/6/84

Compound Naphthalene acetic acid

Registration #264-248, 336, 29, 142, 137 & 141

Accession #252865 & 66

Tox Chem #~~468~~ 589

Registrant Union Carbide

Action Requested

The registrant has submitted for review reports of a range-finding and a full teratology study of NAA in the rabbit.

Conclusion

The studies submitted satisfy the requirement for a teratology study in the rabbit. NAA is not a teratogen in this species.

Discussion

The following reports were submitted by the Registrant and DERs on them are attached.

Citation

Range-finding Teratology Study in Rabbits. B.H. Cuddeback, J.L. Schardeiun & M. Blair, International Research and Development, 369-111, Oct 28, 1983

Conclusion

The major effect on reproduction was a dose-related increase in mean preimplantation loss at all doses in the treated animals. This effect may be an artifact of the small number of animals per group.

Citation

Teratology Study in Rabbits, L.G. Miller, J.L. Schardein & M. Blair, International Research and Development Corp. 369-105, Nov 28, 1983

Conclusion

The compound was not teratogenic at the doses tested.

The observation of preimplantation loss in the range-finding study appears problematical. Histroical control data on 343 animals submitted with the range-finding study show a preimplantation loss of 30.8%. Historical control data on 75 animals submitted with the full teratology study show a preimplantation loss of 32.6 %. The range-finding study shows a preimplantation loss of controls 11.4%, 28mg/kg 23.2%, 80mg/kg 39.2% and 240mg/kg 42.1%. The full study shows preimplantation loses of controls 32.5%, 37.5mg/kg 46.7%, 75mg/kg 39.2% and 150mg/kg 41.8%.

The range-finding study had 3, 4, 4 and 3 gravid animals per respective treatment group and the full study had 15, 16, 14 and 15 gravid animals per respective treatment group. thus a very small difference in preimplantation loss in the range-finding control group produces a large percentage change.

Maternal toxicity was observed at the high dose in both studies.

NOELS

Range finding	Full study
Teratogenic 240mg/kg/day HDT	Teratogenic 150mg/kg/day HDT
Fetotoxic 240mg/kg/day HDT	Fetotoxic 150mg/kg/day HDT
Maternal Toxicity 80mg/kg/day	Maternal Toxicity 75mg/kg/day
Maternal LEL 240mg/kg/day, lethality	Maternal LEL 150mg/kg/day, lethality

Data Evaluation Report

Compound Naphthalene acetic acid

Citation

Range-finding Teratology Study in Rabbits. B.H. Cuddeback, J.L. Schardeiun & M. Blair, International Research and Development, 369-111, Oct 28, 1983

Reviewed by 6/18/84
Robert P. Zendzian PhD
Pharmacologist

Core classification Supplimentary

Tox Catagory N/A

Conclusion

The major effect on reproduction was an increase in mean preimplantation loss, compared to controls, at all doses in the treated animals. This effect may be an artifact of the small number of animals per group.

Materials

Naphthalene acetic acid, 98.55%, Lot#RTS2846AC, Prod Code S80258

Sexually mature 4 1/2 to 5 month old female Dutch Belted rabbits, from Langshaw Farms

Methods

Animals were assigned, randomly, to four groups of five animals each and dosed orally at 0, 28, 80 and 240mg/kg/day on days 6 through 27 of gestation.

Animals were superovulated three weeks prior to insemination with 50 USP units of chorionic gonadotropin IV. Semen was provided by five proven male of the same strain. Females were inseminated and immediately dosed IV with 100 USP units of chorionic gonadotropin. The day of insemination was designated day zero of gestation.

Animals were observed twice daily for mortality and once daily for toxic signs during the dosing period. Animals that died were necropsied. Body weights were taken on days o, 6, 12, 18, 24 and 28. Surviving animals were sacrificed on day 28 and the uterus and ovaries examined for viable and nonviable fetuses, resorptions, number of inplantations and number of corpra lutea.

Results

One animal dosed at 80mg/kg/day died on gestation day 17 with no clinical signs of toxicity. One animal dosed at 240mg/kg/day aborted on gestation day 28 following signs of toxicity consisting of hair loss, decreased feces and significant weight loss. No other animals showed compound-related signs of toxicity.

The major effect on reproduction was an increase in mean preimplantation loss at all doses in the treated animals. Controls 11.4%, Low dose 23.2%, intermediate dose 39.2% and high dose 42.1%. This is reflected in a decreased number of viable fetuses in the intermediate and high doses relative to control.

Discussion

The observation of preimplantation loss in this study appears problematical. Historical control data on 343 animals which was submitted with the report shows a preimplantation loss of 30.8 %.

The range-finding study had 3, 4, 4 and 3 gravid animals per respective treatment group, thus a very small difference in preimplantation loss in the control group can produce a large percentage change.

NOELS

Teratogenic 240mg/kg/day HDT
Fetotoxic 240mg/kg/day HDT
Maternal Toxicity 80mg/kg/day
Maternal LEL 240mg/kg/day, Lethality

Data Evaluation Report

Compound Naphthalene acetic acid

Citation

Teratology Study in Rabbits, L.G. Miller, J.L. Schardein & M. Blair, International Research and Development Corp. 369-105, Nov 28, 1983

Reviewed by 6/18/84
Robert P. Zendzian PhD
Pharmacologist

Core classification Minimum

Tox Catagory N/A

Conclusion

The compound was not teratogenic at the doses tested.

Materials

Naphthalene acetic acid, 98.55%, Lot#RTS2846AC, Prod Code S80258

Sexually mature 4 1/2 to 5 month old female Dutch Belted rabbits, from Langshaw Farms

Methods

Animals were assigned, randomly, to four groups of 16 animals each and dosed orally at 0, 37.5, 75 and 150mg/kg/day on days 6 through 27 of gestation.

Animals were superovulated three weeks prior to insemination with 50 USP units of chorionic gonadotropin IV. Semen was provided by 8 proven male of the same strain. Females were inseminated and within one hour dosed IV with 100 USP units of chorionic gonadotropin. The day of insemination was designated day zero of gestation.

Animals were observed twice daily for mortality and gross signs of toxicity throughout the study once daily in detail for toxic signs on days 6 through 28 of gestation. Animals that died were necropsied. Body weights were taken on days 0, 6, 12, 18, 24 and 28. Surviving animals were sacrificed on day 28 and the uterus and ovaries examined for viable and nonviable fetuses, resorptions, number of implantations and number of corpra lutea.

All fetuses were weighed and examined for external abnormalities including the palate and ears. Fetuses were examined for organ malformations, including the brain and the eviserated carcass processed for skeletal examination.

Statistical analysis was performed on appropriate numerical data.

Results

One low dose and three high dose animals died on study. All of these animals were gravid. Only two of the high dose animals showed signs of toxicity prior to death. No signs of compound related toxicity were observed in the surviving animals.

Weights of the pregnent animals varied over the gestation period with some indication of a dose related loss in the high dose. However the variation was such as to obscure possible compound effects in the low and intermediate doses.

No compound-related abmormalities in the pregnent animals were observed at necropsy.

No compound-related effect was observed on implantation or fetal viability.

No teratological effects were observed.

NOELs

Teratogenic 150mg/kg/day HDT
Fetotoxic 150mg/kg/day HDT
Maternal Toxicity 75mg/kg/day
Maternal LEL 150mg/kg/day, lethality