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CASWELL FILE
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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, DC 20460

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OFFICE OF
PESTICIDES AND
TOXIC SUBSTANCES

FEB - 5 1990

MEMORANDUM

SUBJECT: CYPROCONAZOLE-SUPPLEMENTAL DATA FOR A DEVELOPMENTAL TOXICITY STUDY IN RATS.

TO: S. LEWIS/GRABLE PM 21
REGISTRATION DIVISION (H7505C)

FROM: K. CLARK SWENTZEL K. Clark Swentzel 2/2/90
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EPA ID No. 55947-RGG
MRID No. NONE
PROJECT No. 9-2120
CASWELL No. 272E
REGISTRANT: SANDOZ CORP.

REQUESTED ACTION

REVIEW SUPPLEMENTAL DATA.

TB II REVIEW OF SUBJECT STUDY

THE PRESENT SUBMISSION IS THE REGISTRANT'S RESPONSE TO THE TB II REVIEW (MEMORANDUM, SWENTZEL, HED, TO ROSSI, RD, JANUARY 17, 1989) OF A DEVELOPMENTAL TOXICITY STUDY (STUDY No. 048712) IN WHICH A SUSPENSION OF CYPROCONAZOLE TECHNICAL IN DISTILLED WATER MIXED WITH CARBOXYMETHYLCELLULOSE SODIUM SALT (CMC, 4%) WAS ADMINISTERED DAILY TO PREGNANT WISTAR/HAN RATS (25/GROUP) VIA ORAL GAVAGE FROM DAY 6 THROUGH 15 OF GESTATION AT DOSAGE LEVELS OF 6, 12, 24 OR 48 MG/KG.

IT WAS CONCLUDED IN THE REVIEW THAT ALTHOUGH INHIBITED BODY WEIGHT GAIN DURING TREATMENT AMONG FEMALES IN THE 12, 24 AND 48 MG/KG/DAY GROUPS WAS EVIDENCE OF MATERNAL TOXICITY, THE NOTED BODY WEIGHT DIFFERENCES APPEARED TO BE INFLUENCED BY TREATMENT-RELATED INTRA-UTERINE EFFECTS (INCREASED NUMBER OF RESORPTIONS AND DECREASED FETAL WEIGHT). THEREFORE, TB II CONSIDERED 6 MG/KG/DAY TO BE AN EQUIVOCAL NOEL FOR MATERNAL TOXICITY. ALSO, A NOEL FOR DEVELOPMENTAL TOXICITY WAS NOT ESTABLISHED BECAUSE THERE WAS AN INCREASED FETAL INCIDENCE OF SUPERNUMERARY RIBS OBSERVED AT 6 MG/KG/DAY, THE LOWEST DOSE ADMINISTERED, SO THE STUDY WAS CLASSIFIED CORE-SUPPLEMENTARY.

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HOWEVER, IT WAS INDICATED THAT THE STUDY MIGHT BE UPGRADED IF THE REGISTRANT COULD SUBMIT DATA SHOWING THE LITTER INCIDENCE OF SUPERNUMERARY RIBS WITH APPROPRIATE STATISTICAL ANALYSES TO AID IN THE DETERMINATION OF A POSSIBLE NOEL FOR DEVELOPMENTAL TOXICITY.

REGISTRANT'S RESPONSE

MATERNAL TOXICITY

THE REGISTRANT INDICATED THAT IT WAS "INAPPROPRIATE" TO RELY ON FINAL CORRECTED BODY WEIGHT GAIN (I.E., TOTAL WEIGHT GAIN DURING TREATMENT LESS TOTAL INTRA-UTERINE WEIGHT) TO DETERMINE MATERNAL TOXIC DOSAGE LEVELS. THIS POSITION WAS BASED ON INHIBITED BODY WEIGHT GAIN (-18, -29 AND -35% OF CONTROL AT 12, 24 AND 48 MG/KG, RESPECTIVELY, DURING THE INITIAL DAYS OF TREATMENT (GESTATION DAYS 6-11) AND THE ABSENCE OF INTRA-UTERINE EFFECTS AT 12 MG/KG/DAY. ALTHOUGH IT CAN BE ARGUED THAT THE THE INHIBITED BODY WEIGHT GAIN OBSERVED AMONG FEMALES IN THE 24 AND 48 MG/KG GROUPS MAY BE ATTRIBUTED TO PREVIOUSLY NOTED INTRA-UTERINE EFFECTS, IT IS TB II'S OPINION THAT, WITH CONSIDERATION OF THE REGISTRANT'S ARGUMENTS, 6 MG/KG CAN BE ESTABLISHED AS A NOEL FOR MATERNAL TOXICITY. HOWEVER, TB II STILL CONSIDERS THE MATERNAL TOXIC EFFECTS OBSERVED IN THIS STUDY (PREVIOUSLY NOTED INHIBITED BODY WEIGHT GAIN DURING TREATMENT AND DECREASED FOOD CONSUMPTION AT THE 24 AND 48 MG/KG DOSAGES) TO BE MINIMAL TOXIC EFFECTS, SO THE DEVELOPMENTAL EFFECTS OBSERVED IN THIS STUDY (SEE BELOW) SHOULD NOT BE CONSIDERED SECONDARY EFFECTS FROM MATERNAL TOXICITY.

SUPERNUMERARY RIBS

THE REGISTRANT SUBMITTED THE FOLLOWING LITTER INCIDENCE DATA FOR SUPERNUMERARY RIBS:

DOSAGE(MG/KG/DAY)	0	6	12	24	48
INCIDENCE	6/23	6/22	9/23	16/25†	16/21*
%	26	27	39	64	76

* $P < 0.05$, FISHER'S EXACT
† REIGISTRANT INDICATED 17/25(68%); THIS DOES NOT CORRELATE WITH TABULATED DATA

THESE DATA SHOW THAT THE LITTER INCIDENCE OF THIS VARIATION AT THE LOW-DOSE LEVEL IS COMPARABLE TO THAT FOR THE CONTROLS, THEREFORE, A NOEL FOR DEVELOPMENTAL TOXICITY CAN NOW BE ESTABLISHED. THE REGISTRANT CONCLUDED THAT THE NOEL FOR THIS EFFECT IS 24 MG/KG/DAY SINCE ONLY THE INCREASED INCIDENCE AT 48 MG/KG/DAY IS STATISTICALLY SIGNIFICANT. IT IS TB II'S OPINION THAT THE NOEL FOR THIS EFFECT IS 6 MG/KG/DAY. ALTHOUGH THE INCREASE AT 12 MG/KG/DAY IS NOT STATISTICALLY SIGNIFICANT, IT IS A SUBSTANTIAL INCREASE THAT IS DOSE-RELATED TO INCREASES OBSERVED AT THE 2 HIGHEST DOSAGES. THEREFORE, 12 MG/KG/DAY IS CONSIDERED THE LEL FOR DEVELOPMENTAL TOXICITY IN THIS STUDY.

HYDROCEPHALY AND CLEFT PALATE

HYDROCEPHALUS INTERNUS WAS SEEN IN 1 FETUS AT 24 MG/KG AND 1 FETUS AT 48 MG/KG WHILE HYDROCEPHALUS EXTERNUS OCCURRED IN 1 FETUS AT 48 MG/KG; BOTH CEREBRAL HEMISPHERES

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WERE INVOLVED IN EACH FETUS AND THE EFFECTS IN THE HIGH-DOSE GROUP WERE SEEN IN 2 LITTERS. THE REGISTRANT INDICATED THAT THE NOTED HYDROCEPHALUS INTERNUS MIGHT ACTUALLY HAVE BEEN DELAYED DEVELOPMENT OF THE LATERAL VENTRICLES OF THE BRAIN WHICH WOULD BE REVERSIBLE WITH CONTINUED GROWTH. IT IS TB II'S OPINION THAT THERE IS NO MEANS TO VERIFY THIS SPECULATION FROM THE AVAILABLE INFORMATION.

CLEFT PALATE WAS OBSERVED IN 2 FETUSES (2 LITTERS) IN THE 48 MG/KG GROUP. THE REGISTRANT INDICATED THAT THE INCIDENCE WAS NOT STATISTICALLY SIGNIFICANT WHEN COMPARED WITH CONTROL VALUES AND THAT THIS MALFORMATION (AS WELL AS HYDROCEPHALY) OCCURRED ONLY AT DOAGES THAT WERE TOXIC TO THE FEMALE. TB II BELIEVES THAT IT SHOULD BE NOTED THAT THE OBSERVED INCIDENCES OF HYDROCEPHALY AND CLEFT PALATE BOTH EXCEEDED RESPECTIVE VALUES REPORTED IN THE REGISTRANT'S HISTORICAL CONTROL DATA (APPENDED PAGES 14-17, MEMORANDUM, SWENTZEL, HED, TO ROSSI, RD, JANUARY 17, 1989) AND THAT CLEFT PALATE WAS ALSO SEEN IN THE PILOT STUDY AT DOSAGES OF 30, 75 AND 120 MG/KG/DAY.

CONCLUSIONS

BASED ON ADDITIONAL INFORMATION IN THE CURRENT SUBMISSION, A NOEL FOR DEVELOPMENTAL TOXICITY CAN BE ESTABLISHED AT 6 MG/KG/DAY; THE LEL IS 12 MG/KG/DAY, BASED ON AN INCREASED INCIDENCE OF SUPERNUMERARY RIBS. HYDROCEPHALY, SEEN IN 1 FETUS AT 24 MG/KG AND 2 FETUSES AT 48 MG/KG, AND CLEFT PALATE, WHICH OCCURRED IN 2 FETUSES (2 LITTERS) AT 48 MG/KG, ARE CONSIDERED TO BE COMPOUND-INDUCED. ADDITIONAL EFFECTS INDICATIVE OF DEVELOPMENTAL TOXICITY AT 24 AND 48 MG/KG INCLUDED DECREASED LITTER SIZE. DECREASED NUMBER OF LIVE FETUSES/LITTER, DECREASED FETAL BODY WEIGHT, INCREASED RESORPTION RATE, INCOMPLETE OSSIFICATION IN PHALANGEAL NUCLEI AND THE ABSENCE OF OSSIFICATION IN CALCANEA. THE NOEL FOR MATERNAL TOXICITY IS ALSO 6 MG/KG/DAY, BASED ON INHIBITED BODY WEIGHT GAIN DURING TREATMENT AT 12 MG/KG. THE MATERNAL TOXICITY INDUCED IN THIS STUDY IS CONSIDERED MINIMAL, THEREFORE, TB II DOES NOT CONSIDER THE NOTED VARIATIONS AND MALFORMATIONS TO BE SECONDARY EFFECTS FROM MATERNAL TOXICITY.

TB II WILL RECOMMEND THAT THE DATA IN THIS STUDY SHOULD BE FURTHER EVALUATED BY THE HED DEVELOPMENTAL TOXICITY PEER REVIEW COMMITTEE.

CORE-CLASSIFICATION: THIS STUDY CAN BE UPGRADED TO CORE-MINIMUM

GUIDELINE REQUIREMENT: THIS STUDY SATISFIES THE DATA REQUIREMENT FOR GUIDELINE NO. 83-3(,