

Chemical: **Metam Sodium**
 From: Developmental/Reproduction RfD Subcommittee

December 1, 1994

The HED Developmental and Reproductive Toxicity Peer Review Committee met on October 15 and December 12, 1991 to evaluate the data package for metam sodium. At that time, the only studies available for review were 1987 developmental toxicity studies in rats (DER #6) and in rabbits (DER #8) conducted by BASF. These two DERs were evaluated by the PRC and the studies were determined to contain deficiencies, but were adequate to determine that metam sodium induced developmental toxicity (see the Peer Review report). In the rat, developmental toxicity (increased skeletal variations, retardations, and anomalies) was suggested at dose levels as low as 4.2 mg a.i./kg/day; the maternal NOEL was 4.2 mg a.i./kg/day and the developmental NOEL was \leq 4.2 mg a.i./kg/day. In the rabbit, the adjusted developmental NOEL was 4.2 mg a.i./kg/day based on postimplantation loss at 12.6 mg a.i./kg/day, and was lower than the maternal NOEL of 12.6 mg a.i./kg/day. (Note: for these studies, the developmental findings which defined the LOEL are appropriate acute and/or short term endpoints for Less-Than-Lifetime risk assessment.)

The 2-generation reproductive toxicity study and two new developmental toxicity studies have been submitted to the Agency after the Reproductive and Developmental Peer Review was conducted. An evaluation of these studies follows.

DER No. 4
Study: 2-Generation Reproduction — Rat
 Drinking water levels: 0.01 (0.008), 0.03 (0.024), and 0.1 (0.08) mg/ml
 Males: 1.2, 3.2, and 11.5 mg/kg/day
 Females: 1.8, 3.9, and 13.5 mg/kg/day

Systemic NOEL	0.03 mg/ml
Systemic LOEL	0.1 mg/ml based on decreased body weights for P and F1 adults, microscopic lesions of Bowmans gland ducts and olfactory epithelium for P and F1 females
Reproductive NOEL	\geq 30 mg/kg/day
Reproductive LOEL	Not determined

Comments: 1) Decreased testes and/or epididymides weights are mentioned for high-dose adults and for F1 and F2 pups (absolute weights, I presume); also, increased male infertility was suspected in F1 treated groups. Even though histopath does not identify a lesion, these data hint at male reproductive toxicity which becomes more severe in the second generation. If this idea is accepted, the reproductive NOEL/LOEL would change. 2) Dosage headings are incorrect in all DER body weight tables.

Consensus:

Adequacy of Study: Acceptable
 Endpoints: Agree, except for comments above

DER Quality: Acceptable; changes in reproductive NOEL/LOEL may be required
 CORE rating: Agree with Minimum

LTL Endpoints: None

DER No. 5
Study: Developmental Toxicity — Rat
 Gavage levels: 5, 20, or 60 mg/kg/day (adjusted for 43.1% purity), days 6-17

Maternal NOEL	5 mg/kg/day
Maternal LOEL	20 mg/kg/day based on decreased body weight gain and food efficiency during treatment
Developmental NOEL	5 mg/kg/day
Developmental LOEL	20 mg/kg/day based on increased resorptions and skeletal observations, decreased fetal weight, increased fetal incidence of skeletal variations (particularly in the cervical vertebrae, odontoid, and calcaneum)

Comments: I agree with the analysis of the data. However, I think that the increased variations in the 5 mg/kg/day dose group can be called "suggestive" of a treatment-related effect, as was done in the previous rat study reviewed by the PRC.

Consensus:

Adequacy of Study: Acceptable
 Endpoints: Agree with findings
 DER Quality: Acceptable
 CORE rating: Agree with Guideline rating

LTL Endpoints: Acute or short term exposure = Resorptions, body weight decrements, and skeletal alterations at 20 mg/kg/day (NOEL = 5 mg/kg/day)

DER No. 7
Study: Developmental Toxicity — Rabbit
 Gavage levels: 5, 20, or 60 mg/kg/day (adjusted for 43.1% purity), days 8-20

Maternal NOEL	5 mg/kg/day
Maternal LOEL	20 mg/kg/day based on decreased body weight gain, food consumption, and food efficiency
Developmental NOEL	5 mg/kg/day
Developmental LOEL	20 mg/kg/day based on increased incidence of skeletal observations (increased sutural bones between parietals, misshapen hyoid, partial ossification of cervical

transverse process)

Comments: I agree with the analysis of the data.

Consensus:

Adequacy of Study: Acceptable
Endpoints: Agree with findings
DER Quality: Acceptable
CORE rating: Agree with Minimum rating

LTL Endpoints: Acute or short term exposure = Skeletal variations at 20 mg/kg/day

OVERALL CONCLUSIONS:

Evidence of developmental or reproductive toxicity?

In the additional reproductive and developmental toxicity studies submitted, supported the previous determination by the PRC, that metam sodium is a developmental toxicant in both rats and rabbits. In addition, the presence of a male reproductive toxic effect was suggested by reduced F1 male fertility and decreased testes and/or epididymis weights in treated adult and weanling male rats.

In essence, the NOEL and LOEL on the 1993 developmental toxicity studies confirm the levels of developmental toxicity that were observed previously (1987 studies), although the specific findings were not precisely equivalent.

In the previous (1987) studies, there was a concern generated regarding meningocoeles observed in both rats and rabbits; one appeared at the HDT in the new (1993) rat study as well, and three incidences of internal hydrocephaly, another neural tube defect occurred at the same dose. The DER for the 1993 rabbit study does not present low incidence external/visceral findings, but because neural tube defects are not mentioned, one can probably assume they were not observed in the new rabbit study.

For rats, skeletal variations in the 1987 study included no mention of the calcaneum or odontoid, and vertebral variations were mostly concentrated in the thoracic vertebrae, rather than the cervical vertebrae which is the location of most of the variations on this study. This may be a result of variations in technician training. The alterations in the cervical vertebrae observed in the rat study are also seen in the new (1993) rabbit study. Skeletal data from the 1987 study was conducted by X-ray; therefore, there are no skeletal findings that can be compared with those observed on this study.

Recommend developmental neurotoxicity study? Yes, based upon the presence (even though at a low level) of suspected neural tube defects/brain malformations in rats and rabbits.

Recommend for Developmental Peer Review? I would like to suggest that these data be reviewed by an ad hoc meeting of the OPP reproduction and developmental toxicology experts and that a consensus opinion be generated (as an addendum to the Peer Review).

Submitted by:
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