CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

2- (HYDROXYMETHYL)-AMINO ETHANOL

Chemical Code # 1662, Tolerance # 50614
SB 950 # 704

Original: January 8, 2002
Revised: 9/9/02

I. DATA GAP STATUS

Chronic toxicity, rat:	Data gap, no study submitted.
Subchronic, rat, dermal:	No data gap, possible adverse dermal effects.
Chronic toxicity, dog:	Data gap, no study submitted
Oncogenicity, rat:	Data gap, no study submitted
Oncogenicity, mouse:	Data gap, no study submitted
Reproduction, rat:	Data gap, no study submitted.
Teratology, rat:	No data gap, no adverse effect.
Teratology, rabbit:	Data gap, no study submitted.
Gene mutation:	No data gap, possible adverse effect.
Chromosome effects:	No data gap, no adverse effect.
DNA damage:	No data gap, no adverse effect.
Neurotoxicity:	Not required at this time

Toxicology one-liners are attached.

All record numbers through 187819 were examined.

** indicates an acceptable study.

Bold face indicates a possible adverse effect.

File name: T020909

Original: M. Silva, 1/8/02
Revised: M. Silva, 9/9/02

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, RAT

No study submitted

CHRONIC TOXICITY, RAT

No study submitted

SUBCHRONIC DERMAL TOXICITY, RAT

**** 011 187819** "2 [(Hydroxymethyl) Amino] Ethanol 13 Week Dermal Toxicity Study in Rats," (Perry, C.J., Mulhern, M., Jones, M., Hudson, P.; Inveresk Research International, Tranent, Scotland; IRI Project #: 438047; Report #: 7250; 1/5/90). 2 [(Hydroxymethyl) Amino] Ethanol (2HMAE, 98.5% pure) was dermally administered (with occlusion) to Sprague-Dawley rats (10/sex/dose) at 0 (distilled water vehicle), 50, 250 and 1000 mg/kg/day for 6 hours/day, 5 days/week for 13 weeks. Dermal NOEL < 20 mg/kg (There was reaction, as observed both macro and microscopically (scabbing, inflammation, dermal fibrosis, epithelial hyperplasia, ulceration), at the treated sites at all doses, but primarily at 1000 mg/kg.) Systemic NOEL > 1000 mg/kg (There were no systemic effects.) This study is acceptable, with adverse dermal effects at all doses. (Silva, 9/9/02)

No chronic study submitted.

CHRONIC TOXICITY, DOG

No study submitted.

ONCOGENICITY, RAT

No study submitted

ONCOGENICITY, MOUSE

No study submitted

REPRODUCTION, RAT

No study submitted.

TERATOLOGY, RAT

<u>Range-finding Study:</u>

50614 - 006 114817 "2- [(Hydroxymethyl) Amino] Ethanol Dose Range Finding Study in Rats Preliminary to Teratogenicity Study," (Wilson, J.A., Barton, S.J.; Inveresk Research International, Ltd., Tranent, Scotland; IRI Project #: 438026; Report #: 5972; 8/20/89). 2- [(Hydroxymethyl)-Amino] Ethanol (2HMAE, 98.5% pure) was administered via gavage to mated female Charles River CD

Sprague-Dawley rats (10/dose) at 0, 150, 300, 600 1200 mg/kg during days 6 through 16 of gestation. Mortality was considered excessive at 1200 mg/kg; therefore, treatment at this dose was discontinued and a new high dose of 900 mg/kg (5 mated females) was initiated two days later. Animals from the 1200 mg/kg group were then continued, without treatment, through gestation. Maternal NOEL = 300 mg/kg/day (Excessive mortality at 1200 mg/kg and only 1 litter produced at 900 mg/kg. Body weight and body weight gain were decreased by 11% at 600 mg/kg and by 39% at 900 mg/kg. Food consumption days 6-16 was decreased by 10% at 600 mg/kg and by 36% at 900 mg/kg. Incidence of red stained fur and of salivation was increased at 900 mg/kg.) Developmental NOEL = Insufficient numbers of dams/litters at the high dose to evaluate the developmental effects of HMAE on rat fetuses.) Not acceptable and not upgradeable (Too few pregnant females at 900 mg/kg. No individual fetal data. Too few litters at 900 mg/kg. Incomplete and confusing results and individual data sections, primarily at 900 mg/kg.) Too few fetuses to evaluate the possibility of adverse health effects. This study is supplemental, since it is a rangefinding for the definitive developmental test in rats. (Kishiyama & Silva, 10/22/01).

Definitive Teratology Study:

** 50614 - 006 114818 "2- [(Hydroxymethyl) Amino] Ethanol Teratogenicity Study in Rats," (Wilson, J.A. and S.J. Barton; Inveresk Research International, Ltd., IRI Project #: 438031; 3/5/90). 2HMAE (98.5% pure) was administered via gavage to mated female Sprague-Dawley CD rats (25/dose) at 0, 10, 31.6,100, 250 and 500 mg/kg days 6 through 16 of gestation. Maternal NOEL = 31.6 mg/kg (There were increased gastro-intestinal abnormalities (chronic ulceration), decreased body weight gain and food consumption at 500 mg/kg. Increased effects in liver (mottled, reddened) occurred, primarily at $\geq$ 100 mg/kg.) Developmental NOEL = 250 mg/kg (There was an increase in advanced ossification, along with a reduction in patchy ossification on both a per fetus and a per litter basis, primarily at 500 mg/kg.) No adverse effects. ACCEPTABLE. (Kishiyama & Silva, 10/25/01).

TERATOLOGY, RABBIT

No study submitted.

GENE MUTATION

**** 50614 - 005 115449** "2-[(Hydroxymethyl)-amino] Ethanol (HMAE) Batch No. 8904-5016: Testing for Mutagenic Activity with *Salmonella typhimurium* TA 1535, TA 1537, TA 1538, TA 98 and TA 100," (Riach, C.G.; Inveresk Research International, Ltd., Musselburgh, Scotland; IRI Project #: 740837, Report #: 6232, 7/17/90). HMAE (Troysan 174, 98.5%) was tested for mutagenicity at concentrations ranging from 1.7 to 1000 : g/plate, both with and without metabolic activation (S9 mix) using *Salmonella typhimurium* strains TA 1535, TA 1537, TA 1538, TA 98 and TA 100. Repeat tests were performed. **Positive response was observed with *Salmonella typhimurium* strain TA100.** Although some of the descriptions of the "rejected" tests were not very detailed, the "defective" tests were repeated to the point where results were clear. This test is acceptable. ACCEPTABLE (Kishiyama and Silva, 12/28/01).

**** 50614 - 005 115454** "2-[(Hydroxymethyl)-Amino] Ethanol (HMAE) Batch No. 9011-6630 Mouse Lymphoma Mutation Assay," (Cattanach, P.J., Riach, C.G.; Inveresk Research International, Ltd., Tranent, Scotland; IRI Project No. 752161, Report No. 8480; 1/3/92). HMAE (98.2% pure) was evaluated for mutagenicity with L5178Y mouse lymphoma cells at concentrations ranging from 1.25 to 80 ug/ml, with and without metabolic activation (S9 Mix; 2 cultures/dose & 3 plates/culture). Vehicle control had 4 cultures and positive controls had 4 cultures/control (3 plates/culture for positive controls). Earlier tests indicated HMAE was cytotoxic at 50 ug/ml in both the absence and presence of S9 Mix. Both with and without S9, extensive toxicity occurred at 50 ug/ml in this study. HMAE at 10 and 20 ug/ml, in the absence of S9 Mix, caused an increased incidence of mutations relative to the vehicle control (Assay 1). HMAE at 20 ug/ml, with S9 Mix, caused an increased

incidence in mutation relative to the control (Assay 2). HMAE over the entire range: 8 - 32 & 12 - 40 ug/ml increased the incidence in mutant frequency (Assay 3 & 4). Cononies were sized into large and small. Both point mutations/small deletions and large deletions occurred with an apparent increase in large chromosomal deletions at more toxic concentrations. Mutation Fraction (MF) was within the normal range for vehicle control. The high MF was within normal ranges for the positive controls (EMS & 3-MC). ACCEPTABLE. Possible adverse effect. (Kishiyama & Silva, 1/2/02).

**** 50614 - 005 115467** "2-[(Hydroxymethyl)Amino] Ethanol (HMAE) Batch No. 8904-5016: Testing for Mutagenic Activity with *Salmonella typhimurium* TA 1535, TA 1537, TA 1538, TA 98 and TA 100 and 2-[(Hydroxymethyl)Amino] Ethanol (HMAE) Batch No. 9011-6630: Testing for Mutagenic Activity with *Salmonella typhimurium* TA100 and *Escherichia coli* WP2uvrA$^-$ (pKM101)," (Dillon, D.M., Riach, C.G.; Inveresk Research International, Ltd., Tranent, Scotland, IRI Project No. 751220; 4/20/91). HMAE (Troysan 174; 98.5% pure; Lot #: 9011-630) was evaluated for mutagenicity at concentrations from 100 - 450 ug/plate (+S9) and 100 - 600 ug/plate (no S9) using *S. typhimurium* strain TA100 and *E. coli* strain WP2uvrA$^-$ (pKM101). [See Record #: 115449 for results with Batch #: 8904-5016]. The test was repeated. **A dose related mutagenic effect (increased revertants) was observed for both *S. typhimurium* strain TA100 and *E. Coli* strain WP2uvrA$^-$.** ACCEPTABLE. Possible adverse effect. (Kishiyama & Silva, 1/7/02)

CHROMOSOME EFFECTS

** 50614 - 005 115459 "2-[(Hydroxymethyl)-Amino] Ethanol: Micronucleus Test in Bone Marrow of CD-1 Mice," (Holmstrom, M., Innes, D.; Inveresk Research International, Tranent, Scotland, IRI No. 751388, Report No. 8216; 8/16/91. 2-[(Hydroxymethyl)-amino] Ethanol (98.8% pure) was administered as a single dose *via* gavage to CD-1 mice (5/sex/dose) at 0 (distilled water), 200, 400, or 800 mg/kg. Bone marrow was harvested at 24, 48 and 72 hours post-dosing for 800 mg/kg and controls and at 24 hours at 400 and 200 mg/kg. There was no treatment-related increase in micronuclei at any dose. The negative and positive controls functioned as expected. No adverse effect. ACCEPTABLE. (Kishiyama & Silva, 1/4/02).

50614 - 005 115465 "2[(Hydroxymethyl)Amino] Ethanol: Micronucleus Test in Bone Marrow of CD-1 Mice," (Holmstrom, L.M.; Inveresk Research International, Tranent, Scotland; IRI No. 740858; 1/3/90). 2-[(Hydroxymethyl)-amino] Ethanol (HMAE; 98.8% pure) was initially administered *via* gavage (single dose) to CD-1 mice (2/sex/dose) at 1000, 2000, 3000, 4000 and 5000 mg/kg in a <u>dose-range finding</u> study for the definitive micronucleus assay. Along with the definitive micronucleus test, a <u>Main Toxicity Test (and a repeat test</u>) were performed in CD-1 mice (5/sex/dose), using a single gavage dose at 100, 250, 750 or 1250 mg/kg. Mice were observed immediately after dosing, at 0.5, 1, 2 and 4 hours after exposure. In the definitive micronucleus test, CD-1 mice (5/sex/dose/time-point) were treated with a single gavage dose of 175 mg/kg HMAE, with cyclophosphamide (80 mg/kg) used as a positive control. Bone marrow samples were taken at 24, 48 and 72 hours post-dosing. MTD for CD-1 mice varied widely between tests #1 and #2 and ranged from 100 to 250 mg/kg and 750 to 1000 mg/kg, respectively. No micronucleus induction was detected in the bone marrow erythrocytes of CD-1 mice treated with 175 mg/kg of HMAE. This study is not acceptable or upgradeable because the HMAE was tested at only one dose and the adequacy of that dose uncertain, since the two toxicity tests had a great deal of variance. UNACCEPTABLE. Not upgradeable. (Kishiyama & Silva, 1/7/02).

DNA DAMAGE

** 50614 - 005 115446 "2-[(Hydroxymethyl)-amino] Ethanol: Assessment of Genotoxicity in Unscheduled DNA Synthesis Assay Using Adult Rat Hepatocytic Primary Cultures," (Downey, E., Riach, C.G., Mohammed, R.; Inveresk Research International, Ltd., Scotland, IRI Project #: 740842; 12/13/89). Troysan 174 (HMAE, 98.5% pure) was evaluated in two assays, at 0.78125 to 100 : g/ml (8 concentrations total), using primary cultures of rat hepatocytes. HMAE was cytotoxic at $\geq$ 50

:g/ml and did not induce UDS. The positive controls functioned as expected. Acceptable. No adverse effect. (Kishiyama & Silva, 12/27/01).

NEUROTOXICITY

Not required at this time.

MISCELLANEOUS

50614 - 007 115470 "Thirteen Week Subchronic Dermal Toxicity Study in Albino Rats; The Safety Evaluation of an Antimicrobial Raw Ingredient AMINE CS-1135 (IMC Chemical Group, Inc.)," (Pennisi, S.C.; AVON Products Inc., Sullorn, NY; Study Project Code AT0156; 4/24/80). Amine CS-1135 (78% ai) was administered dermally at 0, 1.95, 19.5, or 195 mg/kg to the anterior dorsal shaved skin area of Sprague-Dawley rats (15/sex/dose) once/day, 5 days/week for 67-68 days over 13 weeks. NOEL = 19.5 mg/kg (There was an increased incidence in skin irritation at > 19.5 mg/kg. In addition,at 195 mg/kg, there was a decrease in body weight gain in females and an increased incidence in skin and liver histopathology.) Unacceptable, not upgradeable (no ophthalmology, limited histopathology. No adverse effect indicated. (Kishiyama & Silva, 12/16/01)