CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

Ethyl Formate

Chemical Code # 278, **Tolerance #** 53176
SB 950 # NA

6/21/12

I. DATA GAP STATUS

Chronic toxicity, rat:	Data gap, no study on file
Chronic toxicity, dog:	Data gap, no study on file
Oncogenicity, rat:	Data gap, no study on file
Oncogenicity, mouse:	Data gap, no study on file
Reproduction, rat:	Data gap, no study on file
Teratology, rat:	Data gap, no guideline study on file
Teratology, rabbit:	Data gap, no study on file
Gene mutation:	No data gap, no adverse effect
Chromosome effects:	Data gap, no study on file
DNA damage:	Data gap, no study on file
Neurotoxicity:	Data gap, no study on file

Toxicology one-liners are attached.

All record numbers through #265062 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
indicates a study on file but not yet reviewed.
File name: T120621
Revised by T. Moore, 6/21/12

Note: Ethyl formate readily hydrolyzes to ethanol and formic acid in the presence of water. Enzyme-mediated hydrolysis also occurs. In mammals, the formic acid is further metabolized to CO_2 via the tetrahydrofolate-mediated pathway. Ethanol is metabolized in the liver to acetaldehyde, acetic acid and finally to CO_2. Among these metabolites, formic acid presents the toxicity profile of most concern. Formic acid is presently a registered active ingredient with California Department of Pesticide Regulation. No additional SB-950 mandated studies are being required at this time based on ethyl formate's hydrolysis into two biochemicals physiologically present in the body.

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.

CHRONIC TOXICITY, DOG

No study submitted.

ONCOGENICITY, RAT

No study submitted.

ONCOGENICITY, MOUSE

No study submitted.

REPRODUCTION, RAT

No study submitted.

TERATOLOGY, RAT

53176-0003; 265062; "Developmental Toxicity of Formate and Formic Acid in Whole Embryo Culture: A Comparative Study with Mouse and Rat Embryos"; (J.E. Andrews, M. Ebron-McCoy, R.J. Kavlock, J.M. Rogers; Developmental Toxicity Division, Health Effects Research Laboratory, US EPA, Research Triangle Park, NC; Publication: Teratology 51: 243 - 251 (1995)); CD-1 mouse and Sprague-Dawley rat embryonic explants were exposed to either **sodium formate** or **formic acid**. For the mice, explants were procured from gravid females on gestation day 8 (3 to 5 somite stage). These embryos were cultured for 24 hours at 37° C with concentrations of **sodium formate** ranging from 0.4 to 3.0 mg/ml or concentrations of **formic acid** ranging from 0.27 to 2.0 mg/l. There were a total of 20 explants/treatment level for the **sodium formate** assay and up to 24 explants/treatment level for the **formic acid** assay. Pregnant female rats were euthanized on day 9 of gestation (0 somite stage) and embryos were transferred to culture medium containing concentrations of **sodium formate** ranging from 0.2 to 2.0 mg/l or concentrations of **formic acid** ranging from 0.14 to 1.08 mg/ml. Two embryos were co-cultured for 24 hours at 37° C at these concentrations, a total of 48 embryos/treatment level in all. Each co-cultured embryo was then placed in fresh medium. For one embryo, the exposure to the respective test material was continued for another 24 hours. For the other embyro, the fresh medium was free of the test material. These embryos were cultured for another 24 hours as well. Examination of the mouse explants treated with **sodium formate** revealed a treatment-related incidence of anomalies related to CNS origin; open anterior and posterior neuropore and erratic neural seam. In addition, enlarged maxillary processes and pericardium and delayed heart development were noted. Results were not affected by embryolethality. The yolk sac diameter (YSD), crown-rump length (CRL), head length (HL), somite number (SOM), and developmental score (DEVSC) values were all reduced when compared to the control group ($p<0.01$ or 0.001). For the mice explants treated with **formic acid**, a treatment-related increase in the number of explants exhibiting anomalies was noted. The YSD, CRL, HL, SOM, and DEVSC values were all reduced when compared to the control group ($p<0.01$ or 0.001). The pH of the culture medium decreased with increasing concentrations of the **formic acid** ($p<0.001$). Embryolethality increased as the **formic acid** concentration approached 44 mM. For the rat explants treated with **sodium formate** for either 24 or 48 hours, similar anomalies were evident as those reported for the mice explants. The incidence of anomalies was increased in a dose-related manner. The YSD, CRL, HL, SOM, and DEVSC values were all reduced when compared to the control group ($p<0.01$ or 0.001).

Embryolethality increased in a dose-related manner for those explants treated for 48 hours. For the rat explants which were treated with **formic acid**, embryolethality was also evident in a dose-related manner. The YSD (24-hour treatment only), CRL, HL, SOM, and DEVSC values were all reduced when compared to the control group (p<0.001). Only the 0.81 mg/ml treatment group in the 48-hour treatment group demonstrated an increase in the number of explants exhibiting anomalies (NS). The pH of the culture medium decreased with increasing concentrations of the formic acid (p<0.01or 0.001). **At concentrations of sodium formate and formic acid in the milimolar range, significant adverse developmental effects are manifested.** However, a NOEL can not be readily elucidated from these data. **Study supplemental.** (Moore, 5/31/12)

TERATOLOGY, RABBIT

No study submitted.

GENE MUTATION

** 53176-0003; 265056; "Mutagenic Evaluation of Compound FDA 75-49 000109-94-4, Ethyl Formate (Food Grade)"; (no author cited; Litton Bionetics, Inc., Kensington, MD; Project No. 2468; 5/31/76); Ethyl formate (food grade) (lot no. and purity not reported) were incubated with *Salmonella typhimurium* strains TA-1535, TA-1537 and TA-1538 and *Saccharomyces cerevisiae,* strain D4 at concentrations ranging from 1.25 to 5.0% in the suspension assay with and w/o activation. In a plate incorporation assay, *Salmonella typhimurium* strains TA-1535, TA-1537 and TA-1538 were exposed to concentrations ranging from 1.25 to 5.0% with and w/o activation, as well. In the suspension assay, S9 fractions were derived from the liver and lungs of mouse, rat and monkey. In the plate incorporation assay, the S9 fractions were derived from the livers of these three species. In the suspension assay, there was no indication of a treatment-related increase in the mutagenic frequency for either the *S. typhimurium* strains or the *S. cerevisiae* strain under conditions of either activation or non-activation. However, the positive controls under conditions of activation were frequently non-functional, particularly for the *S. cerevisiae* strain. There was no apparent difference between the different S9 fractions. In the plate incorporation assay, there was no treatment-related increase in the mutant colonies under (+/-) activation with the various S9 fractions. The positive controls were functional. **No adverse effect indicated. Study acceptable.** (Moore, 5/23/12)

CHROMOSOME EFFECTS

No study submitted.

DNA DAMAGE

No study submitted.

NEUROTOXICITY

No study submitted.