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HIGH PRODUCTION VOLUME (HPV) CHALLENGE PROGRAM

TEST PLAN  
FOR  
3-ETHOXYPROPIONIC ACID ETHYL ESTER  
(CAS NO.: 763-69-9)

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## **OVERVIEW**

The Eastman Chemical Company and The Dow Chemical Company hereby submit for review and public comment the test plan for 3-ethoxypropionic acid ethyl ester (EEP; CAS NO.: 763-69-9) under the Environmental Protection Agency's (EPA) High Production Volume (HPV) Chemical Challenge Program. It is the intent of these two companies to use existing data in conjunction with EPA-acceptable predictive computer models to adequately fulfill the Screening Information Data Set (SIDS) for the physicochemical, environmental fate, ecotoxicity test, and human health effects endpoints. We believe that these data are completely adequate to fulfill all the requirements of the HPV program without need for the conduct any new or additional tests.

3-Ethoxypropionic acid ethyl ester (EEP) is a colorless liquid manufactured to a high degree of purity (>99%). It has a very characteristic pungent odor that can be detected at 0.02 ppm. The pungent nature of its odor actually tends to preclude its use in consumer products, and at this time there is very little, use of this chemical in products sold directly to the general population. Thus, this solvent finds its primary uses in industrial settings where exposures can be better managed. The primary use for EEP solvent is as a retarder solvent in various coating applications such as: lacquers and enamels, auto original equipment manufacture and refinish coatings, automotive refinish thinner blends, epoxy maintenance coatings, polyurethane coatings, primers, photoresist coatings, coil coatings, aerospace coatings, appliance enamels, container coatings, and marine coatings. It can also be used as a solvent in various industrial cleaners, paint removers, purge-thinner solvent blends, as well as a process solvent for acrylic resins.

**TEST PLAN SUMMARY**

CAS No. 763-69-9	Information	OECD Study	Other	Estimation	GLP	Acceptable	New Testing Required
STUDY	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N
<b>PHYSICAL-CHEMICAL DATA</b>							
Melting Point	Y	-	-	Y	N	Y	N
Boiling Point	Y	-	-	Y	N	Y	N
Vapor Pressure	Y	-	-	Y	N	Y	N
Partition Coefficient	Y	-	-	Y	N	Y	N
Water Solubility	Y	-	-	Y	N	Y	N
<b>ENVIRONMENTAL FATE ENDPOINTS</b>							
Photodegradation	Y	-	-	Y	N	Y	N
Stability in Water	Y	-	-	Y	N	Y	N
Biodegradation	Y	Y	-	-	Y	Y	N
Transport between Environmental Compartments (Fugacity)	Y	-	-	Y	N	Y	N
<b>ECOTOXICITY</b>							
Acute Toxicity to Fish	Y	Y	-	-	Y	Y	N
Acute Toxicity to Aquatic Invertebrates	Y	Y	-	-	Y	Y	N
Toxicity to Aquatic Plants	Y	Y	-	-	Y	Y	N
<b>TOXICOLOGICAL DATA</b>							
Acute Toxicity	Y	Y	-	-	Y	Y	N
Repeated Dose Toxicity	Y	Y	-	-	Y	Y	N
Genetic Toxicity – Mutation	Y	-	Y	-	Y	Y	N
Genetic Toxicity – Chromosomal Aberrations	Y	Y	-	-	Y	Y	N
Developmental Toxicity	Y	-	Y	-	Y	Y	N
Toxicity to Reproduction	Y	Y	-	-	Y	Y	N

## **TEST PLAN DESCRIPTION FOR EACH SIDS ENDPOINT**

### **A. Physicochemical**

- Melting point - A value for this endpoint was obtained using a computer estimation model (1,2).
- Boiling Point - A value for this endpoint was obtained using a computer estimation model.
- Vapor Pressure - A value for this endpoint was obtained using a computer estimation model.
- Partition Coefficient - A value for this endpoint was obtained using a computer estimation model.
- Water Solubility - A value for this endpoint was obtained using a computer estimation model.

**Conclusion:** All end points haven been satisfied by the utilization of data obtained from the various physical chemical data modeling programs within EPIWIN(1). The results from the utilization of the models within this program have been noted by the Agency as acceptable in lieu of actual data or values identified from textbooks. No new testing is required.

### **B. Environmental Fate**

- Photodegradation - A value for this endpoint was obtained using a computer estimation model.
- Stability in Water - A value for this endpoint was obtained using a computer estimation model. This estimation program is noted as being applicable for compounds that are esters
- Biodegradation - This endpoint was satisfied through the use multiple studies that were available. All studies were conducted following established guidelines and GLP assurances. Specifically the study protocols followed the OECD test guideline 301B (2 studies), 301E, and 302B.
- Fugacity - A value for this endpoint was obtained using the EQC Level III partitioning computer estimation model (1,2).

**Conclusion:** All endpoints have been satisfied using actual data or through the utilization of Agency-acceptable estimation models. In total they are of sufficient quality to conclude that no additional testing is needed.

### **C. Ecotoxicity Data**

- Acute Toxicity to Fish - This endpoint is filled by data from an OECD TG-203 study conducted under GLP assurances.
- Acute Toxicity to Aquatic Invertebrates - This endpoint is filled by data from an OECD TG-202 study conducted under GLP assurances.
- Toxicity to Aquatic Plants - This endpoint is filled by data from an OECD TG-201 study conducted under GLP assurances.

**Conclusion:** All endpoints have been satisfied with data from studies that were conducted following established OECD guidelines and GLP assurances. In total they are of sufficient quality to conclude that no additional testing is needed.

#### D. Toxicological Data

Acute Toxicity -	This endpoint is filled by data from an oral toxicity study conducted using an established protocol (OECD: TG-401) and GLP assurances. Data are also presented from an acute inhalation study that did not follow OECD testing guidelines, but was nevertheless conducted under GLP assurances.
Repeat Dose Toxicity -	This endpoint is filled by data from a 28-day oral exposure and a 90-day inhalation exposure toxicity studies. The oral study followed an established protocol (OECD: TG-407) while the inhalation study followed a protocol comparable to an OECD #413 guideline study. Both studies were conducted under GLP assurances.
Genetic Toxicity Mutation -	This endpoint is filled with a single “Ames-assay” study in <i>Salmonella typhimurium</i> strains: TA98, 100, 1535, 1537, and 1538. This study was conducted under GLP assurances and followed a protocol similar to OECD guideline test-guideline #471.
Aberration -	This endpoint is filled with data from an <i>in vitro</i> study using Chinese hamster ovary (CHO) cells that followed OECD protocol #473 and was conducted under GLP assurances.
Developmental Toxicity -	This endpoint is filled by data from inhalation exposure studies in rats and rabbits. The rat study followed a protocol similar to that of an OECD TG-414 study while the rabbit study followed an EPA guideline (560/6-84-002). Both studies were conducted under GLP assurances.
Reproductive Toxicity -	This endpoint was fulfilled through the availability of histological and organ weight data on reproductive organs from rodents exposed to EEP for a period of 90-days. The study was conducted under GLP assurances. Such information, when present in conjunction with studies assessing developmental toxicity, is deemed adequate for use in lieu of actual reproductive toxicity studies (3).
<b>Conclusion:</b>	All endpoints have been satisfied with data from studies that were conducted following established guidelines (OECD or EPA) or utilized methods that were very similar and scientifically appropriate. All studies were conducted under GLP assurances. In total, they are of sufficient quality to conclude that no additional testing is needed.

## SIDS DATA SUMMARY

Data assessing the various physicochemical properties (melting point, boiling point, vapor pressure, partition coefficient, and water solubility) for EEP were all obtained from EPA-acceptable computer estimation modeling programs found in EPIWIN (Version 1.2, Syracuse Research Corporation, Syracuse, NY). These data indicate that EEP is a liquid at room temperature with a low vapor pressure. It has a low estimated octanol to water partition coefficient and accordingly is quite soluble in water. The use of these modeled data meet the requirements of the various endpoints to preclude the need for any additional testing of physical chemical properties.

Data from actual studies or acceptable estimation modeling programs were available, and of sufficient quality, to complete the assessment of all the environmental fate endpoints (photodegradation, biodegradation, stability in water, and fugacity). As a result of its ready solubility in water and relatively low volatility, fugacity estimations predict that EEP will distribute primarily to soil and water. Although the results from the computer modeling estimation program indicate its ester bond is not readily hydrolyzed, the available biodegradation data indicate EEP is likely to be readily degraded in the environment. Nevertheless, releases into the environment will primarily occur through evaporative emissions from its use in various types of coating applications. Under such conditions, atmospheric hydroxyl radicals are predicted to rapidly break down the molecule.

The toxic potential of EEP to fish and aquatic invertebrates were determined through studies conducted under established OECD guidelines and GLP assurances. The results of these studies demonstrate fish to be the most sensitive species with a NOEC of 25 ppm. The other aquatic organism, *Daphnia*, appeared much more tolerant to exposure with a NOEC of about 470 ppm. No effects were noted on algal growth in a limit study at a nominal concentration of 120 ppm. The potential for exposure to aqueous organisms is very unlikely due to its primary uses in industrial applications.

The potential to induce toxicity in mammalian species following acute oral and inhalation exposures is very low with LD<sub>50</sub> values ranging from >3200 mg/kg in females to >5000 mg/kg in males, and LC<sub>50</sub> values in males of LC<sub>50</sub> >998 ppm (5,967 mg/m<sup>3</sup>). Repeat exposure data of both 28 and 90 days duration indicate the material is well tolerated with minor effects noted on serum clinical chemistries not accompanied by any histological alterations in any of the organs examined. The NOAEL following 90-day inhalation exposure was 250 ppm (1,495 mg/m<sup>3</sup>). Results from mutagenicity and chromosomal aberration studies indicate these compounds do not induce genotoxicity. Studies assessing developmental toxicity were available in two different species (rat and rabbit). Results from both these studies indicate EEP was not teratogenic at dose levels up to 1000 ppm (5,979 mg/m<sup>3</sup>). Evidence of maternal toxicity was noted in both studies at 250 ppm and was characterized by significantly lower weight gains at various time intervals. In rats, this maternal toxicity is believed to have induced fetotoxicity at the 1000 ppm exposure level. The NOAEL for maternal toxicity in both studies was 125 ppm (747 mg/m<sup>3</sup>). Data from a metabolism study (not summarized) has shown there is no evidence of alkoxyacetic acid metabolites, such as those produced by metabolism of some low molecular weight ethylene glycol ethers (*Xenobiotica*, 1990, **20:10**; pp 989-997). Reproductive toxicity was assessed through the absence of any effects on the reproductive organs (i.e., changes in weight or morphological appearance) following 90 days of inhalation exposure at a concentration of 1000 ppm (5,979 mg/m<sup>3</sup>).

In conclusion, an adequate assessment and summarization of all the Screening Information Data Set (SIDS) endpoints has been completed to satisfy the requirements of the HPV program without need for the conduct of any new or additional tests. This data set consists of results from studies conducted on EEP that followed established protocols under GLP assurances. Where appropriate, some endpoints have been fulfilled through the utilization of data from modeling programs accepted by the EPA. The summarized data indicate that this chemical, as used in commerce, constitutes a low risk to both workers and the general population.

## **EVALUATION OF DATA FOR QUALITY AND ACCEPTABILITY**

The collected data were reviewed for quality and acceptability following the general US EPA guidance (4) and the systematic approach described by Klimisch *et al.* (5). These methods include consideration of the reliability, relevance and adequacy of the data in evaluating their usefulness for hazard assessment purposes. This scoring system was only applied to ecotoxicology and human health endpoint studies per EPA recommendation (4). The codification described by Klimisch specifies four categories of reliability for describing data adequacy. These are:

- (1) **Reliable without Restriction:** Includes studies or data complying with Good Laboratory Practice (GLP) procedures, or with valid and/or internationally accepted testing guidelines, or in which the test parameters are documented and comparable to these guidelines.
- (2) **Reliable with Restrictions:** Includes studies or data in which test parameters are documented but vary slightly from testing guidelines.
- (3) **Not Reliable:** Includes studies or data in which there are interferences, or that use non-relevant organisms or exposure routes, or which were carried out using unacceptable methods, or where documentation is insufficient.
- (4) **Not Assignable:** Includes studies or data in which insufficient detail is reported to assign a rating, e.g., listed in abstracts or secondary literature.

## **REFERENCES**

1. EPIWIN, Version 3.10, Syracuse Research Corporation, Syracuse, New York.
2. US EPA (1999). The Use of Structure-Activity Relationships (SAR) in the High Production Volume Chemicals Challenge Program. OPPT, EPA.
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4. USEPA. 1999b. Determining the Adequacy of Existing Data. Guidance for the HPV Challenge Program. Draft dated 2/10/99.
5. Klimisch, H.-J., Andreae, M., and Tillmann, U. (1997). A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data. *Regul. Toxicol. Pharmacol.* 25:1-5.