201-16814

JuanB Perez/DC/USEPA/US
08/14/2009 08:11 AM

To NCIC HPV@EPA
cc
bcc
Subject Reply to EPA Comments on the ExxonMobil Chemical Company HPV Challenge Program Test Plan and Dossier for sec-Butyl Ether (CAS #6863-58-7) Registration Number

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Sent by:
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08/12/2009 11:45 AM

To NCIC OPPT@EPA, Rtk Chem@EPA
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Subject Reply to EPA Comments on the ExxonMobil Chemical Company HPV Challenge Program Test Plan and Dossier for sec-Butyl Ether (CAS #6863-58-7) Registration Number

(See attached file: sec Butyl Ether HPV - CAS 6863-58-7 - Reply to EPA - 2009Aug12.pdf)

sec Butyl Ether HPV - CAS 6863-58-7 - Reply to EPA - 2009Aug12.pdf

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201-16814

ExxonMobil
Chemical

August 12, 2009

Mark W. Townsend
Chief HPV Chemicals Branch
Office of Pollution Prevention and Toxics (OPPT)
U.S. Environmental Protection Agency (EPA)
1200 Pennsylvania Ave., NW
Washington, DC 20460-0001

Re: EPA Comments on the ExxonMobil Chemical Company Test Plan and Dossier for sec-Butyl Ether (CAS #6863-58-7) under the HPV Challenge Program (ExxonMobil Chemical Company Registration Number for HPV Challenge Program)

Dear Mr. Townsend:

ExxonMobil Chemical Company (EMCC) is strongly committed to the chemical industry's Responsible Care® program and takes seriously its commitment to the responsible manufacture, testing, and safe use of its products. As further evidence of this commitment, EMCC agreed to provide sufficient data to characterize the U.S. Environmental Protection Agency (EPA) High Production Volume (HPV) Program physical and biological endpoints.

Your letter of May 29, 2009, provided comments on the sec-butyl ether (sBE; CAS #6863-58-7) test plan and dossier submitted to EPA under the HPV Program by EMCC in November 2006. EMCC addresses these comments below and will update the sBE dossier accordingly and submit the revised dossier by September 30, 2009.

For physical chemical properties, EPA recommended that the estimated boiling point value be replaced with an existing measured value. EMCC will update the dossier with the measured boiling point value.

EPA also suggested development of a measured water solubility value. EMCC believes that sufficient read-across measured and calculated data are available for structurally similar substances which justify the use of the calculated value for sBE. The measured water solubility of n-butyl ether is reported as 300 mg/L (Riddick *et al.*, 1986) in comparison to its calculated value of 594 mg/L, as estimated from a fragments model (EPI SuiteTM, 2000; v1.01). The measured solubility of n-propyl ether is reported as 4,900 mg/L (Riddick *et al.*, 1986) in comparison to its calculated value of 5,528 mg/L as estimated from the fragments model (v1.01). For sBE, the estimate from fragments model (v1.01) has been selected over data calculated using the WSKOW model (EPI SuiteTM, 2000; v1.41) because the fragments model better aligns with the measured data. The fragments model calculates water solubility for sBE of 1,669 mg/L. This value will replace the value originally provided in the dossier (327 mg/L) and the dossier will be updated accordingly.

For environmental fate properties, EPA suggested that measured biodegradation data be developed for sBE. EMCC believes that measured data are not needed for sBE as sufficient data are available to assess its biodegradability.

Read-across data and the supporting rationale were provided in the original sBE test plan and dossier to support this assessment. The data included results from a modified MITI test conducted on the analog substance n-butyl ether (nBE). The 28-day study reported 3 to 4% biodegradation, based on biological oxygen demand (CITI, 1992). The BIOWIN model, a subroutine within the EPI SuiteTM (2000) computer model, further supports an assessment of low biodegradability and estimates that the biodegradation of both sBE and nBE will occur at a slow rate. Although a number of published studies have demonstrated that alkyl ethers can be degraded by pure strains and mixed cultures of bacteria when incubated under aerobic conditions (Fujiwara, *et al.*, 1984; Kim and Engesser, 2004), their rate of biodegradation will be slow because a higher level of dissociation energy (approximately 360kJ mol^{-1}) is required to break the ether bond (Kim and Engesser, 2004). Additional biodegradation data developed in a standard 28-day study for diisopropyl ether (DIPE) were also provided EPA under the HPV program (Stone and Watkinson, 1983). DIPE showed no biodegradation in this study. Based on both the measured and calculated data for low molecular weight ethers, it can be concluded that low molecular weight ethers will exhibit a low extent of biodegradability in standard 28-day biodegradation tests. Based on existing data for nBE and DIPE, sBE would be expected to biodegrade to a similar low extent.

For health effects properties, EPA requested data on the change in female reproductive organ weights and additional information on the male and female reproductive organs from the DIPE 13-week inhalation repeated-dose test be added to the robust summaries for this study.

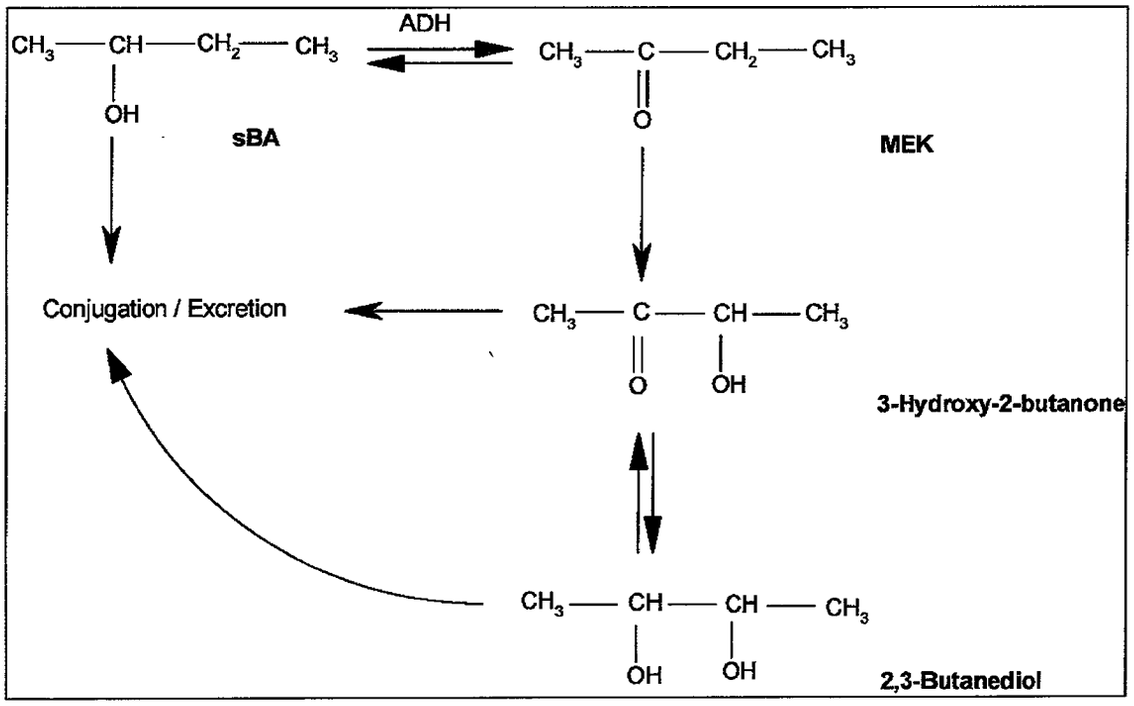
The published study (Dalbey and Fueston, 1996) was reviewed and data on organ weights were not included. However, it was stated by the study authors that although study results showed evidence of systemic toxicity at 3300 and 7100 ppm, there were "no changes in reproductive organ weights and structure or sperm and spermatid number" at any concentration tested (maximum 7100 ppm) relative to the controls. All organs, per the protocol, were evaluated from the high dose and control and those organs that showed effects, e.g., liver and kidney, were examined at the intermediate and low dose levels. Additionally, a robust study summary for the 78-week cancer study (Belpoggi *et al.,* 2002) described in the sBE test plan will be added to the dossier for DIPE. These data will provide important supplemental information from an oral study for the repeat-dose toxicity endpoint (the other studies provided results from an inhalation exposure).

With regard to analog justification and metabolism, the following information will also be added to the sBE dossier:

- sBE is a structural analog of DIPE, in that both are small molecular weight molecules containing two short-chain alkyl groups linked by an oxygen on the secondary carbon. The metabolism of DIPE was investigated by Stagliola and Schatz (2007) to determine if the two major metabolites were as predicted, isopropyl alcohol (IPA) and acetone (dimethyl ketone or DMK). Using rat nasal mucosa microsomes *in vitro*, they found that the metabolites, IPA and DMK, were produced in a concentration-dependent manner. P450 isoforms, CYP2A3 and 2E1, were identified as the key enzymes involved in DIPE metabolism. *In vivo* studies showed rapid systemic clearance of DIPE, IPA, and DMK from the blood of rats within 24 hours following a 6-hour inhalation exposure. It can be

postulated, given the close structural similarity between DIPE and sBE, that following exposure to sBE, P450 enzymes in the nasal mucosa, lung tissue, and liver would be involved with metabolizing sBE to 2-butyl alcohol (sBA) and 2-butanone (MEK), as illustrated below from work by Dietz *et al.* (1981).

Dietz *et al.* (1981) developed a physiologically based pharmacokinetic model for sBA and its metabolites MEK, 3-hydroxy-2-butanone, and 2,3-butanediol in rats. The model examined the observed blood levels of sBA and its metabolites after oral administration of sBA, and was compared to blood levels of these compounds following oral exposure to MEK. The predicted blood concentrations of sBA and the metabolites were in good agreement with observed data. The authors reported that that 97% of sBA administered orally at 1,776 mg/kgbw to rats was oxidized via alcohol dehydrogenase to MEK. Equimolar doses (1,776 mg/kg/bw) of sBA and MEK produced very similar maximum blood concentrations (Cmax) and areas under the concentration curve (AUC) for MEK and 2,3-butanediol. As shown below in a metabolic scheme, sBA and MEK would be metabolized and eliminated.



For ecological effects, EPA suggested development of acute fish, invertebrate, and algal data for sBE or adequate data on an appropriate analog for these endpoints be provided. Since the submission of the sBE test plan in 2006, additional analog data have become available for DIPE that can be used in conjunction with measured data for nBE and calculated data for sBE to adequately characterize the aquatic toxicity potential of sBE.

The following data can be used to characterize the aquatic toxicity of sBE and will be added to the updated sBE dossier.

Toxicity Endpoint	DIPE (mg/L)	sBE (mg/L)	nBE (mg/L)
Fish Acute 96-hr LC50	91.7* 98.2**	- 14.7**	32.5* 7.0**
Daphnid Acute 48-hr EC50	190.0* 104.4**	- 16.7**	- 8.2**
Alga Toxicity 72-hr EC50	566 (growth rate)* 385 (biomass)* 64.8 (96-hr)**	- - 11.0 (96-hr)**	- - 5.5 (96-hr)**
Alga Toxicity 72-hr NOEC	194 (growth rate)* 194 (biomass)* 6.0 (96-hr ChV) **	- - 1.8 (96-hr ChV) **	- - 1.1 (96-hr ChV) **

* measured data

** calculated data; calculated toxicity data used log K_{ow} values for DIPE, sBE, and nBE of 1.88, 2.87, and 3.21, respectively

A comparison of the measured data for the two analogs, DIPE and nBE, and the calculated data for all 3 substances show that the calculated data are conservative and would be appropriate for use in a screening level risk assessment should it be needed for sBE. As the final DIPE dossier was recently submitted to EPA under the HPV program, the robust study summaries for these studies are available to EPA for review.

Please contact me if you require any further information on the status of EMCC commitments to the U.S. HPV Program.

Sincerely,

Susan K. Blevins

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References

Belpoggi F, Soffritti M, Minardi F, Bua L, Cattin E and Maltoni C (2002). Results of long-term carcinogenicity bioassays on tert-amyl-methyl-ether (TAME) and diisopropyl ether (DIPE) in rats. Ann. N.Y. Acad. Sci. 982: 70-86.

CITI (Chemicals Inspection and Testing Institute, 1992). Biodegradation and bioaccumulation data of existing chemicals based on the CSCL Japan. CITI (ed.). Chemical Products Safety Division, Basic Industries Bureau, Ministry of International Trade and Industry, Japan. Japan Chemical Industry Ecology-Toxicology and Information Center.

Dalbey W and Fueston M (1996). Subchronic and developmental toxicity studies of vaporized diisopropyl ether in rats. J. Toxicol. Environ. Health 49: 29-43.

Dietz F, Rodriguez-Giaxola M, Traiger G, Stella V and Himmelstein K (1981). Pharmocokinetics of 2-butanol and its metabolites in the rat. J. Pharmokinet. Biopharm. 9: 533-576.

EPI SuiteTM (2000). Estimation Program Interface Suite, version 3.12. Syracuse Research Corporation, Syracuse, NY, USA.

Fujiwara Y, Kinoshita T, Sato H, Kojima I. (1984). Biodegradation and bioconcentration of alkyl ethers. Yukagaku, 33: 111-114.

Kim, Y-H and K-H Engesser (2004). Degradation of alkyl ethers, aralkyl ethers, and dibenzyl ether by *Rhodococcus* sp. strain DEE5151, isolated from diethyl ether-containing enrichment cultures. App. Environ. Micro. 70 (7): 4398-4401.

Riddick J, Bunger W and Sakano T (1986). Organic solvents: Physical properties and methods of purification. In: Techniques of Chemistry, 4th ed. New York, Wiley-Interscience 2: 336-337.

Stagliola E and Schatz R (2007). *In vivo and in vitro* metabolism of diisopropyl ether (DIPE). The Toxicologist, Abstract 971.

Stone C and Watkinson R (1983). Isopropyl ether: An assessment of ready biodegradability. Report # SBGR.83.428. Shell Biosciences Laboratory, Sittingbourne Research Centre, Sittingbourne, Kent, England.

Veith G, Call D and Brooke L (1983). Structure-toxicity relationships for the fathead minnow, *Pimephales promelas*: Narcotic industrial chemicals. Can. J. Fish. Aquat. Sci. 40: 743-748.

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