

ORIGINAL

8EHQ. 0375-1338



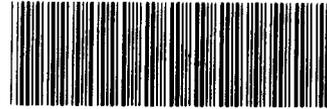
INIT 03/27/95

Shell Oil Company



One Shell Plaza  
P.O. Box 4320  
Houston, Texas 77210

(A)



88950000170

March 16, 1995

Document Processing Center (TS-790)  
Office of Toxic Substances  
U.S. Environmental Protection Agency  
401 M Street, S.W.  
Washington, D.C. 20460  
ATTN: 8(e) Coordinator

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**Contains No CBI**

Dear Sir:

SUBJECT: DNA ADDUCTS MEASURED IN RATS AND MICE EXPOSED TO ETHYLENE  
The following information is submitted under TSCA 8(e).

In a molecular dosimetry study in which F-344 rats and B<sub>6</sub>C<sub>3</sub>F<sub>1</sub> mice were exposed to 0 (control), 40, 1000 or 3000 ppm ethylene (CAS Number 74-85-1) for 1-4 weeks (6 hrs/day, 5 days/wk), DNA and hemoglobin adducts to ethylene were observed in ethylene exposed animals compared to controls.

These findings are based on results summarized in a letter from Dr. James A. Swenberg to Dr. Elizabeth Moran, Manager-Olefins Panel at the Chemical Manufacturers Association (attached). The study, which was conducted at the University of North Carolina, was sponsored by a grant from the Chemical Manufacturers Association Olefins Panel, to which Shell is a member.

Based on the reported information, there appears to be a connection between ethylene exposure in rodents and the metabolite ethylene oxide (EO), since both chemicals produce DNA adducts in rodent tissues. Although ethylene has been tested in a cancer bioassay in rats at an inhalation dose as high as 3000 ppm and did not produce cancer, and IARC does not consider ethylene a carcinogen, Shell is reporting this new information under TSCA 8(e), since it might possibly provide information on a mechanism which could have implications regarding human health.

This report is filed to provide information EPA may find useful. In no way is it intended as a waiver of any rights or privileges belonging to Shell Oil Company as the reporting corporation, its agents or employees. The reporting corporation, its agents and employees, reserve the right to object to this report's use or admissibility in any subsequent judicial or administrative proceeding against the corporation, its agents or employees.

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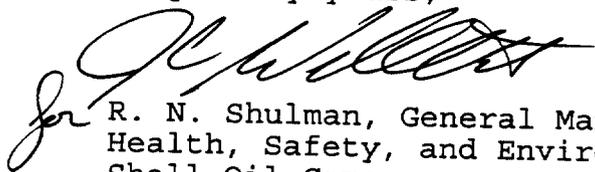
This report has been compiled based on information available as of the date of filing. The corporation, its agents and employees reserve the right to supplement the data contained in this report, and to revise and amend any conclusions drawn therefrom.

This report contains no confidential business information.

The following person should be contacted if you have questions or a need for discussion.

J. C. Willett  
Manager, Product Safety and Compliance  
Shell Oil Company  
P.O. Box 4320  
Houston, TX 77210  
Telephone No. 713-241-6958  
Fax. 713-241-3325

Very truly yours,



R. N. Shulman, General Manager  
Health, Safety, and Environment  
Shell Oil Company

THG/sjh

Attachment



THE UNIVERSITY OF NORTH CAROLINA  
AT  
CHAPEL HILL

The School of Public Health  
Department of  
Environmental Sciences and Engineering

The University of North Carolina at Chapel Hill  
CB# 7400, Rosenau Hall  
Chapel Hill, N.C. 27599-7400

**LABORATORY OF MOLECULAR CARCINOGENESIS AND MUTAGENESIS**  
**THE UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL**  
**CAMPUS BOX 7400**  
**CHAPEL HILL, NC 27599**

**FAX TRANSMISSION**

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FEB 08 1995

SEARCHED  
BUSINESS SUPPORT

**TO:** Bette Moran

**FAX NUMBER:** (202)887-5427

**Company:** CMA

**FROM:** Peter S. Kernan, Administrative Assistant  
Dr. James A. Swenberg's office

**TELEPHONE:** (919) 966-6142 - Administrative Assistant  
(919) 966-6139 - Dr. James A. Swenberg's office  
(919) 966-6123 - FAX

**DATE:** February 7, 1995

**PAGES:** (INCLUDING THIS PAGE) 5

**COMMENTS:** Bette, here is the Olefins panel report, hard copy to follow



## THE UNIVERSITY OF NORTH CAROLINA

AT

CHAPEL HILL

The School of Public Health  
Department of  
Environmental Science and Engineering

The University of North Carolina at Chapel Hill  
CB# 7400, Rosenau Hall  
Chapel Hill, N.C. 27599-7400

February 7, 1995

Dr. Elizabeth J. Moran  
Manager, Olefins Panel  
Chemical Manufacturers Association  
2501 M Street, NW  
Washington, DC 20037

Dear Betty:

I enjoyed having the opportunity to present our most recent research on ethylene/ethylene oxide to the CMA Olefins group last week. This letter will provide you with a brief summary of our data and place it in perspective to previously published material. This project was undertaken to understand better the relationship between ethylene exposure and the formation of ethylene oxide through metabolism. Ethylene had previously been evaluated in a large well conducted 2-year carcinogenicity study and found negative. We undertook a mechanistic study that examined the induction of micronuclei, *hprt* mutation, abasic sites, and DNA and hemoglobin adducts in F344 rats and B6C3F1 mice exposed by inhalation for 1-4 weeks to 0, 40, 1000, or 3000 ppm ethylene, or 200 ppm ethylene oxide. No ethylene exposure-related increases were seen in micronuclei, *hprt* mutations, or abasic sites. We found exposure- and time-related increases in hemoglobin adducts in mice and rats. The hemoglobin adducts reached a plateau between 1000 and 3000 ppm that was ~150-fold higher than the amount present endogenously in control rats and 18-fold lower than the 200 ppm ethylene oxide exposed rats. Mice tended to have slightly higher amounts of hemoglobin adducts at 3000 ppm, compared to 1000 ppm. The rat data are in excellent agreement with the extent of metabolism predicted by Filser (Filser, Arch. Toxicol., 55:219-223, 1992).

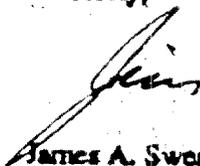
We have made outstanding progress in developing our GC/high resolution mass spectrometry assay for 7-hydroxyethylguanine (HEG), the major DNA adduct of ethylene oxide. We can now measure the amount of this adduct that is present endogenously in several tissues of rats and mice. In addition, we have measured the adduct in tissues of rats exposed to 3 or 10 ppm ethylene oxide for 4 weeks. While the previous method was not sensitive enough to quantitate HEG at these

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exposures (Walker et al, Cancer Res. 52: 4328-4334, 1992), we now can easily measure the adducts with our new method. A simple extrapolation of the ethylene oxide data from 3 ppm down to 1 ppm demonstrates that the endogenous levels of HEG are 1/5 (lung) to nearly equal (spleen) that expected for 1ppm. Based on our current data set of 2-4 animals, the number of HEG adducts present in rats and mice exposed to 40 ppm ethylene is similar to what is extrapolated for 1 ppm ethylene oxide. This is consistent with Filser's prediction that 40 ppm ethylene will produce ~ 1 ppm of ethylene oxide. Exposure of rats and mice to 3000 ppm ethylene resulted in 2-30-fold increases in HEG over control animals. The formation of this adduct was previously shown following an 8 hour exposure of mice to 11 ppm <sup>14</sup>C-ethylene (Segerbäck, Chem.-biol. Interactions 45:139-151, 1983). We will extend our observations to 5-7 animals/tissue/species at the completion of the project. While the actual adduct numbers will change with increased samples, I think that the general pattern will be similar.

A number of conclusions can be drawn from these data. First, the metabolism of ethylene to ethylene oxide is saturable. As shown in the attached tables, the number of DNA adducts that are formed at saturation is 10-30-fold lower than occurs at carcinogenic exposures of ethylene oxide (100 ppm) (Walker et al, Cancer Res. 52: 4328-4334, 1992). No significant increase in tumors was seen in rats exposed to 10 or 33 ppm ethylene oxide (Snellings, Toxicol. appl. Pharmacol.75: 105-117, 1984). Comparison of hemoglobin and DNA adducts shows that the number of DNA adducts is 1/5 to 1/5 the amount of hemoglobin adducts. This difference is most likely due to the presence of DNA repair and suggests that risk estimates based on hemoglobin adducts will over estimate risk to DNA.

Sincerely,



James A. Swenberg, D.V.M., Ph.D.  
Director, Curriculum in Toxicology  
Professor, Environmental Sciences and  
Engineering, and Pathology

# 7-HEG in Tissues of Rats Exposed to Ethylene Oxide

Exposure (ppm)	7-HEG (pmol/mmol guanine)			
	Liver	Brain	Lung	Spleen
Control	0.20 ± 0.05 (n=4)	0.13 ± 0.06 (n=4)	0.25 ± 0.22 (n=3)	1.73 ± 1.26 (n=2)
3	1.78 ± 0.87 (n=2)	1.88 ± 0.42 (n=2)	1.38 ± 0.10 (n=2)	2.83 ± 0.22 (n=2)
10	3.60 ± 0.82 (n=2)	4.58 ± 0.24 (n=2)	3.77 ± 1.39 (n=2)	*ND
100†	49 ± 1	87 ± 7	105 ± 4	81 ± 2

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\*ND: not determined

†Walker et al., Cancer Research, 1992

# 7-Hydroxyflavinol Exposure to Ethylene

<u>Exposure</u> (ppm)	<u>7-HFG (pmol/μmol guanine)</u>			
	Liver	Brain	Lung	Spleen
Control	0.2 ± 0.05 (n=4)	0.13 ± 0.06 (n=4)	0.25 ± 0.22 (n=3)	1.73 ± 1.26 (n=2)
40	1.05 ± 0.25 (n=4)	0.65 ± 0.64 (n=3)	ND*	1.74 ± 1.04 (n=2)
1000	4.31 ± 0.25 (n=4)	4.12 ± 1.80 (n=4)	4.38 ± 0.74 (n=2)	3.25 ± 0.02 (n=2)
3000	6.49 ± 1.97 (n=4)	3.23 ± 0.68 (n=4)	5.73 ± 1.27 (n=3)	4.03 ± 0.25 (n=3)

\*ND- not determined

## Triage of 8(e) Submissions

Date sent to triage: \_\_\_\_\_

**NON-CAP**

**CAP**

Submission number: 13381A

TSCA Inventory: **(Y)** N D

Study type (circle appropriate):

Group 1 - Gordon Cash (1 copy total)

ECO            AQUATO

Group 2 - Ernie Falke (1 copy total)

ATOX            SBTOX            SEN            w/NEUR

Group 3 - HERD (1 copy each)

STOX                    CTOX                    EPI            RTOX                    **(GTOX)**  
STOX/ONCO            CTOX/ONCO            IMMUNO            CYTO                    NEUR

Other (FATE, EXPO, **(MET)** etc.): \_\_\_\_\_

Notes:

- This is the **original** 8(e) submission; refile after triage evaluation.
- This **original** submission has been **split**; rejoin after triage evaluation.
- Other:

Photocopies Needed for Triage Evaluation				
entire document:	<b>(0)</b>	1	2	3
front section and CECATS:	<b>(0)</b>	1	2	3
Initials: <u>JW</u>	Date: <u>4/11/96</u>			

