

CALIFORNIA DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

ETHYLENE OXIDE

Chemical Code #: 000277, Tolerance #151
SB #: 061

October 3, 1986

Revised 10/19/87, 10/11/88, 11/29/89, 5/25/90, 12/3/91, 7/18/95, 10/28/96

I. DATA GAP STATUS

Combined rat (chronic + onco): No data gap, possible adverse effect

Chronic monkey: No data gap¹

Onco mouse: No data gap, possible adverse effect

Repro rat: No data gap, possible adverse effect

Terato rat: No data gap, possible adverse effect

Terato rabbit: No data gap, no adverse effect

Gene mutation: No data gap, possible adverse effect

Chromosome: No data gap, possible adverse effect

DNA damage: No data gap, possible adverse effect

Neurotox: Not required at this time

¹ Study does not meet guideline requirements, however taking other studies and information available into consideration the data gap may be closed.

Note, Toxicology one-liners are attached

** indicates acceptable study

Bold face indicates possible adverse effect

File name T961028

Toxicology Summary revised by Silva, 5/90; by Gee, 12/91, by Iyer, 7/18/95, 10/28/96.

Rectified through volume #:051; record #: 145875

These pages contain summaries only. Individual worksheets should be reviewed as they may contain additional effects.

II. TOXICOLOGY SUMMARY

COMBINED RAT

**** 004 034243** "Two-Year Inhalation Study in Rats," Bushy Run Research Center, 1/28/81, Pittsburgh, PA. Ethylene oxide, refined, from tank car #GATX84731 (purity not indicated, analyses for acidity, aldehydes, etc. in Table 1); 120/sex/group of Fischer 344 rats were exposed to 10, 33 or 100 nominal ppm over 2 years; exposed for 6 hrs/day, 5 days/week; interim sacrifices of 10/sex/group at 6 and 12 months, 20/sex/group at 18 months and survivors at 25 months; whole body exposure; exposure conditions over the study are presented; virus infection with sialodacryoadenitis occurred during weeks 62 and 63 in all groups including controls resulting in cessation of treatment for 2 weeks after which symptoms subsided -- increase in mortality in 33 and 100 ppm males and 100 ppm females began in week 15; systemic NOEL = 10 ppm; NOEL for oncogenicity not established -- **adverse effect in all groups:** increased incidence of combined brain neoplasms in both sexes with trend extending to 33 ppm; increased incidence of mononuclear cell leukemias in females at all exposures, significant in males at 33 and 100 ppm; dose related increase in peritoneal mesotheliomas in males at 33 and 100 ppm; evidence of shortened latency in several tumor types, especially pituitary adenomas in females. Conclusion: ethylene oxide should be regarded as an oncogen in rats. Initially reviewed as unacceptable due to lack of individual data but upgradeable. In reconsideration in response to the rebuttal, the study was upgraded to **acceptable** status with the comment that the individual data are not needed at this time in view of the clear oncogenic effects. (C. Aldous, 10/2/85 and 9/87)

004 034242 Appendix to 034243

008 051593 "A Two-Year Inhalation Study of the Carcinogenic Potential of Ethylene Oxide in Fischer 344 Rats" (Toxicology and Applied Pharmacology **75**, 105-117 (1984); Bushy Run Research

Center, Export, Pennsylvania; Journal article is summary of record #034243 in 151-004. No one-liner. (NLH, 9/87).

008, 027 051614, 098617 "Effects on Monkeys and Rats of Long-Term Inhalation Exposure to Ethylene Oxide--Major Findings of the NIOSH Study," Lynch, D. W. et al., NIOSH, 11/22/83. Ethylene oxide (99.7%) by inhalation at 0, 50 or 100 ppm, 7 hours/day, 5 days/week for 24 months to 30 male Fischer 344 rats (Harlan Industries), starting at 6 weeks of age. Possible adverse effects - decreased survival at 100 ppm, increased mononuclear cell leukemia in both exposed groups, increased peritoneal mesotheliomas: control - 3/77, 50 ppm - 9/77 and 100 ppm - 17/77, increased mixed cell gliomas: control - 0, 50 ppm - 2 and 100 ppm - 5; NOEL < 50 ppm (decreased body weight gain, neoplasm incidence). **Unacceptable** (Table 2 missing, no analysis of actual exposures, no individual data and marginal summary data, use of males only) - **Not upgradeable** (no females). (J. Gee, 9/23/87). Contained in record 098617 is a copy of the publication for this study. Gee, 11/22/91.

039 124630 "Final Report on Ethylene Oxide Two-Year Inhalation Study on Rats - Detailed Histologic Evaluation of Brains for Primary Neoplasms" (R.H. Garman and W.M. Snellings) June 1983, Bushy Run Research Center. A reassessment of all brains previously examined and the preparation and examination of brains not originally examined from animals exposed to ETO at 0, 10, 50 and 100 ppm was conducted. An increased incidence (biologically significant) of primary brain neoplasms in males and females at 33ppm and 100 ppm was noted. The granular cell tumors noted were not considered to be of much significance since they were restricted to the meninges and were not thought to be associated with meningeal carcinomas. Iyer, 3/2/95.

CHRONIC DOG

No study on file.

CHRONIC MONKEY

051 145870 "Upgrade submission: Chronic inhalation exposure study of ethylene oxide in monkeys," (F. Jay Murray, Murray & Associates, 3/26/96). Supplementary to 051614 086092, 088552, 098617, 112627.

Pursuant to a meeting at DPR (3/6/96) attended by F. Jay Murray (Murray & Associates, on behalf of AlliedSignal Inc., and ARC Chemical Division, Balchem Inc.) and DPR scientists Joyce Gee and Poorni Iyer, material was submitted to upgrade the chronic non-rodent study. The submission includes other record #s: 145871, 145872, 145873 and 145875 (For one-liners see Supplemental section). The purpose of a chronic study (non-rodent) is to provide data on the effects of the compound on both sexes after prolonged and repeated exposure and to determine dose-response relationships in a species other than rodents. Being an alkylating agent, the mutagenic effects of ethylene oxide are well known. The adverse effects on male reproductive parameters and early embryonic mortality are also well established. Although the reproduction study in rodents did not reveal effects on the female organs such as the ovaries, this does not indicate that testing in a non rodent species would be the same. Since effects on male reproductive parameters have been documented and related studies on females have suggested a possible reduction in female reproductive potential by impairing oocyte maturation or ovulation (Hardin B.D. et al., "Reproductive-toxicological assessment of the epoxides ethylene oxide, propylene oxide, butylene oxide and styrene oxide." Scand. J. Work. Environ. Health: 1983: 9; 94-102), information on the effects on the histopathology of female reproductive organs of a non rodent species is warranted. Therefore a chronic study in a non rodent species without females is unacceptable. Upon closer examination of the publication suggesting a possible reduction in female reproductive potential (Hardin B.D. et al., 1983), it appears that the effects of ethylene oxide are probably marginal and not as well characterised as those of propylene oxide, the other compound studied. Hence, although the study remains unacceptable by guideline standards, with all the information on the effects of ethylene oxide and the apparent absence of a gender-related effect for the specific metabolic pathways for ethylene oxide, the data gap may be closed (Iyer P. 10/28/96).

028 112627 "Assessment of proposed use of data from male cynomolgus monkeys in lieu of guideline canine studies for the evaluation of the chronic effects of ethylene oxide," (Carl

C. Smith, Prof. Emeritus University of Cincinnati) December 1991. It has been stated that the differences in response to agents between males and females are sufficiently small and do not mandate a gender-based adjustment in dose for most chemicals. While this is true, there are no data to suggest that humans do not react in a gender-related manner to Ethylene Oxide. Females may therefore be presumed to react in a similar manner to males with a NOEL < 50 ppm. However the possibility of a lower value cannot be overlooked. Information on the metabolism of ethylene oxide, particularly the involvement of glutathione and related enzymes, is needed to predict the occurrence of any gender-related differences in the metabolism of ethylene oxide. In the absence of experimental data, evidence from epidemiological studies to substantiate this issue may be considered.

Recent findings have documented the existence of individuals (approximately one-quarter of the population) who lack the specific activity of glutathione transferase and lymphocytes from this population (identified as non-conjugators) demonstrate a marked increase in sister chromosome exchanges upon exposure to ethylene oxide in vitro ("Polymorphism of glutathione conjugation of methyl bromide, ethylene oxide and dichloromethane in human blood: influence on the induction of sister chromatid exchanges in lymphocytes." E. Hallier et al., Arch. Toxicol., 1993, 67: 173-178). This polymorphism of glutathione transferase in human erythrocytes may be an important factor in individual susceptibility to the toxic and carcinogenic effects of ethylene oxide. While the population identified as non-conjugators is not determined by gender, this polymorphism may have unpredictable epidemiological consequences, emphasizing the importance of complete chronic studies. Also since this enzyme activity is not found in the erythrocytes of laboratory animals, species extrapolations for risk assessment of ethylene oxide should be reconsidered. Supplementary to 051614 086092, 088552, 098617 (Iyer, 8/1/94).

008, 022, 023, 027 051614, 086091, 086092, 088552, 098617 "Effects on Monkeys and Rats of Long-Term Inhalation Exposure to Ethylene Oxide - Major Findings of the NIOSH Study," (Lynch, D.W., Lewis, T.R., Moorman, W.J., et al., Centers for Disease Control, NIOSH, Cincinnati, OH; Environmental Health Research and Testing, Lexington, KY; Environmental Pathology Laboratories, INC., Herndon, VA; Midwest Research Institute, Kansas City, MO, 11/22/83 for 008

051614; Andersen, M., CIIT; 8/8/89 for 086091; CIIT Activities, 1989, 9 (6-7): 1-8 for 086092). Revisions (088552 and 098617 by P. Leber, 9/18/91, 027 for the most complete version. Ethylene oxide (99.7% pure) was administered by inhalation at 0 (vehicle = air), 50 or 100 ppm (7 hours/day, 5 days/week) for 24 months to adult male (12/group) cynomolgus monkeys (Primate Imports, N.Y.). **Possible adverse effects indicated.** NOEL < 50 ppm (weight gain significantly decreased at 100 ppm; cataract incidence: 0/12, 2/11 & 4/12 for 0, 50 & 100 ppm respectively; decrease in sperm counts & motility at \geq 50 ppm; increased sister chromatid exchanges/metaphase at \geq 50 ppm and increased chromosomal aberrations (minus gaps) at 100 ppm). Evaluated as Unacceptable (no individual data, no hematology data, no analysis of ETO in exposure chamber, inadequate summary data--the full report is required.) Possibly upgradeable (metabolism data pertaining to monkeys and ETO, justification for use of males only, analysis of ETO in exposure chamber and individual data--the full report are required). 022 086091 & 086092 are general information, no data related to 051614 were included. M. Silva, 5/21/90. With the submissions of 023 and 027, the individual data and analysis of ETO (for 3 days) have been submitted and no longer are deficiencies. The study remains **unacceptable but upgradeable**. There are still some data being generated with regard to the study, as discussed in March, 1991. Gee, 11/22/91.

023 088552 "Chronic inhalation exposure study of ethylene oxide in monkeys: NIOSH study." (Leber, P., Chem-Tox Consulting of Akron, 5/18/90) Rewrite of NIOSH study with much more complete data than in 008 051614. Gee, 11/20/91.

023 088550 Exact duplicate of 022 086092. Gee, 11/20/91.

027 098617 More complete version of 088552. Review of NIOSH study based on this revision by P. Leber. Gee, 11/22/91.

CHRONIC NON-RODENT

Epidemiology studies were submitted in support of chronic non-rodent data requirement. No worksheets.

033 124388 Wong et al., "An Epidemiological Study of Workers Potentially Exposed to Ethylene Oxide", British Journal of Industrial Medicine, 1993 (50) 308-316.

No dose response with duration of employment (time of exposure to Ethylene Oxide) was observed and neither was consistency (data in females did not corroborate findings in males) noted. Men demonstrated an increase in death due to Non-Hodgin's lymphoma, while women have a lowered incidence of non-Hodgin's lymphoma.

033 124389 Bisanti et al., "Cancer Mortality in Ethylene Oxide workers", British Journal of Industrial Medicine, 1993 (50) 317-324.

This study emphasizes that the excess of cancers of the lymphatic and hemopoietic tissues was statistically significant and consistent with previous studies (probably the Swedish studies by Hogstedt et al.,). But the lack of information on exposure to other chemicals makes the study not conclusive.

033 124390 Steenland et al., "Mortality Among Workers Exposed to Ethylene Oxide", New England Journal of Medicine 1991, 324, 1402-7.

The incidence of cancer could not be correlated with either job category or duration of exposure. However, a trend for increase in hematopoietic cancers and time since first exposure was observed. Additionally, the rate of death due to Non-Hodgin's lymphoma was increased in men though this pattern was not observed for the entire cohort. While an excess in Non-Hodgin's lymphoma was noted in men, women had a lower mortality rate from hemopoietic cancers than the rest of the U.S. population.

033 124391 Same as 042 127023 below.

042 127023 Shore et al., "Ethylene Oxide: An Assessment of the Epidemiologic Evidence on Carcinogenicity", The Ethylene Oxide Industry Council of the Chemical Manufacturers Association, June 1993.

This report includes a comprehensive meta analysis of previously published epidemiology studies 124388, 124389 and 124390 above. (P. Iyer, 10/26/94).

ONCOGENICITY, MOUSE

**** 012 065516** "Toxicology and Carcinogenesis Studies of Ethylene Oxide in B6C3F1 Mice (Inhalation Studies)," (U.S. Department of Health and Human Services, 11/87). B6C3F1 mice (50/sex/group) were exposed to air containing ethylene oxide technical (purity > 99%) at 0, 50 or 100 ppm for 6 hours/day, 5 days/week for 102 weeks. **Adverse effect indicated.** NOEL < 50 ppm (A significant increase in lung and harderian gland tumors in both sexes and uterine and mammary tumors in females was observed at both doses of ethylene oxide administered). **Acceptable.** M. Silva, 10/3/88.

008 051626 "On the Oncogenic Activity of Ethylene Oxide and Propylene Oxide in Mice" (Brit. J. Cancer **39**: 588 (1979); Ethylene oxide (J. T. Baker), tested by IR, GC and fluorescence; given by subcutaneous injection to 100 female NMRI mice per group at 0 (tricaprylin), 0.1, 0.3 or 1.0 mg/animal, once weekly for 91 weeks; increase in sarcomas at injection site with first tumor at 50th week; **Unacceptable** (summary only, inadequate data; need full study report). (J. Gee, 9/25/87).

008 051624 "NTP Technical Report on the Toxicology and Carcinogenesis Studies of Ethylene Oxide in B6C3F Mice," (NTP TR 326, Publ. no. 86-2582, 8/19/86). This volume contains a 3-page draft of the full report (012-65516). J. Gee, 9/25/87.

008 051594 "A Subchronic Inhalation Study on the Toxicologic Potential of Ethylene Oxide in B6C3F₁ Mice," Bushy Run Research Center, Export, Pennsylvania (Toxicology and Applied

Pharmacology 76, 510-518 (1984); Journal article is summary of record #034243 in 151-004.
No one-liner. (NLH, 9/87).

REPRODUCTION, RAT

**** 029 123115**, "Two-Generation Reproduction Study of Inhaled Ethylene Oxide Vapor in CD* Rats", (J. S. Chun and T. L. Neeper-Bradley, Bushy Run Research Center (BRRC), PA. Report # 91N0058, 7 May 1993). Ethylene oxide in nitrogen (98.6% purity) was used as test article. Outbred albino CD* rats (28/sex/group) received whole-body inhalation exposure for 6 hours per day (5 days/week-prebreeding, 7 days/week thereafter) at 0, 10, 33, and 100 ppm through 2 generations with 1 litter per generation. F0 exposure began 10 weeks prior to mating. **Possible adverse effects are indicated:** reduced pup weight gain (F1 and F2) and increased postimplantation loss (F0 dams) at 33 and 100 ppm. Parental NOEL = 10 ppm (reduced body weight in F0 males at 33 ppm and higher, reduced maternal food consumption during lactation at 100 ppm). Reproductive NOEL = 10 ppm (increased postimplantation loss, reduced pup weight gain at 33 and 100 ppm). **Acceptable.** (H. Green and P. Iyer, 10/25/94).

004 034235 "Ethylene Oxide, One-Generation Reproduction Inhalation Study," Carnegie-Mellon Institute of Research, Pittsburgh, 5/79. Ethylene oxide, commercial grade (purity not stated, chemical analysis in Appendix A; drum #7JNC45, G581); Fischer 344 rats, 30/sex/test group, and 60/sex/control were exposed by inhalation to 10, 33 or 100 ppm in air for 6 hours/day, 5 days/week, for 12 weeks prior to mating; during mating and 3 weeks after mating, exposure was 7 days/week; exposure was suspended for 5 days post-partum and resumed days 6-21 of lactation; one generation only; no deaths; histopathol. limited to reproductive organs of F0 parents; NOEL = 33 ppm, LEL = 100 ppm (prolonged gestation, decreased implants, decreased live fetuses/implant); **Unacceptable** (study does not substitute for a 2-generation study) - **Not upgradeable.** (C. Aldous, 10/3/85).

016 068207 "Heritable Translocation and Dominant-Lethal Mutation Induction with Ethylene Oxide in Mice," (Biology Division, Oak Ridge National Laboratory: Mutation Research, 73 (1980): 133-142). For 1-liner, see MUTAGENICITY, CHROMOSOMES (DOMINANT LETHAL).

TERATOLOGY, RAT

**** 032 123768**, "Ethylene Oxide: Developmental Toxicity Study of Maternally Inhaled Vapor in CD* Rats", (T. L. Neeper-Bradley and M. F. Kubena, Bushy Run Research Center (BRRC), Union Carbide Chemicals and Plastics Company Inc., PA. Report 92N1045, 26 May 1993). Mated female CD* rats 25/group received whole-body inhalation exposure to ethylene oxide (CAS # 75-21-8) in nitrogen (99.8% purity), for 6 hours/day on gestation days 6 through 15 at concentrations of 0, 50, 125 and 225 ppm. **A possible adverse effect is indicated:** delayed fetal development and intra uterine growth retardation. Maternal NOEL = 125 ppm (reduced body weight and food consumption at 225 ppm). Developmental NOEL < 50 ppm (delayed skeletal development and reduced fetal weights at 50, 125 and 225 ppm). **Acceptable.** (H. Green and P. Iyer, 10/27/94).

031 123767 No worksheet. See Background in worksheet for 032 123768 above.

034 124501 Summary of 123768

014 067757 "Teratogenic Study of Ethylene and Propylene Oxide and n-Butyl acetate," (U.S. Department of Health and Human Services, 5/82). Mated CD rats (detection of sperm = day 1 of gestation), were exposed to 0 (vehicle = air) or 150 ppm ethylene oxide (purity > 99.7%; Linde lot #01901) for 7 hours/day from day 7-19 (group 2), or 7-16 of gestation (group 3) at 44-45/group or 5 days/week for 3 weeks prior to mating and daily from day 1-16 of gestation (group 4--50 rats). Group 1 = air control. **No adverse effect indicated.** Maternal NOEL < 150 ppm for treatment schedules received (decreased food consumption, weight gain and weight of uterus; increased weight of kidney and spleen occurred in all groups compared to control). Developmental NOEL < 150 ppm (decreased body weights, crown-rump length; reduced ossification

of skull and sternebra in groups 2-4 and an increase in hydroureter in group 2 only). **Not acceptable** (no individual maternal or fetal data, only one dose level was tested, a NOEL was not established). **Not upgradeable** (dose range was not sufficient to establish a NOEL). M. Silva, 10/5/88.

004 034241 "Ethylene Oxide Teratology Study," Carnegie-Mellon Institute of Research, Pittsburgh, PA, 7/2/79. Ethylene oxide (drum 7JNC45, G581; no purity given), Fischer 344 rats exposed by inhalation for 6 hours/day, days 6-15 of gestation, to 0, 10, 33 or 100 ppm; 22/group with two control groups; maternal NOEL = 100 ppm, fetal NOEL = 33 ppm (decreased fetal weight with no maternal toxicity); **Unacceptable** (no maternal body weights or food consumption, no maternal necropsy findings, all fetuses need to be examined - not just control and high dose, no clinical observations). **Possible adverse fetal effects**. Justification of dose selection in response dated February 3, 1987, in 008. (J. Parker, 9/24/85 and 10/15/87)

004 051595 "Teratology Study in Fischer 344 Rats Exposed to Ethylene Oxide by Inhalation," Bushy Run Research Center, Export, PA (Toxicology and Applied Pharmacology **64** (1982)); Journal article summary of record #034241 in 151-004. No one-liner. (NLH, 9/87).

Conclusion: Study 014 067757 had no adverse effect indicated but only one dose was tested. In the study, the dose was sufficiently high that a NOEL was not established. Study 004 034241 utilized a range of doses which encompassed a NOEL and MTD and within this range, indications of a possible adverse effect were revealed. Therefore, it must be considered that ethylene oxide may cause developmental effects in rat. Silva, 10/88. In study 032 123768 the developmental effects were observed at levels below the maternal NOEL, indicating possible adverse effects (Iyer, P., 2/8/95).

TERATOLOGY, RABBIT

014 067757 "Teratogenic Study of Ethylene and Propylene Oxide and n-Butyl acetate," (U.S. Department of Health and Human Services, 5/82). Inseminated New Zealand White rabbits (day after insemination = day 1 of gestation) were exposed to 0 (vehicle = air) or 150 ppm ethylene oxide (purity > 99.7%; Linde lot #01901) 7 hours/day from day 7-19, or day 1-19 of gestation (32-35/group). **No adverse effect indicated.** Maternal NOEL > 150 ppm (no effects observed with either treatment regimen). Developmental NOEL > 150 ppm (no effects observed with either treatment regimen). **Not acceptable** (no individual maternal or fetal data, only one dose level was tested, an MTD was not established). **Not upgradeable** (dose range was not sufficient to establish a NOEL). M. Silva, 10/5/88.

*** 014, 021 067758, 076024 "Teratologic Evaluation of Ethylene Oxide (CAS NO. 75-21-8) in New Zealand White Rabbits," (Research Triangle Institute, 12/2/80). Ethylene oxide (purity and grade not stated) was administered i.p. to inseminated New Zealand White rabbits in 2 groups. TREATMENT GROUP A: 0 (vehicle = 5% sterile dextrose), 9, 18 or 36 mg/kg/day (24-27/group) on days 6-14 of gestation (day of insemination = day 0 of gestation) and TREATMENT GROUP B: 0, 18 or 36 mg/kg/day (15-18/group) on days 6-9. **No adverse effect indicated.** TREATMENT GROUP A: **Maternal NOEL** = 18 mg/kg/day (decreased gravid uterine weight; decrease in body weight gain on days 14-30; increase in resorptions/litter and %resorptions; decrease in #litters). **Developmental NOEL** = 18 mg/kg/day (significant increase in %fetuses affected--non-live and malformed at 36 mg/kg/day). TREATMENT GROUP B: **Maternal NOEL** ≤ 18 mg/kg/day (maternal weight gain was significantly decreased during the entire gestation period at 18 and 36 mg/kg/day). **Developmental NOEL** > 36 mg/kg/day (no significant effects were observed at any dose level). Previously reviewed as unacceptable (M. Silva, 10/7/88), upon receipt and evaluation of requested information (analysis of ethylene oxide and individual maternal and fetal data), the study is upgraded to **acceptable**. M. Silva, 10/7/88.

Comment: Although in 067758 there are clearly adverse effects to the fetuses in TREATMENT GROUP A, the study is not labeled as such because the maternal and developmental NOELs are the same. Silva, 11/89.

TERATOLOGY, MICE

008 051612 "The Teratogenicity of Ethylene Oxide Administered Intravenously to Mice" (Toxicology and Applied Pharmacology **56**: 16-22 (1980)), National Center for Toxicological Research, CD-1 mice given 0, 75 or 150 mg/kg by I.V. injection days 4-6 (I), 6-8 (II), 8-10 (III) or 10-12 (IV) of gestation, approximately 40 per group; nominal maternal NOEL = 75 mg/kg (deaths in periods I, III and IV but not in II, decreased body weight gain in III and IV), nominal developmental NOEL = 75 mg/kg based on significant increase in skeletal malformations in II at 150 mg/kg without overt maternal toxicity. **Unacceptable** (no analysis of dosing solutions, no individual data). (J. Gee, 9/23/87).

MUTAGENICITY, MISCELLANEOUS

008 051602 "Mutational Consequences of Exposure to Ethylene Oxide - Review of Literature on Mutational Effects of Ethylene Oxide" (Journal of Environmental Pathology and Toxicology **2**: 1289-1303 (1979)); Literature review of sub-mammalian and mammalian mutagenicity tests on a variety of species; Gene mutation effects observed in barley, wheat, rice, Salmonella spp., Klebsiella spp. and Neurospora; Chromosomal mutations in Drosophila, chromosomal aberrations in rat bone marrow (in vivo), increase in micronuclei in rats (in vivo) and decreases in number of pregnancies and implants in a dominant lethal study, and DNA repair inhibition in polymerase-deficient E. coli; **Unacceptable - Summaries**. (J. Gee, 9/18/87)

MUTAGENICITY, GNMU

008 051600 "Mutagenicity and Cytotoxicity of Ethylene Oxide in the CHO/HGPRT System" (Environmental Mutagenesis **3**: 683-686 (1981)); Ethylene oxide (no purity information), 0 to 10 mM, three trials; Chinese hamster ovary cells (CHO-K₁-BH₄) treated by ethylene oxide diluted in ice water; Cytotoxicity evaluated in triplicate samples of 200 cells each, Mutagenicity

evaluated with 5 replicate plates of 200,000 cells; Cells treated for 5 hours with and without rat liver S-9; Ethylene oxide reported to be both cytotoxic and mutagenic with and without metabolic activation, but insufficient information for independent adverse effects assessment; **Unacceptable - Summary.** (J. Gee, 9/18/87)

MUTAGENICITY, CHROMOSOMES

DOMINANT LETHAL

034 134856 "Ethylene Oxide - Dominant-Lethal Mutagenicity Inhalation Study on Rats," (Bushy Run Research Center, PA 15632., 6/13/84. Fischer 344 rats (male) 10/group, were exposed to Ethylene oxide (99.9%) via inhalation to 10, 33 or 100 ppm for 6 hours/day, 5 days/week for 10 weeks. Two groups exposed to air served as controls and TEM (triethylene melamine) by injection served as the positive control. No exposure-related effects were observed in body weights, clinical signs or necropsy findings (gross lesions). After the exposure period, males were mated with unexposed females to examine for dominant lethal effects. Mating was for 3 one-week periods with females changed each week. If no vaginal plug was visible in 4 days, the female was mated with another male for the remaining 3 days. Preimplantation loss was increased in the 100 ppm group compared with the air-control (0 ppm) group. While the number of resorptions in the 100 ppm group was higher than the 10 and 33 ppm, and could indicate a dominant lethal effect, the high variance in the two control groups do not support this conclusion. No dominant lethal effects were noted at the 10 and 33 ppm exposure level. Possible effects of dominant lethal mutagenicity was observed at 100 ppm. Unacceptable, not upgradable, inadequate number of animals, fertility problems in all groups. No worksheet (P. Iyer, 10/25/94).

004 034238 "Ethylene Oxide - Dominant Lethal Mutagenicity Inhalation Test in Rats," Bushy Run Research Center, Export, PA, 1/28/83. Draft Report for dominant lethal study; ethylene oxide by inhalation at 0, 10, 33 or 100 ppm, 6 hours/day, 5 days/week for 10 weeks, 10 male

Fischer 344 rats per group with two negative control groups; mated for weekly intervals over 3 weeks after the termination of the exposure; TEM as positive control injected i.p.; results with the TEM during weeks 1 and 2 when an effect is anticipated to occur were equivocal by statistical analysis as were results with 100 ppm when compared with concurrent controls; one-page report (no data) states that no dominant lethal effect occurred at 10 or 33 ppm; the test should be repeated; **unacceptable, incomplete** (concurrent positive control was not statistically different from negative controls so no conclusion can be drawn, only one-page report submitted). (J. Remsen, 10/3/85)

016 068207 "Heritable Translocation and Dominant-Lethal Mutation Induction with Ethylene Oxide in Mice," (Biology Division, Oak Ridge National Laboratory: Mutation Research, 73(1980)133-142). Ethylene oxide (purity and grade not stated) was administered in a single i.p. injection at 0 (distilled water) or 150 mg/kg to male mice. Two dominant lethal experiments were performed: 1. Treated T-stock males (12/group) were mated with (SEC x C57Bl)F1 females and uterine analysis was performed 12-15 days after observation of a vaginal plug. 2. Treated (101 x C3H)F1 males (96/group) were divided into 4 groups and mated with (SEC x C57BL)F1, (101 x C3H)F1 and (C3H x C57BL)F1 or T-stock females. Females were killed for uterine analysis 12-15 days after observation of a vaginal plug. In a heritable translocation test, T-stock males were injected i.p. for 5 weeks with 0, 30 or 60 mg/kg (25, 50 and 75 males respectively) then mated with 3 (SEC x C57BL)F1 females for 1 week. Then each male was left with 1 of the 3 females for 5 months to assess effects of ethylene oxide on progeny. **Adverse effect indicated.** Dominant lethal and heritable translocation effects were observed at all doses tested. **Not acceptable** (no analysis of dosing material; positive controls were not used; data for individual animals were not presented; no statistics were performed). **Not upgradeable.** M. Silva, 10/3/88.

008 051597 "Mutagenic Action of Ethylene Oxide on the Reproductive and Somatic Cells of Male White Rats," Strekalova, 1975 (publ. article, unknown source); Ethylene oxide (no purity information), 24 animals exposed to $3.6 \pm 0.6 \text{ mg/m}^3$ (2.0 ppm), and 14 animals exposed to $112 \pm 20.2 \text{ mg/m}^3$ (60 ppm) for 66 days by inhalation; 21 animals in control group; Exposed males

mated to untreated females for 4 days; females sacrificed 21 days after mating; Increase in number of pre-implantation embryo deaths (dominant lethal effect) and increase in chromosomal aberrations (also referred to as "chromosomal rebuilding," Insufficient information for independent adverse effects assessment; **Incomplete, Unacceptable - Not upgradeable** (no positive controls conducted, insufficient protocol information, no individual data). (J. Gee, 9/18/87).

008 051619 "The Mutagenic Potential of Ethylene Oxide Using the Dominant Lethal Assay in Rats" (Toxicol. Appl. Pharmacol. **40**: 261-267 (1977); Ethylene oxide ("pure") by inhalation for 4 hours at 0 or 1000 ppm to 10 (controls) and 15 (EO) male rats, mated 1:2 for 10 one-week periods; TEM as positive control; increase in dead implants and in dead implants per total implants in weeks 1-5 but not 6-10; **Possible adverse effect; Unacceptable** (summary data only). (J. Gee, 9/24/87)

008 051611 "Studies on Ethylene Oxide: Whole-body Autoradiography and Dominant Lethal Test in Mice," (publ. in Clinical Toxicology, 1977), Nat. Board of Health and Welfare, Stockholm; Ethylene oxide (no purity stated); by intravenous injection once at 0, 0.025, 0.05 or 0.1 g/kg to 5/group or one-half these dosages in two consecutive doses; males mated to 3 females per week for 8 weeks; no dominant lethal effect reported; **Unacceptable** (inadequate numbers of animals, summary data only) - **Not upgradeable**. (J. Gee, 9/24/87)

008 051628 "Mutagenic Effects of Inhaled Ethylene Oxide in Male Mice," Oak Ridge Natl. Laboratory, Tennessee; Ethylene oxide administered by inhalation at 500 ppm for four 8-hour periods to male mice or five 8-hour periods at 400 or 300 ppm; Dominant lethal effect at 500 and 400 ppm; Non-linear increase in UDS portion indicating inhibition of repair capacity; **Unacceptable** (abstract with no data; need full report). (J. Gee, 9/25/87)

MICRONUCLEUS

008 051622 "Testing of Ethylene Oxide for Mutagenicity Using the Micronucleus Test in Mice and Rats" (Acta pharmacol. et toxicol. **43**: 69-71 (1978)); Ethylene oxide in water was injected intravenously 30 and 6 hours before sacrifice at 0, 0.05, 0.10, 0.15, 0.20 or 0.30 g/kg to NMRI mice or at 0, 0.10, 0.15 or 0.20 g/kg to Sprague-Dawley rats; 1000 PCE's scored per animal; no sex stated; 4-11 per group; increase in percentage of PCE's with micronuclei; **Unacceptable** (summary data only, no purity stated, single harvest time, protocol). (J. Gee, 9/25/87).

CHROMOSOMAL ABERRATIONS

004 034240 "Long-Term Ethylene Oxide Inhalation Study on Rats: Report on Cytogenetic Studies of Bone Marrow Cells - 12-Month Sacrifice Interval," Bushy Run Research Center, Pittsburgh, PA, 7/7/80). Ethylene oxide, commercial grade (details given in 2-year inhalation study); 10/sex/group were exposed to 0 or 100 ppm 6 hours/day, 5 days/week over 1 year; No increase in marrow chromosomal aberrations is reported; **Complete, Unacceptable** (single dose, wide variability among samples) - **Not upgradeable**. A separate study should be conducted which addresses genotoxicity specifically rather than using animals from another study in which the dosing is curtailed by the length of the exposure period. (J. Remsen, 10/3/85).

004 034239 Appendix to 034240 including protocol and illustration of aberrations.

008 051599 - 051598 "On the Problem of the Mutagenic Effect of Ethylene Oxide on the Mammals" (Toxicology of New Industrial Chemicals **12**: 72-78 (1978)) Ethylene oxide (no purity information) per os in aqueous solution to 6 rats (strain not stated) per harvest interval at 9 mg/kg; Rats sacrificed at 24 and 48 hours; Increase in chromosome aberrations at 24 hours, but insufficient information for independent assessment; **Incomplete, Unacceptable - Not upgradeable** (no positive control group, only one dose level, use of males only). (J. Gee, 9/18/87)

008 051596 "Mutagenic Action of Some Industrial Poisons as a Function of Concentration and Exposure Time" (Tuksikol. Nov. P. Khim Veshchesto, **13**: 51-57 (1973)), Rat bone marrow; Ethylene oxide (no purity information) by inhalation, low dose level: 0.001-0.003 mg/l (0.6-1.7 ppm), high dose level: 0.030-0.060 mg/l (17 ppm - 33 ppm); 6 per group (sex not stated); Increase in the quantity of chromosomal aberrations at the high dose level after the 4th, 8th & 30th 24-hour periods, Increase in chromosome reorganization at the low dose level after the 30th day of inhalation; **Incomplete, Unacceptable** - (missing protocol information and individual data). (J. Gee, 9/18/87).

008 051606 "Cytogenetic Damage in Workers Exposed to Ethylene Oxide" (Mutation Research **138**: 185-195 (1984)); Ethylene oxide (no purity information); High exposure level: 10.7 ±4.9 ppm ETO 8-hour TWA 19 workers (14 males); Low exposure level: 0.35 ± 0.12 ppm ETO 8-hour TWA 22 workers (14 males); Control: Each exposed worker paired with a control of similar age and smoking habits; SCE's and chromosome aberrations analyzed in peripheral lymphocytes; Increase in frequencies of SCE's and of chromosome aberrations in exposed workers; **Unacceptable** (no purity data, aberrations not described other than gaps, method of monitoring air not presented). (J. Gee, 9/23/87).

008 051607 "Cytogenetic, Immunological, and Haematological Effects in Workers in an Ethylene Oxide Manufacturing Plant," (British Journal of Industrial Medicine **42**: 19-26 (1985)); Ethylene oxide (ETO); Male workers exposed for 1-14 years to mean air concentration of <0.12 ppm; No effects on chromosome or chromatid aberrations or on serum immunoglobulin concentrations or lymphocyte activation; **Incomplete, Unacceptable** (no purity stated, no individual data). (J. Gee, 9/24/87).

008 051615 "Chromosomal Aberrations Induced by Ethylene Oxide in a Human Amniotic Cell Line In Vitro" (Mutation Res. **104**: 255-260 (1982)); Ethylene oxide (no purity stated); FL cell line (Flow Labs); Human amniotic cells exposed one hour in vitro to 0, 5, 7.5 or 10 mM x h, 3 experiments; scored 150 per concentration; survival at 100, 58, 25 and 9.2%; harvested at 48, 72 and 96 hours; cell doubling of controls at 60 hours; Increase in breaks, exchanges and

complexes with concentration, especially at 48 hours; **Unacceptable** (no activation, no purity stated). (J. Gee, 9/23/87).

See also 008 051597 (listed under DOMINANT LETHAL), rat cells.

SISTER CHROMATID EXCHANGES

008 051604 "Sister Chromatid Exchanges Induced in Rabbit Lymphocytes by Ethylene Oxide After Inhalation Exposure" (Environmental Mutagenesis **4**: 121-134 (1982)); Ethylene oxide (99.7%) administered by inhalation 6 hours per day, 5 days per week for 12 weeks to 8 New Zealand rabbits per dose level; Dose levels were 0, 10, 50 and 250 ppm; SCE's (50 cells/animal) and hematology evaluated in 3 rabbits per dose level; glutathione content of liver analyzed in 4 animals/dose level; positive control was Mitomycin C injected i.p. in 4 animals; Dose related increase in SCE's after 12 weeks exposure at 50 & 250 ppm, No detectable effect observed at 10 ppm; **Incomplete** (missing some protocol information, positive control data); **Unacceptable** (no justification for the testing of males only). (J. Gee, 9/18/87).

008 051603 "Exposure to Ethylene Oxide at Work Increases Sister Chromatid Exchanges in Human Peripheral Lymphocytes" (Science **219**: 1221-1223 (1983)); Sister chromatid exchange rates in peripheral lymphocytes were studied in a small group of hospital workers exposed to ethylene oxide over 6 months; cumulative doses of low (<100 mg) or high (>100 mg); Significant increase observed in the mean number of SCE's per cell in the high exposure group (2 nonsmokers and 3 smokers); scored 50 cells per coded sample after 72 hours of PHA-M stimulation in vitro; **Unacceptable - Summary**. (J. Gee, 9/18/87).

008 051610 "Ethylene Oxide: Evidence of Human Chromosomal Effects" (Environmental Mutagenesis **1**: 375-382 (1979)); Ethylene Oxide (max. ambient level of 36 ppm found by infrared spectroscopy, quantitative estimates by GC not possible due to poor recovery); SCE frequency analyzed in workers (8 women and 4 men) exposed in a hospital sterilization facility; Controls included unexposed and incidentally exposed workers; Increase in SCE frequencies in

individuals with respiratory and neurologic symptoms, levels in these individuals remained elevated 8 weeks post exposure; Increase in SCE frequencies in 8 other exposed workers with lesser symptoms studied 8-9 weeks post-exposure; Elevated SCE rates in incidentally exposed workers 7-9 weeks post-exposure; SCE's not correlated with smoking; Insufficient information for independent adverse effects assessment; **Unacceptable** (some individual data missing). (J. Gee, 9/23/87).

008 051613 "Sister Chromatid Exchange and Chromosome Aberrations in Lymphocytes of Laboratory Personnel." (Publication in: J. Toxicol. Environ. Health 6: 1237 - 1243 (1980)); Ethylene oxide, five female subjects exposed to ethylene oxide in a German sterilization plant, no exposure data; frequency of sister chromatid exchanges were compared with smoking and nonsmoking controls and laboratory personnel. The frequency of SCE's was increased in ETO workers. **Unacceptable**, summary data only. (J. Gee, 10/9/87).

027 098617, pg. 175 "Factors Influencing the Detection of Persistently Elevated SCE after in vivo Inhalation Exposure to Ethylene Oxide in Non-human Primates." (Kelsey, K. T., J. K. Weincke, E. A. Eisen, D. Lynch, T. Lewis and J. B. Little, Harvard School of Public Health, etc., publication in: Environmental and Molecular Mutagenesis **11**: 52 (1988)) Abstract. When peripheral blood lymphocytes were put into culture, the detection of high SCE frequency cells was influenced by serum and time of harvest. Harvest at 55 hours gave maximal results while at 96 hours there was a lack of detection. The elevations in SCE's persist for years. No worksheet. Gee, 11/20/91.

027 098617, pg. 175 "Persistently Elevated SCE in Ethylene Oxide-Exposed Primates Involve a Subpopulation of High Frequency Cells." (Kelsey, K. T., J. K. Weincke, E. A. Eisen, D. Lynch, T. Lewis and J. B. Little, Harvard School of Public Health, etc., publication in: Environmental and Molecular Mutagenesis **11**: 52 (1988)) Abstract. The data collected in 1987 from treated monkeys were compared to the data of 1981. Although the mean SCE decreased over time, the mean SCE in the top 5% did not diminish over time. No worksheet. Gee, 11/20/91.

027 098617, pg. 176 "Karyotypic Analysis of Bone Marrow in Monkeys with Persistently Elevated SCE After Chronic ETO Exposure." (Kelsey, K. T., M. Burrell, J. K. Weinke, D. W. Lynch and J. B. Little, Harvard School of Public Health, etc., publication in: Environmental and Molecular Mutagenesis **14**: 100 (1989)) Abstract. The karyotype of 20-25 bone marrow cells was determined from 2 high dose (100 ppm), 2 low dose (50 ppm) and 4 controls. All were normal suggesting that ETO did not induce stem cell karyotype alteration. No worksheet. Gee, 11/20/91.

027 098617, PG. 177 "Sister-Chromatid Exchanges and Chromosome Aberrations in Lymphocytes from Monkeys Exposed to Ethylene Oxide and Propylene Oxide by Inhalation." (Lynch, D. W., T. R. Lewis, W. J. Moorman, J. R. Burg, D. K. Gulati, P. Kaur and P. S. Sabharwal, publication in: Toxicology and Applied Pharmacology **76**: 85-95 (1984), multiple laboratories) See 098617, chronic monkey study above, for additional details. In brief, the monkeys were exposed to ethylene oxide, 99.7% purity, for 7 hours/day, 5 days per week for 2 years. About 4 ml of peripheral blood was collected per animal during the last month of exposure. For SCE, lymphocytes in whole blood were stimulated with phytohemagglutinin. After 18 hours, bromodeoxyuridine was added. Duration of culture was 68 to 74 hours. For chromosome aberrations, no BrdUrd was added and cultures were harvested 48 to 52 hours. Fifty metaphases per monkey were scored for SCE and 200 for aberrations. The mean SCE were statistically increased in both ETO groups: control, 5.4 (12 animals); EO 50, 10.2 (10 animals) and EO 100, 15.1. For aberrations, the mean chromatid plus chromosome-type were also statistically significantly increased. **Possible adverse effect indicated.** Not acceptable (publication lacking details). Gee, 11/20/91

027 098617, pg. 188 "Sister Chromatid Exchange in Chronic Ethylene Oxide-exposed Primates: Unexpected Effects of in vitro Culture Duration, Incubation Temperature and Serum Supplementation." (Kelsey, K. T., J. K. Weincke, E. A. Eisen, D. W. Lynch, T. R. Lewis and J. B. Little, publication in: Cancer Research **49**: 1727-1731 (1989)) See 098617, chronic monkey study above, for additional details. Venous blood was drawn in 1987, with exposure to ethylene oxide ending in 1981. Triplicate cultures were initiated with BrdUrd added 24 hours

after start. Harvests were at 55, 72 or 96 hours. The % high frequency cell (HFC) with >40 SCE/cell were scored as well as SCE/cell in general. Results showed that at the 55 hour harvest time, the difference between treated and controls was greatest. The mean values at 55 hours for HFC were 0 for controls, 4.5% for 50 ppm (7 monkeys) and 12% for 100 ppm (7 monkeys). The SCE/cell also increased in a dose-dependent manner: 7.6 for control, 10.40 for 50 ppm and 14.8 for 100 ppm. At 72 hours, there was still an increase with exposure but to a lesser degree. The % HFC and the replication index increased with temperature (35, 37 or 39^o). The results confirm that exposure to ethylene oxide increases the incidence of sister chromatid exchanges in primates and these exchanges can persist for a number of years.

Possible adverse effect indicated. Study is unacceptable (details not included). Gee,
11/21/91.

027 098617, pg. 193 "Persistently Elevated Sister Chromatid Exchanges in Ethylene Oxide-exposed Primates: The Role of a Subpopulation of High Frequency Cells." (Kelsey, K. T., J. K. Weincke, E. A. Eisen, D. W. Lynch, T. R. Lewis and J. B. Little, publication in: Cancer Research **48**: 5045-5050 (1988)) See 098617 under chronic monkey study for additional details. Male monkeys were exposed for two years to 0, 50 or 100 ppm ethylene oxide by inhalation, 1979-1981. The blood samples used were collected in 1987. Triplicate whole blood cultures were initiated with phytohemagglutinin. At 24 hours, bromodeoxyuridine was added. Lymphocytes were harvested at 72 hours, fixed and stained. One hundred (100) metaphases per animal were scored. When the SCE/cell is broken down into the lower 90% and the upper 10%, the increase in the incidence of SCE's in the lower 90% in 1981 is no longer found in 1987. Analysis of the upper 10%, however, shows that the mean SCE/cell is still increased in a dose-dependent manner. This is attributed by the authors to a subpopulation of long-lived cells. SCE/cell: control, 14.1; 50 ppm, 24.4; 100 ppm, 38.8. **Possible adverse effect indicated with increase in sister chromatid exchanges.** Unacceptable (not a guideline study). Gee,
11/21/91.

Summary - see below.

MUTAGENICITY, DNA

UNSCHEDULED DNA SYNTHESIS

**** 008 051605** "In Vivo and In Vitro Ethylene Oxide Exposure of Human Lymphocytes Assessed by Chemical Stimulation of Unscheduled DNA Synthesis" (Mutation Research **83**: 271-289 (1981)); Lymphocytes from 17 female workers exposed to 0.5 - 1.0 ppm ethylene oxide/hour/40 hour work week were tested with NAAF; Decreased UDS response resulted after in vivo exposure to ETO; in vitro exposure to 0 to 100 mM ethylene oxide (pure) resulted in an increase in UDS at low (0 - 5 mM) concentrations but a decrease at higher concentrations; ETO was also cytotoxic; **Complete, Acceptable.** (J. Gee, 9/24/87).

See also 008 051628 for UDS study in mice cells (listed under DOMINANT LETHAL).

B. SUBTILIS

008 051601 "Application of Bacillus subtilis Spores in the Detection of Gas Mutagens: A Case of Ethylene Oxide" Mutation Research **64**: 433-435 (1979)), Radiobiology Division, National Cancer Center Research Institute, Tokyo, Japan, Ethylene oxide (no purity information or concentration given); B. subtilis strains HA 101, TKJ5211 and TKJ8201; Spores in deionized water layered on a membrane filter and exposed to ethylene oxide gas in a polyethylene bag; spores plated on selective media for one day for cytotoxicity assessment and for 3 days on same media for mutagenicity assessment; Ethylene oxide reported to be a direct acting mutagen, but insufficient information presented for independent adverse effects assessment; **Unacceptable - Summary.** (J. Gee, 9/18/87).

MISCELLANEOUS

008 051616 "Evaluation of Genetic Risks of Alkylating Agents: Tissue Doses in the Mouse From Air Contaminated with Ethylene Oxide," U. of Stockholm, Sweden, 4/9/74; [1,2-H³] Ethylene

oxide, 56 mCi/mole; 6-8 week old male CBA mice exposed by inhalation to 6.3 to 41.1 ppm-h for 60 to 107 minutes in replicate experiments; radioactivity in liver, kidney, testis and spleen quantitated with time; approximately 80% excreted within 48 hours; alkylates N-7 of guanine in DNA and also proteins; *in vitro* alkylation of DNA and proteins also measured with $t_{1/2}$ for depurination = 340 hours; Discusses dose rate compared with ionizing radiation; 5 ppm for 40 h/week at approx. 4 rad equivalents; **Unacceptable** (not a guideline study). (J. Gee, 9/24/87).

No Record Number "Macromolecular adducts of ethylene oxide: a literature review and a time-course study on the formation of 7-(2-hydroxyethyl)guanine following exposures of rats by inhalation." (Walker, V. E., T. R. Fennell, J. A. Boucheron, N. Fedtke, F. Ciroussel and J. A. Swenberg, publication in: *Mutation Research* **233**: 151-164 (1990), multiple laboratories) The review section cites many published papers on alkylation, metabolism, others. In the study section, ethylene oxide (90% ethylene oxide, 10% nitrogen) was given by inhalation to groups of 10 male Fischer 344 rats at 300 ppm, 6h/day, 1 or 3 days, or 1, 2, or 4 weeks (5 days/week). Another set of animals were given 300 ppm for 4 weeks and groups of 10 were sacrificed at 1, 3, 5 or 10 days after the end of exposure. The average analytical concentration was 301 ppm. WBC's, RBC's and selected tissues were collected and frozen until DNA was isolated. Formation of 7-HEG was quantitated by chromatography for brain, lung, spleen, kidney, WBC's, liver and testis. Adduct formation was similar for target and non-target tissues, being lowest in the testis. Persistence was measured over 10 days following exposure with a half-life of approximately 7 days. The authors concluded that tumor induction was due to factors in addition to adduct formation. **Supplemental data.** No worksheet. Gee, 12/3/91.

SUMMARY: Although each study was found unacceptable due to flaws in design or in reporting of data, CDPR believes collectively they provide sufficient data to determine that ethylene oxide is genotoxic in a number of tests and presents a potential adverse effect to humans. Gee, 10/87, 12/91.

Induction of DNA Strand Breaks by Ethylene Oxide in Human Diploid Fibroblasts. J. Nygren et al., 1994, Environ. Mol. Mut., 24: 161-167.

In this study four techniques were used to test if the large deletions after ethylene oxide exposure were due to the induction of DNA strand breaks. The techniques were i) alkaline DNA unwinding - ADU ii) neutral filter elution -NFE, iii) pulsed field gel electrophoresis - PFGE and iv) comet assay. Also the PGFE and comet assay were used to investigate how the ethylene oxide-induced damage to DNA is repaired in normal human diploid fibroblasts (strain VH-10). The data collected indicate that the damage measured is biologically relevant and not simply due to DNA degradation. Possible adverse effect indicated. No worksheet (P. Iyer, 11/22/94).

NEUROTOXICITY

Not required at this time.

MISCELLANEOUS

005, various record numbers: "Occupational Safety and Health Administration Proposed Rule: Occupational Exposure to Ethylene Oxide," U.S. Dept. of Health, Education & Welfare, NIOSH, 7/83.

002/007 049370 "Technical Report; Toxicity of Ethylene Oxide and its Relevance to Man: Review of Literature," European Chemical Industry, ECETOC, 9/82.

SUPPLEMENTAL STUDIES

023 088551 Proposed plan of Chemical Industry Institute of Toxicology (CIIT) for a pharmacokinetic study. The development of a PB-PK model for ethylene oxide to address the relevance of a rodent carcinogen to humans. The study is to be conducted in two phases. The study is not on file as of 11/91. Gee, 11/20/91.

No worksheets for the following studies:

151-030 123110 Progress report regarding the metabolism studies being generated. As part of the information being developed by the Chemical Industry Institute for Toxicology on Ethylene Oxide (ETO) metabolism, studies describing the pharmacokinetic properties of ETO in the rat, designed specifically for use in risk assessments were published in peer reviewed journals and made available to CAL-EPA, DPR. P. Iyer, 10/25/94.

030 123111 A Physiologically Based Description of Ethylene Oxide Dosimetry in the Rat. Krishnan K., Gargas M.L., Fennell T.R., and Andersen M.E. (1992) Toxicol. Ind. Health 8: 121-140.

This paper describes the development of a physiologically based pharmacokinetic (PB-PK) model for Ethylene Oxide in the rat. Studies involved in vivo inhalation exposure to 1.2 - 1200 ppm of ETO and intravenous exposure to 1 - 100 mg/kg ETO. Animals tested were male Fischer 344 and Sprague Dawley rats. The model comprised of nine tissue compartments and rate constants were estimated for GSH conjugation, hydrolysis and DNA and hemoglobin adducts. Using a number of parameters including species-specific data on blood flow, and tissue: air partition coefficients for ETO, mass balance equations were solved with computer software programs. The PB-PK modeling approach allowed for the characterization of several components of the elimination process (first order) including GSH conjugation, hydrolysis, exhalation, DNA binding and hemoglobin binding. Non linearities were found to occur in major elimination pathways at various exposure concentrations (high) at which whole body elimination still followed first order kinetics. Therefore an increase in dose of ETO did not increase the formation of DNA and hemoglobin adducts. This mechanistic understanding based on the physiological reality of dosimetry models can serve for prediction in humans and other species. (P. Iyer, 10/25/94).

030 123112 A Model for the Formation and Removal of Hemoglobin Adducts. Fennel T.R., Sumner S., and Walker V. E. (1992) Cancer Epidemiology, Biomarkers & Prevention. 1, 213-219.

The kinetics of total ETO adduct formation and the use of the hydroxyethyl adduct bound to red blood cell (RBC) hemoglobin as a 'biomarker' were explored. The variables noted include species-dependent RBC half life (this in turn is dependent on RBC senescence and their removal), adduct instability (determines how much will accumulate), and ETO exposure conditions (continuous or repetitive-discontinuous). (P. Iyer, 10/25/94).

030 123113 Molecular Dosimetry of Ethylene Oxide: Formation and Persistence of N-(2-Hydroxyethyl)valine in Hemoglobin following Repeated Exposures of Rats and Mice. (1992). Walker V.E., MacNeela, J.P., Swenberg J.A., Turner M.J. Jr., and Fennell T.R. Cancer Research. 52, 4320-4327.

The binding of ETO to specific amino acids, valine and histidine (reported earlier in Terat. Carcinog. Mutagen., 3L 395-405, 1983) within hemoglobin in rodents was examined. It was noted that HEVal (Hemoglobin adduct) accumulates in mice and rats during multiple exposures to ETO, and these adducts accumulate in a parabolic fashion over the life span of the erythrocyte. While results indicated that valine adducts related to repeated exposures over four weeks to ETO at concentrations up to 33 ppm were linear, nonlinear responses were observed at higher exposures in rats. The decline in adducts could be because of dilution by accelerated erythropoiesis, adduct instability and accelerated erythrocyte loss/removal. Since repeated exposures to ETO can perturb (reduce) the life span of RBCs in a concentration- and time- dependent manner, examination of other hematological parameters such as reticulocytes is needed. The measurement of hemoglobin adducts in the presence of a diminished RBC lifespan could thus result in the underestimation of ETO exposure, however the erythroclastic effects of ETO appear to be at doses above the OSHA standard of 1 ppm (8 hr time-weighted average). (P. Iyer, 10/26/94).

030 123114 Molecular Dosimetry of Ethylene Oxide: Formation and Persistence of 7-(2-Hydroxyethyl)guanine in DNA following Repeated Exposures of Rats and Mice. (1992). Walker V.E., Fennell T.R., Upton P.B., Skopeck T.R., Prevost V., Shuker D.E.G., and Swenberg J.A., Cancer Research. 52, 4328-4334.

The formation of 7-(2-Hydroxyethyl)guanine (7-HEG) in DNA of target and non-target tissues was examined in male B6C3F1 mice exposed to 100 ppm ETO for 1 or 3 days or 1, 2, or 4 weeks and in F344 rats exposed to 0, 3, 10, 33, 100 or 300 ppm ETO by inhalation for 6 hr/day for 4 weeks (week= 5 days). The dose-response relationships for 7-HEG were nonlinear in both mice and rats with the alkylating efficiency of ETO increasing at higher exposures. Repeated exposures to lower concentrations of ETO could lead to species and tissue differences in the molecular dose of 7-HEG suggesting that ETO-induced carcinogenesis caused by DNA adduct formation is dependent on concentration, pattern and duration of exposure as well as tissue and species. (P. Iyer, 10/27/94).

034 124462 Assessment of the Epidemiological Evidence on Carcinogenicity.

IgE against Ethylene Oxide-Human Serum Albumin (ETO-HSA) in patients who have had acute dialysis reactions (L.C. Grammer et al., 3/28/85).

IgE to ETO-HSA was measured in two groups (one with allergic reactions and one without) of hemodialysis patients. Three animals not exposed to ETO were used as controls. The amount of ETO-HSA bound per ml of serum in the reactor group (2.0 ± 8.0) was more than in the non-reactor group (0.2 ± 8.0), demonstrating an association between the presence of IgE to ETO-HSA, and allergic reactions to dialysis. While the antigen may be some other chemical contaminant of dialysis equipment or a reactive product like ethylene chlorhydrin that alters human serum albumin, it appears that a large proportion of dialyzer reactors have IgE to ETO-HSA. (P. Iyer, 10/28/94).

034 124489 "Ethylene Oxide: An Assessment of the Epidemiologic Evidence on Carcinogenicity" (R. Shore and M. Gardner, June 1993) for the ETO Industry Council of the Chemical Manufacturers Association.

This report is a meta analysis evaluating the association of ETO with carcinogenicity for different types of cancers, mortality, duration of exposure and sex-related differences. This document would be suitable for risk assessment. (P. Iyer, 10/28/94).

037 124650 "Men Assigned to Ethylene Oxide Production or Other Ethylene Oxide Related Chemical Manufacturing: a Mortality Study" (H.L. Greenberg, M.G. Ott and R.E. Shore, 1990., Brit. J. Indust. Med., 47: 221-230).

The increased incidence of leukemia and pancreatic cancer observed in workers of the Chlorohydrin department is suggestive of an association of these cancers with the production of ethylene chlorohydrin. This finding is further supported by the absence of such an association with ethylene oxide alone. Although both pancreatic cancer and pancreatitis have been observed in cohorts exposed to short chain hydrocarbons, the epidemiology studies are not consistent and are limited. While experimental studies have documented mutagenic, carcinogenic and and genotoxic effects upon exposure to ethylene oxide, a similar independent effect has not been corroborated in epidemiology studies. (P. Iyer, 10/31/94).

037 124651 Abstracts of the following three studies were submitted.

1) "A Cohort Study of Industrial and Hospital Workers Exposed to Ethylene Oxide" (M.J. Gardner, D. Coggon, C. Harris and B. Pannett).

Insufficient information provided. The study does not appear to demonstrate consistent findings.

2) "Final Report on a Multicentral Epidemiological Study on Ethylene Oxide," (N. Kiesselbach, H. - J. Lange and K. Ulm.

Insufficient information provided. The report submitted indicates that comparison of the standard mortality ratios for the cohort exposed to ethylene oxide and groups not exposed, showed no significant differences.

3) "A Cohort Study on Cancer Mortality of Ethylene Oxide Workers," (L. Bisanti, M. Maggini et al.,)

Although confounding factors (e.g. smoking) may contribute to the effects attributed to ethylene oxide, they cannot be responsible for all the effects noted. (P. Iyer, 10/31/94).

Review from the California Department of Health Services. A lifetime risk of 10^{-5} was selected as the defined level of "no significant" risk under Proposition 65. July 1988.

037 124666 "Molecular Dosimetry Studies with Ethylene Oxide. II. Determination of Alkylation of DNA in the Brain of Fischer 344 Rats Exposed to [¹⁴C] Ethylene Oxide (1ppm and 33 ppm) by the Inhalation Route," (D. Potter, R. Davies et al., 1986, Shell Research Ltd, U.K.).

Alkylation frequencies in brain DNA were similar to those found in DNA from lung, liver, kidney and spleen. No explanation for the lower alkylation frequencies in testes DNA could be gleaned. (P. Iyer, 11/1/94).

037 124672 "Molecular Dosimetry Studies with Ethylene Oxide. I. Determination of Alkylation of DNA in the Brain of Fischer 344 Rats Exposed to [¹⁴C] Ethylene Oxide by the Inhalation Route," (D. Potter, R. Davies et al., 1984, Shell Research Ltd, U.K.).

The dose of ethylene oxide delivered to the DNA in the tissues was an approximately linear function of exposure dose. Measurement of DNA alkylation indicates rapid absorption and equilibration of ethylene oxide throughout the tissues, though the dose penetrating the testes may be slightly lower than the majority of the tissues. The apparent uniform distribution pattern of ethylene oxide and the varied tissue metabolism capacity suggests a likely correlation between Hb doses and tissue DNA doses of ethylene oxide in mammals. (P. Iyer, 11/1/94).

037 124675 "Allergic Reactions in Healthy Plateletpheresis Donors Caused by Sensitization to Ethylene Oxide Gas," (S. Leitman, H. Boltansky et al., 1986, N. Engl. J. Med., 315: 19 pp 1192-1196).

The studies demonstrate that sensitization to ethylene oxide gas can occur in healthy plateletpheresis donors and may result in hypersensitivity reactions during donation. The prevalence of such reactions was 1% in the population studied. (P. Iyer, 11/2/94).

037 125856 "Ethylene Oxide Neuropathy in Rats," (A. Ohnishi, N. Inoue et al., 1986, J. Neurolo. Sci., 74:215-221).

In Wistar rats, exposure to 250 ppm ethylene oxide (6 hours; 5 times/week for 9 months) produces central-peripheral distal axonal degeneration of primary sensory neurons. Although no abnormality in gait or posture was detected in the rats, histopathology revealed distal axonal

degeneration of myelinated fibers similar to the findings noted in patients suffering from ethylene oxide toxicity. (P. Iyer, 11/2/94).

037 125857 "Workers exposed to ethylene oxide: a follow up study," (M.J. Gardner, D. Coggon, B. Pannett and E.C. Harris).

A substantial portion of the British workforce exposed to ethylene oxide was examined in this study. The findings indicate that the risk of cancer from current exposures is small, but do not exclude the possibility of human carcinogenic effects at higher exposures as noted in Italian (Bisanti, L., et al., Stockholm, 1988) and Swedish (Hogstedt, C., et al., 1986, JAMA, 255:1575-8) studies. The reason why such a powerful mutagen is not more carcinogenic is unclear. (P. Iyer, 11/3/94).

037 125858 "Chronic ethylene oxide poisoning in a factory manufacturing medical appliances," (T. Fukushima, et al., J. Soc. Occup. Med., 1986, 36:118-123).

Patients with chronic ethylene oxide poisoning (4 Workers) presented symptoms of multiple neuropathy. The chief complaints were sensory disturbance of the lower limbs and gait disturbance. In this article, clinical observations and causative factors from the industrial epidemiology standpoint are analyzed and safety measures needed to be implemented in the future are discussed. (P. Iyer, 11/4/94).

037 125859 "Ethylene oxide fumigation: review of current status. S. Paulikas, Precision Materials Corporation." 1986.

Ethylene oxide and its degradative products (ethylene glycol and 2-chloroethanol or ethylene chlorohydrin) have been detected in various food stuffs exposed to ethylene oxide at 0.1 ppb levels. Ethylene oxide and its derivatives have been demonstrated to have carcinogenic capability. (P. Iyer, 11/7/94).

037 125860 "The Use of Ethylene Oxide for the Sterilization of Medical Devices; the Possible Health Risks Involved and Indications of the Measure Which Should be Taken," (Dutch National

Institute of Public Health and Environmental Hygiene, 1986. Submitted by Union Carbide Corporation., CT).

The carcinogenic and mutagenic properties of ethylene oxide may not result in specific cases of high risk, however the lack of standardized conditions of local sterilization units provide cause for concern. Additionally, even when the amount of ethylene oxide absorbed contributes negligible or marginal carcinogenic/mutagenic risk, acute clinical symptoms of irritation, inflammation and sensitization can be experienced in some situations (intraocular lenses, hemodialysis) from residues of ethylene oxide. (P. Iyer, 11/8/94).

037 125862 "Cooking Study:¹⁴C-EtO," (American Spice Trade Association, Inc., 1993).

Spices exposed to ethylene oxide revealed residues of ethylene oxide, ethylene chlorohydrin, ethylene glycol and conjugates and ethylene bromohydrin. Cooking by baking, boiling and frying reduced the amount of ethylene oxide residues by 99.7% of initial values. (P. Iyer, 11/10/94).

037 124685 "Mortality and cancer morbidity among workers in a chemical factory," (L. Hagmar, et al., 1986, Scand. J. Env. Health 12: 545-551).

The study was essentially descriptive of the incidence of cancers in a cohort exposed to ethylene oxide and other chemicals. Due to the complicated pattern of varying exposure to many chemicals over time, it is not clear whether the observed tumor clusters are a result of one or several carcinogens or because of historical exposure. Insufficient information to arrive at a conclusion. (P. Iyer, 11/10/94).

037 124692 "Issues in assessing the carcinogenic hazards of ethylene oxide," (S. Austin., Environmental Health Consultants, Inc. and R. Sielken, Jr., Sielken Inc., 1987).

This report analyzes the risk assessments conducted on the carcinogenic capabilities of ethylene oxide by regulatory agencies (OSHA 1974, and EPA, 1985) and other scientists (Golberg, 1986). (P. Iyer, 11/10/94).

Supplemental Studies

038 124962 "Ethylene oxide residues on sterilized medical devices," (A Risk Assessment prepared by ENVIRON Corporation, Washington, DC., for Health Industry Manufacturer's Association, Washington, DC., March 1988).

The carcinogenic potency for ethylene oxide was estimated to be $4.8 \times 10^{-2} (\text{mg/kg/day})^{-1}$ and the NOEL for chronic toxicity was determined to be 2 mg/kg/day. Although the Swedish epidemiological study by Hemminki et al., (1982) reported an association between ethylene oxide exposure (around 0.1 ppm) and the incidence of spontaneous abortions, the reproductive toxicity NOEL was determined to be 9 mg/kg/day based on the experimental data by Snelling et al., 1982. The breakdown products of ethylene oxide (ethylene chlorohydrin and ethylene glycol) did not demonstrate evidence of carcinogenicity. The chronic toxicity NOEL for ethylene chlorohydrin was estimated to be 16 mg/kg/day and the LOEL for reproductive toxicity was 60 mg/kg/day. Ethylene glycol was estimated to have a LOEL = 40 mg/kg/day for chronic toxicity and the NOEL = 22mg/kg/day for reproductive toxicity. Based on the data reviewed, ethylene oxide was considered a direct-acting mutagen and the non-linear dose-response in a dominant lethal study was acknowledged. The mutagenic potential strengthened the weight of evidence for the carcinogenicity of ethylene oxide. The cancer potency estimated by different regulatory agencies using different models were compared. (P. Iyer, 11/16/94).

038 124977 "A Time-to-Response Perspective on Ethylene Oxide's Carcinogenicity" (R. Sielkin Jr., Sielkin Inc., 1987).

This report draws attention to the evaluation of the data by USEPA focussing on the use of statistical quantitative risk assessment methodology to address the time-to-response information available from experimental data. The report points out that the long period of time without any adverse carcinogenic impact is being ignored. (P. Iyer, 11/16/94).

038 124989 "Evidence of Neurologic Dysfunction Related to Chronic Ethylene Oxide Exposure" (W. Estrin et al., 1986).

See 039 124630.

039 124606 "Public exposure to, environmental fate of, and sources of, atmospheric ethylene oxide in California - Part A" (prepared by the Air Resources Board).

This report includes a review of chemical and physical properties of ethylene oxide used to determine emissions and atmospheric fate. Although a discussion on overall ethylene oxide exposure is included, the emphasis is on exposure from the distribution and manufacturing of surfactants and other sources subject to regulation by the Air Resources Board. A number of toxicity endpoints (carcinogenicity, mutagenicity, teratogenicity etc) were discussed. Evidence that inhalation exposure may interfere with oocyte maturation or ovulation was indicated. (P. Iyer, 11/16/94).

039 124617 "Health Effects of Ethylene Oxide - Part B" (prepared by Department of Health Services, CA., 9/16/86). DHS staff concur with the IARC that ethylene oxide is probably carcinogenic in people. No evidence for a carcinogenic threshold level was found. Fitting a multi-staged model to the animal data, a risk of 5-7 cases per million persons exposed was estimated for a 24 hour/day lifetime exposure to 0.08 ug/cubic meter (P. Iyer, 2/9/95).

039 124619 "NTP Report on the Toxicology and Carcinogenesis Studies of Ethylene Oxide" (T. Lewis, 1986). The experimental design and results from a two-year inhalation study of ethylene oxide were presented. B6C3F₁ mice (male and female) were exposed to ethylene oxide at 0, 50, or 100 ppm. The level of evidence of carcinogenic activity was clear as indicated by increased incidences of neoplasms of the lung and harderian gland. (P. Iyer, 11/16/94).

ECETOC Statement on ethylene oxide toxicology (1986): The latest experimental results reinforce the previous conclusion (ECETOC, 1984) that ethylene oxide is a 'putative human chemical carcinogen'. Although the later epidemiological study by Hogstedt et al., 1986 was not conclusive, the observed excess incidence of leukemias is consistent with the experimental data and reason for concern. (P. Iyer, 11/16/94).

Duplicate of 012 065516.

039 124621 "Health Effects of Ethylene Oxide Exposure in a Petrochemical Plant" (Susan G. Austin and D. Glenn, 7/18/85).

The health effects attributed to chronic, low level exposures to ethylene oxide among 37 operators in a petrochemical manufacturing plant were investigated. This report is an update of a previous study by Joyner (1964). The types of cancers noted in this study (skin, bladder, rectum; one each) have not been previously associated with ethylene oxide either in the epidemiological or experimental findings. The explanation offered is that the workers were possibly exposed to other chemicals. This study failed to detect long term adverse effects with occupational exposure to ethylene oxide. (P. Iyer, 11/17/94).

039 124625 "Exposure of female mice to ethylene oxide within hours after mating leads to fetal malformation and death" (Generoso, W. M., et al., 1986). Submitted in this volume 039 is a draft of the article that was published later. The findings in this article (Mutation Research 1987, 269-274) have been referred to in the worksheet W112627.831 for the chronic non-rodent toxicity end point. Essentially, mated female mice exposed to inhaled ethylene oxide at the time of fertilization or during early pronuclear stage of the zygote (before DNA synthesis), demonstrated a high incidence of mortality among conceptuses and congenital abnormalities among both the dead and surviving fetuses. The mechanism responsible was suspected to involve genetic damage of the zygote as opposed to maternal physiological damage. (P. Iyer, 11/17/94).

039 124628 "Ethylene Oxide Dose and Dose-Rate Effects in the Mouse Dominant-Lethal Test" (Generoso, W. M., et al., 1986).

Submitted in this volume 039 is a draft of the article that was published later. A dose-related increase in dominant-lethal mutations was observed in the dose-response study and in the dose-rate study, increased dominant-lethal responses were noted with increase in exposure concentrations. (P. Iyer, 11/17/94).

039 124629 "A Preliminary Report of Cancer Incidence in a Group of Workers Potentially Exposed to Ethylene Oxide" (Clinical Epidemiology Unit, University of Pennsylvania School of Medicine, 1986).

An increase in the number of cases of breast cancer over the number expected in the female workers of the cohort was noted. However, no significant increase in cancers previously associated with ethylene oxide exposure - leukemia, stomach cancer and brain cancer was not observed. Additional investigation in the area is required. (P. Iyer, 11/17/94).

"Ethylene Oxide induces central-peripheral distal axonal degeneration of the lumbar primary neurones in rats" (A. Ohnishi et al., 1985, British Journal of Ind. Med., 42: 373-379). Exposure to ethylene oxide 500 ppm (6 hrs/day, 3 times /week for 13 weeks resulted in ataxia in the hind legs of Wistar rats. Axonal degeneration of the myelinated fibers in hind leg nerves and in the fasciculus gracilis without affecting the nerve cell body of the lumbar dorsal root ganglion and the myelinated fibres of the lumbar dorsal and ventral roots was noted. These pathological changes are compatible with central-peripheral distal axonal degeneration. (P. Iyer, 11/17/94).

039 125789 "Ethylene oxide polyneuropathy" (S. Kuzuhara et al., 1983, Neurology, 33: 377-380). Chronic, repeated exposure to ethylene oxide (8 hours/day for approximately 6 months) resulted in the development of sensorimotor polyneuropathy in 3 workers (2 cases reported in detail). Biopsies of the sural nerve revealed axonal degeneration with mild changes in the myelin sheath. Some unmyelinated fibers were also involved. Denervation atrophy was noted in the muscle biopsies. Upon termination of exposure to ethylene oxide, symptoms subsided gradually and cleared in about 1-2 months. (P. Iyer, 11/18/94).

039 125880 "Ethylene Oxide-Induced Polyneuropathy" (P. Finelli et al., 1983, Arch. Neurol., 40: 419-421).

This is a second report documenting subacute polyneuropathy after occupational exposure to ethylene oxide. Bilateral foot drop and denervation potentials on electromyography were the principal abnormalities noted in 3 adults. (P. Iyer, 11/18/94).

039 125881 "Reproductive Hazards of Industrial Chemicals" (S. Barlow and F. Sullivan, 1982, Academic Press).

There is sufficient evidence for the in vivo and in vitro mutagenicity of ethylene oxide. This report found that the then available data were inadequate to evaluate the reproductive toxicity and carcinogenicity of ethylene oxide. (P. Iyer, 11/18/94).

039 124631 "Evidence of Neurologic Dysfunction Related to Chronic Ethylene Oxide Exposure" (W. Estrin et al., 1986).

Eight neurologically asymptomatic hospital workers exposed to ethylene oxide for 8 hour Time-Weighted Average of up to 3 ppm, over a mean of 11.6 years with recurrent peak exposures exceeding 200 ppm. Controls were workers that were age-sex matched and unexposed. The findings suggest the occurrence of subtle central dysfunction from chronic low-dose exposure (common to hospital sterilizer conditions) along with well documented peripheral neuropathy. (P. Iyer, 11/18/94).

039 124632 "Preliminary Results of the Ethylene Oxide Short Term Exposure Limits (STEL) Survey" (Heiden Associates for ETO Industrial Council, Industrial Hygiene Task Group and Chemical Manufacturers Association).

This report deals with ETO emission control costs and workplace exposure levels. (Iyer, 2/28/95).

039 124633 "Emergency and Continuous Exposure Guidance Levels for Selected Airborne Contaminants Vol 6 Benzene and Ethylene Oxide" (National Research Council). Iyer, 2/28/95.

039 124634 "Mortality and cancer morbidity among workers in a chemical factory" (L. Hagmar et al., 1986, Scand. J. Work. Environ. health., 2:545-551). A retrospective cohort study was performed on 644 male workers employed for at least one month during the period 1942-1979 in a chemical factory involving the handling of many chemicals (piperazine, urethane, ethylene oxide, formaldehyde and organic solvents). An increase in cancer morbidity was observed for malignant lymphoma/myelomatosis when at least 6 months of employment and an induction latency of at least 10 years was used, and an increase in bronchial cancer was noted when an induction

latency time of at least 15 years was used. A case-referent study within the cohort did not reveal any significant association between any specific chemical exposure and cancer morbidity. (P. Iyer, 11/18/94).

039 124635 "Ethylene Oxide (ETO) as a Major Cause of Anaphylactoid Reactions in Dialysis (A Review)" (J. Bommer and E. Ritz 1987, Artificial Organs 11: 2 111-117). ETO has been identified to be the causative factor of acute intradialytic anaphylactoid reactions. While other factors cannot be excluded, findings of positive sensitivivty with skin prick and radioallergoabsorbent tests (RAST) support ETO hypersensitivity as the major cause. Since alternatives to sterilization of medical equipment such as high temperature steaming or X-radiation exist, and the potential toxic reactions to ETO have been documented, the discontinuation of ETO for this purpose is recommended. (P. Iyer, 11/18/94).

039 124646 "Risk Assessment and Oncodynamics of Ethylene Oxide as Related to Occupational Exposure" (R. Beliles and J.C. Parker, 1987, Toxicology and Ind. Health., 3: 3 371-383). A risk assessment for carcinogenicity based on two inhalation bioassays was conducted. Brain tumors were selected as the end point for the assessment of risk because the adverse effects on the nervous system from exposure to ethylene oxide were consistent across species. The time-exposure concentration and area under the plasma concentration-time curve were used to calculate effective dose. Two mathematical risk extrapolation models, the probit and the multi-stage were used to estimate the risk from daily exposure to ethylene oxide (1.8 ug/liter for 8 hours for a lifetime exposure). (P. Iyer, 11/21/94).

042 127023 "Ethylene Oxide: An assessment of the epidemiologic evidence on carcinogenicity" (Shore, R.E et al., 1993). This report includes an overview and meta-analysis of previously conducted epidemiology studies in 10 cohorts involving 29,800 workers. Whether ethylene oxide causes the leukemia and non-Hodgkins lymphoma in these cohorts has not been resolved. (P. Iyer, 11/22/94).

051 145871 "Reanalyses of Postimplantation Loss and Pup Body Weight Data from the Bushy Run Research Center Ethylene oxide (EO) Single Generation and Two-Generation Reproduction Studies" (W.J. Breslin et al., The Dow Chemical Company, MI., 1/29/96). Previously submitted one-generation and two-generation reproduction studies conducted ten years apart were reanalyzed using common statistical methods. At 100 ppm ethylene oxide, increased postimplantation loss, decreased litter size and decreased pup growth weight were noted in both the one-generation and two-generation studies. Pup body weights were also decreased at 33 ppm in both studies with statistical significance at multiple points in the two generation study. Accordingly, the NOEL for both postimplantation loss and pup body weight (i.e., reproductive NOEL) was 10 ppm. The authors consider the changes in postimplantation loss noted at 33 ppm to be equivocal due to the lack of an effect at the same exposure level in the second generation of the two-generation study (P. Iyer, 10/28/96).

051 145872 "In vivo and in vitro kinetics of ethylene oxide metabolism in rats and mice" C. Brown et al., Toxicology and Applied Pharmacology 136: 8-19 (1996). The purpose of this investigation was to use the kinetics of ethylene oxide metabolism in rodents to develop ethylene oxide dosimetry models for humans. This study examined the kinetics of ethylene oxide metabolism (mainly elimination) in vivo and in vitro in male and female F344 rats and B6C3F1 mice. Mice eliminated ethylene oxide much more efficiently than rats following in vivo exposure to 100 ppm of ethylene oxide, probably due to a higher specific activity of cGST in the liver and kidney of mice, as reported by the authors. Mice (not rats) showed a concentration-dependent decrease in the rate of elimination of ethylene oxide. Gender differences were noted in rats but not mice in the kinetic constant - V_{max} for liver cGST, however gender differences in ethylene oxide toxicokinetics were observed only in mice with females having a significantly higher C_0 (peak tissue concentration) during exposure (at 100 or 300 ppm) than males. However, due to the multiple isoforms of cGST present in mammals, these gender differences may not hold much value. In conclusion, a marked species difference among rodents in the efficiency of ethylene oxide elimination with minimal (not statistically

significant) intraspecies sex differences is suggested. A trend toward a decreased ability to clear ethylene oxide with increasing animal size was also noted (P. Iyer, 10/28/96).

051 145873 "Reconsideration of the genetic risk assessment for ethylene oxide exposures" R. J. Preston et al., *Env. Mol. Mut.*, 26: 189-202 (1995). This publication reevaluates the genetic risk assessment for ethylene oxide previously conducted (by Rhomberg et al., 1990) using data on the induction of reciprocal translocations in male germ cells. The present article discusses the scientific basis for the reassessment of the EPA model, as well as the shape of the dose-response relationship at low doses. The authors claim that unlike radiation, mutagenic chemicals require DNA synthesis for conversion of the damage into a mutagenic event. During oogenesis, there is no DNA replication between the time of treatment with mutagens at the preovulatory stage and analysis of metaphase I or metaphase II oocytes. Hence, the effects of chemicals requiring DNA replication will not be detected. In stem cells, repair is constantly taking place and these cells are therefore relatively protected from manifesting effects of chemical insult. In females the premeiotic stem cell is present prenatally and till puberty, while in males it is found prenatally and postnatally till the production of spermatocytes from spermatogonia. The post meiotic germ cells such as spermatids and spermatozoa are thus most sensitive to chemical insult. Due to the presumed high probability of DNA repair prior to the next S-phase for a resting oocyte, a low to negligible frequency of translocations in female germ cells after exposure to ethylene oxide is predicted. While this publication provides the rationale for why the female germ cell is less likely to be damaged by an alkylating agent like ethylene oxide, it only considers reciprocal translocations and not other possibilities for overall genetic damage. Most of the conclusions in the publication seem justified, but, it is not complete in reanalysing the genetic risk assessment of ethylene oxide (P. Iyer, 10/28/96).

051 145875 "Calculation of benchmark concentrations for acute and chronic exposure to ethylene oxide." L.T. Haber et al., (1996) *The Toxicologist*, Vol 30: A-744. A variety of systemic, quantal and reproductive endpoints for ethylene oxide were modeled using different definitions

of the benchmark response. For fetal weight i.e., mean fetal weight/litter (a continuous parameter), benchmark effect levels (BMEs) were based on the work of Kavlock et al., 1995 corresponding to either i) a 5% decrease in mean weight, ii) a decrease in weight equal to $sd / 2$ or iii) a 5% increase in the probability of low-weight fetuses (i.e., weight below the 5th percentile of concurrent controls). For the quantal endpoint - the number of litters/group with one or more affected fetus, the BMD corresponding to 10% increase in risk tended to match the associated NOAELs better than 5% or 1% increases. For other continuous non-developmental endpoints "z" was set at 0.5 to be consistent with the recommendation for fetal weight endpoints. Of the continuous data available, only those data with a measure of variability could be modeled. The most sensitive effect was abnormal sperm in a subchronic study, with spermatids being more sensitive than spermatozoa or spermatogonia. The lowest BMCs for systemic effects were for adrenal, renal and nasal histopathology. Reduced fetal weight - the only developmental effect analyzed, occurred at higher levels than even the most sensitive reproductive or systemic effects. The benchmark concentrations were generally consistent with the NOAELs identified (P. Iyer, 10/28/96).