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Reproductive-toxicologic assessment of the epoxides ethylene oxide, propylene oxide, butylene oxide, and styrene oxide

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HARDIN BD, NIEMEIER RW, SIKOV MR, HACKETT PL. Reproductive-toxicologic assessment of the epoxides ethylene oxide, propylene oxide, butylene oxide and styrene oxide. *Scand j work environ health* 9 (1983) 94—102. Ethylene oxide (CAS no 75-21-8), propylene oxide (CAS no 75-56-9), butylene oxide (CAS no 106-88-7), and styrene oxide (CAS no 96-09-3) were tested for teratogenic activity by inhalation exposure of rats and rabbits. Ethylene oxide and propylene oxide were tested at only one concentration in both species (150 ppm for ethylene oxide and 500 ppm for propylene oxide). Butylene oxide was tested at 250 and 1,000 ppm in both species, while styrene oxide was tested at 100 ppm in rats and 15 and 50 ppm in rabbits. For each of these four epoxides, the acute toxicity was similar for pregnant and nonpregnant rats. Styrene oxide was the most toxic in both species, and rabbits were more sensitive than rats. Rats exposed to propylene oxide for 7 h/d, 5 d/week for three weeks before breeding had a significant reduction in the number of corpora lutea. Fetal mortality was not increased, but significantly fewer mated rats were found pregnant following gestational exposure to styrene oxide, a finding suggesting preimplantation loss. In rabbits exposed to styrene oxide, the number of resorptions per litter was increased in a concentrationrelated manner, but differences were not statistically significant. Fetal examinations revealed evidence of fetotoxicity with all four epoxides. There was no overt teratogenic activity, but a number of minor morphologic aberrations were detected.

Key terms: 1,2-epoxybutane, 1,2-epoxyethane, epoxyethylbenzene, 1,2-epoxypropane, ethyloxirane, inhalation teratogenesis, methyloxirane, oxirane.

Ethylene oxide, propylene oxide, butylene oxide, and styrene oxide are widely used in large volumes as intermediates in organic chemical synthesis. Ethylene oxide and propylene oxide are also used as chemical fumigants or as sterilants for medical and scientific supplies, foodstuffs, drugs, and other materials such as motor oil, paper, and furniture. In addition to its use in chemical synthesis, styrene oxide is used as a reactive diluent in epoxy resins.

Ehrenberg & Hussain (1) reviewed the literature available on the mutagenicity of 1,2-epoxides up to 1978; they found evidence that all four epoxides under consideration in the present communication are mutagenic in various test systems. The International Agency for Research on Cancer's review (4) of the data on the potential carcinogenicity of ethylene oxide, propylene oxide, and styrene oxide concluded that only propylene oxide had shown limited evidence of carcinogenicity in animals. All three of these epoxides are currently undergoing chronic toxicity testing.

Very little has been published on the developmental toxicity of these epoxides. Snellings et al (7) reported no developmental defects when pregnant rats were ex-

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posed to 0, 10, 33, or 100 ppm (0, 18, 60, or 180 mg/m^3, respectively) of ethylene oxide on days 6—15 of gestation, although the body weights of fetuses were reduced at 100 ppm. In a reproduction study, Snellings et al (7) exposed both male and female rats to ethylene oxide for 12 weeks before breeding and continued exposing females through day 19 of gestation. The females exposed at 100 ppm had a longer period of gestation, a reduced fertility index, and significantly fewer pups. Because of concern for the intravenous exposure of humans to ethylene oxide leaching from ethylene oxide-sterilized medical devices, LaBorde & Kimmel (5) injected pregnant mice intravenously during four 3-d segments of gestation. Ethylene oxide was clearly teratogenic on days 6—8 of gestation and caused primarily skeletal defects; the frequency of malformations was also increased in groups treated on day 8—10 and 10—12.

Recently completed studies have evaluated the reproductive toxicity of ethylene oxide, propylene oxide, butylene oxide, and styrene oxide. Detailed results of these studies are available from the National Institute for Occupational Safety and Health (NIOSH) in a contract report (2) and in a NIOSH technical report (6). Individual reports on each epoxide are being prepared for publication in the open literature. The present report will present only a general overview of the salient changes observed and will concentrate on comparisons between epoxides. As will be shown, the resulting patterns have important implications for the design and interpretation of reproductive and developmental toxicity studies of materials for which repeated occupational or environmental exposure is of concern.

Materials and methods

Sexually mature female Sprague-Dawley (ethylene oxide & propylene oxide) or Wistar (butylene oxide & styrene oxide) rats and New Zealand white rabbits were used. In all studies each group consisted of 23 to 30 artificially inseminated rabbits and 32 to 45 sperm-positive rats. The number of litters examined ranged from 15 to 23 rabbits per group and from 28 to 46 rats per group. Exceptions occurred when maternal mortality was especially high (one rat and two rabbit groups), and in one rabbit group when pseudopregnancies reduced the number of pregnant dams.

Exposures were conducted in stainless steel dynamic inhalation chambers. All epoxides used were greater than 99 % pure. Butylene oxide and styrene oxide were vaporized in a heated distillation flask with a stream of dry nitrogen which was metered into the chamber inlet. For the propylene oxide exposures, a heated stainless steel cylinder covered with a glass fiber wick was placed in the chamber air inlet, and liquid propylene oxide was pumped onto the wick, from which it vaporized. Liquid ethylene oxide was vaporized in a stainless steel coil and metered into chamber air intakes. Chamber concentrations were monitored by gas chromatography at approximately 40-min intervals throughout exposure.

Slightly different experimental regimens were used for the studies with ethylene oxide and propylene oxide than for those with butylene oxide and styrene oxide. With ethylene oxide and propylene oxide only one exposure concentration was used, selected following preliminary probe studies. Two concentrations were used with butylene oxide and styrene oxide, selected on the basis of published acute toxicity data. The concentrations were selected with the objective of inducing measurable maternal toxicity but no mortality. In the experiments with ethylene oxide, propylene oxide, and butylene oxide the same concentration was used for the exposure of rabbits as was used for the rats, ie, 150 ppm (270 mg/m^3) of ethylene oxide, 500 ppm (1,188 mg/m^3) of propylene oxide, and 250 and 1,000 ppm (737 & 2,950 mg/m^3, respectively) of butylene oxide. Due to the toxicity observed when rats were exposed to 100 and 300 ppm (492 & 1,474 mg/m^3, respectively) of styrene oxide, concentrations of 15 and 50 ppm (74 & 246 mg/m^3, respectively) of styrene oxide were used for the rabbits. Daily exposures were for 7 h in all cases, but exposures were performed during different gestational stages in the ethylene oxide/propylene oxide versus butylene oxide/styrene oxide studies (tables 1 & 2). During the

Table 1. Rat exposure regimens in the epoxide reproduction studies.

Group number	Ethylene oxide and propylene oxide			Butylene oxide and styrene oxide [a]	
	Three weeks before breeding	Gestation days		Three weeks before breeding	Gestation days 1—19
		1—6	7—16		
1	Filtered air	Filtered air	Filtered air	Filtered air	Filtered air
2	Filtered air	Filtered air	Epoxide	Filtered air	Low epoxide concentration
3	Filtered air	Epoxide	Epoxide	Low epoxide concentration	Filtered air
4	Epoxide	Epoxide	Epoxide	Low epoxide concentration	Low epoxide concentration
5	•	•	•	Filtered air	High epoxide concentration
6	•	•	•	High epoxide concentration	Filtered air
7	•	•	•	High epoxide concentration	High epoxide concentration

[a] Only groups 1 through 4 completed the styrene oxide study.

Table 2. Rabbit exposure regimens in the epoxide reproduction studies.

Group Number	Ethylene oxide and propylene oxide (gestation days)		Butylene oxide and styrene oxide (gestation days 1—24)
	1—6	7—19	
1	Filtered air	Filtered air	Filtered air
2	Filtered air	Epoxide	Low epoxide concentration
3	Epoxide	Epoxide	High epoxide concentration

exposures food and water were withdrawn, but both were freely available at all other times. The animals were singly housed in stainless steel cages with wire mesh flooring and were sacrificed on day 21 (rats) or 30 (rabbits) of gestation (day 1 of gestation was the day sperm were detected in vaginal smears from rats and the day following the midafternoon artificial insemination of rabbits).

All the fetuses were examined for external defects. Then half were decapitated, and the heads were preserved in Bouin's fluid for internal examination by the technique of razor blade sectioning (11, 12). All the fetuses were examined for visceral defects by dissection under magnification (8, 10), and all the carcasses were then cleared and stained for skeletal examination (9). The only exception to this procedure was in the butylene oxide/styrene oxide studies, when only half of the rat fetuses were examined by the Staples technique for visceral defects.

Results

Ethylene oxide

Exposure to 150 ppm of ethylene oxide caused no mortality in nonpregnant or pregnant females of either species (table 3), but maternal rats showed toxic signs at necropsy (table 4). Body weight was reduced only in the rats exposed before and during gestation (group 4), but the spleen and kidney weights (both absolute and relative to body weight) were increased in all three ethylene oxide-exposed groups. Rabbits appeared to be unaffected by 150 ppm of ethylene oxide (table 4).

Embryo and fetal toxicity (table 5) was evident in rat litters as a statistically significant increase in the incidence of resorptions in group 4. Fetal body weight and crown-rump length were reduced in all ethylene oxide-exposed groups. External, visceral, and skeletal examinations revealed no treatment-related effects

other than an increased incidence of reduced skeletal ossification (primarily of the skull and sternebrae) in all ethylene oxide-exposed groups. No evidence of embryo or fetal toxicity or of developmental defects was detected in the ethylene

Table 3. Rat and rabbit mortality summary.

	Ethylene oxide (150 ppm)	Propylene oxide (500 ppm)	Butylene oxide		Styrene oxide			
			250 ppm	1,000 ppm	15 ppm	50 ppm	100 ppm	300 ppm
Rats	—	—	—	2 % (19 d)	•	•	16 % (19 d)	42 % (1 d)
Rabbits	—	—	12 % (24 d)	58 % (24 d)	17 % (24 d)	79 % (24 d)	•	•

Table 4. Summary of organ and body weight changes occurring in the rats and rabbits. [Incr = statistically significant increase; decr = statistically significant decrease; (incr)? = trend suggestive of an increase, but not statistically significant;(decr)? = trend suggestive of a decrease, but not statistically significant; ND = not determined; — magnitude nil; • = category not applicable]

	Ethylene oxide (150 ppm)	Propylene oxide (500 ppm)	Butylene oxide		Styrene oxide		
			250 ppm	1,000 ppm	15 ppm	50 ppm	100 ppm
Rats							
Body weight	Decr	Decr	Decr	Decr	•	•	Decr
Liver	—	(Incr)?	—	—	•	•	—
Kidneys	Incr	Incr	—	—	•	•	Incr
Spleen	Incr	(Incr)?	ND	ND	•	•	ND
Lungs	—	(Incr)?	—	—	•	•	Incr
Rabbits							
Body weight	—	—	—	(Decr)?	(Decr)?	Decr	•
Liver	—	—	—	(Incr)?	—	—	•
Kidneys	—	—	—	(Incr)?	—	—	•
Spleen	—	—	ND	ND	ND	ND	•
Lungs	—	—	—	(Incr)?	(Incr)?	(Incr)?	•

Table 5. Summary of the reproductive status of the rats. [Incr = statistically significant increase; decr = statistically significant decrease; (decr)? = trend suggestive of a decrease, but not statistically significant; — = magnitude nil]

	Ethylene oxide (150 ppm)	Propylene oxide (500 ppm)	Butylene oxide		Styrene oxide (100 ppm)
			250 ppm	1,000 ppm	
Pregnant (%)	—	—	—	—	Decr
Corpora lutea (N)	(Decr)?	Decr	—	—	(Decr)?
Implants (N)	—	Decr	—	—	—
Resorptions (N)	Incr	—	—	—	—
Live fetuses (N)	—	Decr	—	—	—
Fetal weight	Decr	Decr	—	—	Decr
Fetal length	Decr	Decr	—	—	Decr
Skeletal alterations					
Rib dysmorphology	—	Incr	—	—	—
Reduced ossification	Incr	Incr	—	—	Incr

oxide-exposed rabbits (table 6).

Propylene oxide

Exposure to 500 ppm of propylene oxide caused no mortality in nonpregnant or pregnant females of either species (table 3). Rats exposed to propylene oxide weighed consistently less than those exposed to filtered air (table 4), and a distinct reduction in the rate of body weight gain was obvious as groups 2 and 3 changed from filtered air to propylene oxide exposure. Relative lung, liver, kidney, and spleen weights were increased in the propylene oxide-exposed rats, particularly those exposed both before breeding and during gestation (group 4). However the three propylene oxide-exposed groups differed significantly from the controls only in the case of relative kidney weight. Other significant observations of the rats involved the numbers of corpora lutea, implants, and live fetuses (tables 5 & 7). All three of these indices were significantly reduced ($p < 0.01$) for rats in group 4, ie, those rats exposed to propylene oxide for three weeks before breeding, relative to the other propylene oxide-exposed rats (groups 2 & 3). Resorptions were increased for the rats in group 2 (exposed to propylene oxide on days 7—16 of gestation), but not in rats of group 3 or 4. Rabbits appeared to be relatively unaffected by 500 ppm of propylene oxide (table 4).

Several indices of embryo and fetal toxicity were significantly affected in the propylene oxide-exposed rats. Fetal body

Table 6. Summary of the reproductive status of the rabbits. [(Incr)? = trend suggestive of an increase, but not statistically significant; (decr)? = trend suggestive of a decrease, but not statistically significant; — = magnitude nil]

	Ethylene oxide (150 ppm)	Propylene oxide (500 ppm)	Butylene oxide		Styrene oxide	
			250 ppm	1,000 ppm	15 ppm	50 ppm
Pregnant (%)	—	—	—	—	—	—
Corpora lutea (N)	—	—	—	—	—	—
Implants (N)	—	—	—	—	(Decr)?	(Decr)?
Resorptions (N)	—	—	—	—	(Incr)?	(Incr)?
Live fetuses (N)	—	—	—	—	(Decr)?	(Decr)?
Fetal weight	—	—	—	—	(Decr)?	(Decr)?
Fetal length	—	—	—	—	(Decr)?	(Decr)?
Skeletal alterations						
Rib dysmorphology	—	—	—	—	—	—
Reduced ossification	—	—	—	—	—	—

Table 7. Average number of corpora lutea in pregnant rats and total group sizes in the ethylene oxide and propylene oxide studies.

	Filtered air exposure (pregestation + gestation days 1—16)			Ethylene (150 ppm) or propylene (500 ppm) oxide exposure								
				Gestation days						Pregestation + gestation days 1—16		
				7—16			1—16					
	Group size	Corpora lutea		Group size	Corpora lutea		Group size	Corpora lutea		Group size	Corpora lutea	
		Mean	SD		Mean	SD		Mean	SD		Mean	SD
Ethylene oxide	41	15.4	2.1	41	15.2	2.9	41	15.4	2.8	39	14.6	3.1
Propylene oxide	46	15.4	3.1	44	15.6	3.3	41	15.4	2.2	43	13.8	3.0 *

* Significantly less than the other propylene oxide-exposed groups ($p < 0.01$).

weight and crown-rump length were significantly reduced in all propylene oxide-exposed groups (table 5). External, visceral, and skeletal examinations of rat fetuses revealed no significant alterations in the developmental process except for an increased incidence of rib dysmorphology (primarily wavy ribs) and reduced skeletal ossification (primarily of the vertebrae and ribs) in the propylene oxide-exposed litters. No evidence of embryo or fetal toxicity or of developmental defects was detected in the propylene oxide-exposed rabbits (table 6).

Butylene oxide

Of the rats exposed to 1,000 ppm of butylene oxide, 1 of 106 died before breeding, and 1 of 80 died during gestational exposure (table 3). A significant reduction in rat body weight was noted at both exposure levels (table 4). Persisting maternal toxicity among the rats was suggested by the fact that weight gain during pregnancy was reduced in both groups that were exposed to butylene oxide before breeding and to filtered air during gestation (groups 3 & 6, table 1), as well as in rats exposed to butylene oxide during gestation. In an earlier summary of results (3), rat maternal toxicity was erroneously tabulated as "absent" (table 5 in that 1981 publication) rather than "present." The corpus luteum counts of the rats were not affected by butylene oxide exposure (table 8).

Rabbits on the other hand were much more severely affected by exposure to butylene oxide at 250 and 1,000 ppm (table 3). Mortality was significantly increased at both concentrations. Suppurative pneumonia was noted in those rabbits that died during exposure. There were no deaths of rabbits exposed to filtered air. Despite the increased mortality at both exposure levels, there was not a statistically significant change in the body weight of surviving rabbits (table 4). The day 30 body weights were markedly reduced for the two pregnant survivors of 1,000 ppm exposure [3.0 vs 3.5 (0.4 SD) kg for the controls], but the survivors of 250-ppm exposure were equal in weight to the control rabbits.

Despite the maternal toxicity noted for rats (reduced body weight), there was no evidence of embryo or fetal toxicity (table 5), and no evidence suggestive of developmental toxicity was noted in the external, visceral, and skeletal examinations. There was significant maternal toxicity for the rabbits at 250 ppm of butylene oxide, although there was no suggestion of embryo or fetal toxicity or of developmental toxicity. For the rabbits suggestive evidence of embryo and fetal toxicity was seen in the two litters from the 1,000 ppm group (table 6), but statistical significance was not demonstrated due to the very small group size.

Styrene oxide

Styrene oxide was unexpectedly toxic for rats at both 100 and 300 ppm (table 3). Some rats died during the first 7-h exposure at 300 ppm, and consequently no further exposures were made at that concentration. Mortality continued during the next 2 d. A total of 42 % died within this 3-d period, and the survivors were

Table 8. Average number of corpora lutea in pregant rats and total group sizes in the butylene oxide study.

Pregestation exposure	Gestation exposure (dg 1—19)								
	Filtered air			Butylene oxide					
				250 ppm			1,000 ppm		
	Group size	Corpora lutea		Group size	Corpora lutea		Group size	Corpora lutea	
		Mean	SD		Mean	SD		Mean	SD
Filtered air	35	17.1	3.9	32	15.8	3.2	28	16.4	4.8
Butylene oxide									
250 ppm	33	15.9	3.6	36	16.0	4.2	•	•	•
1,000 ppm	31	15.3	3.0	•	•	•	30	15.2	2.4

killed at that time. Exposures were completed as planned for the 100-ppm level, with an overall mortality of approximately 16 %. The body weight of the rats exposed to 100 ppm of styrene oxide was significantly reduced (table 4), while the lung and kidney weights were significantly increased in relation to body weight.

Rabbits were exposed at only 15 and 50 ppm, but maternal toxicity was similar to that seen for rats (table 3). Maternal body weight was reduced for the styrene oxide-exposed rabbits, but other than an increase in lung weight, systematic organ weight changes were not noted (table 4).

Embryo and fetal toxicity was evident in rats exposed to 100 ppm of styrene oxide during gestation (table 5). The most striking change was a significant decrease in the fraction of gestationally-exposed sperm-positive rats which became pregnant. Since corpora lutea, but no implantation sites, were found in the nonpregnant animals, it is inferred that this finding represents preimplantation loss of fertilized ova or blastocysts. In addition to a reduction in fetal body weight and length, there was a reduction in skeletal ossification (primarily of the skull and sternebrae) of styrene oxide-exposed litters. However, there was no evidence of an increased incidence of frank structural malformations. The evaluation of the rabbits did not reveal statistically significant evidence of embryo or fetal toxicity at 15 ppm (table 6), but in the four surviving litters exposed to 50 ppm of styrene oxide there were several indices suggestive of toxic effects. There were no significant alterations observed in the external, visceral, or skeletal examinations of rabbit fetuses.

Although the groups did not differ statistically, there was a reduction in the number of corpora lutea in rats exposed to 100 ppm of styrene oxide before breeding [12.4 (SD 1.9) in group 3 and 12.2 (SD 0.8) in group 4] relative to those exposed to filtered air before breeding [14.0 (SD 3.2) in group 1 and 14.2 (SD 3.0) in group 2] (table 9).

Discussion

A comparison of these results is necessarily complex due to the breadth of measures and the slight differences in experimental regimens employed. Nevertheless, several general conclusions can be reached, and consistent patterns are evident. First, none of these epoxides were more lethal in pregnant rats than in nonpregnant rats. There were no apparent differences between the degree of reduced body weight gain or food consumption among pregnant rats versus nonpregnant rats. Although the details were not presented in this communication, maternal body weight gain reductions were invariably accompanied by reduced food consumption. In general, rats were affected more than rabbits by ethylene oxide and propylene oxide exposure, while rabbits were affected more by butylene oxide and styrene oxide. The species difference was the most prominent for styrene oxide, for which the mortality of rabbits at 15 ppm approximated that of rats exposed to 100 ppm. Organ and body weights were affected by exposure to ethylene oxide and propylene oxide in rats but not in rabbits.

Some investigators feel that, in experimental studies, fetal toxicity invariably precedes or is more severe than maternal toxicity, and that maternally toxic doses should be avoided on the assumption that they will necessarily lead

Table 9. Average number of corpora lutea in pregnant rats and total group sizes in the styrene oxide study.

Pregestation exposure	Gestation exposure					
	Filtered air			Styrene oxide (100 ppm)		
	Group size	Corpora lutea		Group size	Corpora lutea	
		Mean	SD		Mean	SD
Filtered air	34	14.0	3.2	12	14.2	3.0
Styrene oxide (100 ppm)	28	12.4	1.9	5	12.2	0.8

to fetal toxicity or developmental defects. In the present studies, developmental effects were minimal in rabbits exposed to the lower concentrations of butylene oxide and styrene oxide even though these levels caused 12 % (250 ppm of butylene oxide) and 17 % (15 ppm of styrene oxide) mortality in adults. The reductions in the fetal body weight and length of rabbits were not statistically significant at these concentrations, and there was no increase in pre- or post-implantation death. Neither was there an increase in the incidence of fetal malformations or minor variations such as reduced skeletal ossification. These results illustrate that some chemicals may not severely affect the conceptus despite marked maternal toxicity. Efforts to identify potentially hazardous chemicals (particularly in the case of those for which exposure may be chronic) may be strengthened by the inclusion of maternally toxic exposures in the test protocol to insure a maximal challenge to the developmental processes. As illustrated by these results, inclusion of a maternally toxic level does not necessarily mean that every chemical so tested will be reported as developmentally toxic. Moreover, such findings may provide an added degree of confidence in setting permissible exposure limits. For chemicals of this kind, levels which are safe for the pregnant worker will also be safe for her conceptus.

The results reported in this communication are consistent with those of the study by Snellings et al (7), in which fetotoxic but not teratogenic effects were seen in rats exposed to 100 ppm of ethylene oxide. In contrast LaBorde & Kimmel (5) found, at doses that were not maternally toxic, that intravenously injected ethylene oxide induced a significant incidence of skeletal malformations in mice. The possibility of a species difference cannot be ruled out since mice have not been tested by inhalation exposure or rats and rabbits by intravenous injection, but this explanation seems unlikely. It thus appears likely that teratogenic doses of ethylene oxide cannot readily be delivered to the fetus by repeated exposure of the pregnant female to ethylene oxide vapor. It may be speculated that the differences in findings relate to the differences in systemic distribution in the dam or to ethylene oxide concentrations attained in the conceptus during sensitive stages of gestation. Systemic concentrations resembling those following intravenous injection might result from brief exposures to extremely high vapor concentrations, but this possibility has not been investigated. Similarly, propylene oxide, butylene oxide, and styrene oxide were not teratogenic in this inhalation study, but if these epoxides are used in applications that may result in their intravenous injection into humans, as is the case with ethylene oxide, that route should be tested. Such testing would be particularly important for propylene oxide since maternally toxic exposures in these studies did induce minor skeletal anomalies in rat fetuses.

Another finding reported by Snellings et al (7) may be related to an unexpected observation by us. Snellings et al reported that in a reproduction study female rats exposed to 100 ppm ethylene oxide for 12 weeks before breeding had a longer gestation period, reduced fertility index, and fewer pups. The time to parturition was not observed in the present studies, and exposure for three weeks before breeding did not alter the proportion of females that became pregnant. However exposure to styrene oxide from day 1 of gestation significantly reduced the proportion of sperm-positive rats that became pregnant, and exposure to propylene oxide for three weeks before breeding significantly reduced the numbers of corpora lutea, implants, and live fetuses (tables 5 & 7). Similarly, rats exposed to ethylene oxide (table 7) and styrene oxide (table 9) before breeding had small (and not statistically significant) reductions in corpora lutea. Butylene oxide exposure was clearly without effect (table 8). The results of this abbreviated form of reproduction testing illustrate the value of exposing nonpregnant females to environmental or industrial chemicals prior to teratologic testing as a convenient and cost-effective means of detecting chemicals with a potential for reproductive toxicity. These data suggest that prolonged exposure to propylene oxide, and possibly ethylene oxide and styrene oxide, may reduce female reproductive potential by impairing

oocyte maturation or ovulation. Several mechanisms might underlie such an effect, such as direct action at the level of the pituitary or ovary or an indirect effect mediated through epoxide binding of circulating hormones. In addition exposure to styrene oxide appears to interfere with implantation. These observations warrant more-detailed studies designed to confirm the effect and investigate the mechanisms of action.

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