DEVELOPMENTAL TOXICOLOGY OF INDUSTRIAL ALCOHOLS: A SUMMARY OF 13 ALCOHOLS ADMINISTERED BY INHALATION TO RATS

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The developmental toxicology of 13 industrial alcohols (methanol, ethanol, 1-propanol, isopropanol, 1-butanol, 2-butanol, tertiary-butanol, 1-pentanol, 1-hexanol, 2-ethyl-1-hexanol, 1-octanol, 1-nonanol, and 1-decanol), and the behavioral teratogenicity of 4 of these alcohols, were assessed in a series of experiments. The results of individual alcohols have been published previously, but the present paper summarizes the results in view of structure-activity relationships among these alcohols. The alcohols were administered by inhalation for 7 hours per day (6 hours/day for 1-decanol) on gestation days 1–19 to groups of approximately 15 pregnant Sprague-Dawley rats. For developmental toxicology evaluations, dams were sacrificed on gestation day 20. Fetuses were serially removed, weighed, sexed, and examined for external malformations. The frequency of visceral malformations and variations was determined in one-half of the fetuses, and the frequency of skeletal deviations was determined in the other half. Behavioral teratology endpoints were investigated in groups of 15 pregnant rats exposed to one of four alcohols (ethanol, 1-propanol, 1-butanol, and tertiary-butanol) and also involved groups of 18 male rats which were exposed to the same concentrations of each alcohol for 6 weeks, and then mated to untreated females. In the behavioral teratology evaluations, all litters were culled to eight pups and fostered to unexposed mothers. Offspring were tested from days 10–90 on a series of behavioral tests designed to evaluate neuromotor integ-

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rity, activity levels, learning, and memory. Additionally, brains were removed from 10 offspring per group at 21 days of age, and were dissected into cerebrum, cerebellum, brainstem, and midbrain; these samples were assayed for steady-state levels of protein and the neurotransmitters acetylcholine, dopamine, norepinephrine, 5-hydroxytryptamine (serotonin), substance P, B-endorphin, and met-enkephalin.

Congenital malformations were noted for methanol, 1-propanol, isopropanol, and 1-butanol, but only at concentrations in excess of 5000 ppm. These concentrations also produced toxicity in the maternal animals; thus, there was little evidence of selective developmental toxicity among the alcohols. Although sporadic behavioral and neurochemical deviations were detected, no consistent pattern of effects was seen for any of the alcohols we tested. It should be noted that alcohols with chain lengths longer than the butyl series could not be generated as vapors at sufficiently high concentrations to produce observable toxicity in the maternal animals. This limits the generality of these findings to the possible developmental effects of these alcohols when taken through other routes of exposure. Thus, rats are unlikely to exhibit developmental toxicity if exposed to these alcohols within current occupational limits. One adverse finding of note from this series of studies was an apparently reversible infertility observed in male rats exposed to a high concentration of 1-propanol, a finding which should be replicated.

INTRODUCTION

This paper summarizes the results from a series of studies investigating the developmental toxicology of aliphatic alcohols administered by inhalation to rats. Consistent with the pattern of toxicity seen in adults, the study was undertaken to investigate the hypothesis that the developmental toxicity of the alcohols would increase as carbon chain length increased, up to 6–8 carbons, after which the developmental toxicity would decrease. The results of individual alcohols have been reported previously, but the present paper examines and summarizes the results of all of the alcohols with a focus on structure-activity relationships.

Due to their chemical and physical properties, these alcohols are widely used as industrial solvents, cosolvents, and chemical intermediates (Rowe and McCollister, 1982). Table 1 lists the alcohols assessed in this series of studies, along with their Chemical Abstract Service (CAS) numbers, recent estimates of the numbers of people exposed to each alcohol (based on the National Occupational Exposure Survey (NOES) conducted from 1981–1983 [see Seta et al., 1988]),

TABLE 1
Estimates of Exposure Populations, with Primary Industries and Occupations in Order of Decreasing Estimated Populations[1]

Alcohol	CAS No.	Est. Pop.	(%Female)	Primary Industries[2]	Primary Occupations
1. Methanol	67-56-1	948,905	25%	Health Services, machinery except electric, electric & electronic, business services, C & A	Assemblers, janitors and cleaners, clinical laboratory technicians, machine operators, mechanics
2. Ethanol	64-17-5	987,768	49%	Health Services, business services, C & A, personal services, printers & publishers	Nurses, assemblers, janitors and cleaners, clinical lab technicians, maids and housemen
3. 1-Propanol	71-23-8	98,429	23%	Printing & publishing, C & A business services, petroleum & coal products, electric & electronics	Printing machine operators, electrical and electronic engineers, mechanics, packers and packagers, chemists
4. Isopropanol	67-63-0	3,141,701	53%	Health services, electric & electronics, machinery, business services, printing & publishing	Nurses, assemblers, janitors and cleaners, printing machine operators, clinical laboratory technicians
5. 1-Butanol	71-36-3	370,333	19%	C & A, special trade contractors, machinery except electric, transportation, furniture finishing	Painters, assemblers, mechanics, janitors and cleaners, laundering and dry cleaning operators, furniture finishers
6. 2-Butanol	78-92-2	42,694	55%	Business services, electric & electronics, C & A, machinery, repair	Janitors and cleaners, assemblers, chemical technicians, painters
7. tert-Butanol	75-65-0	17,014	26%	C & A, paper & allied products, petroleum, metal, machinery	Chemical technicians, machine operators, assemblers, janitors and cleaners, mechanics
8. 1-Pentanol	71-41-0	18,795	37%	Health services, personal services, petroleum & coal, C & A	Laundering and dry cleaning operators, machine operators, clinical laboratory technicians, health aids
9. 1-Hexanol	111-27-3	9,896	25%	C & A, printers & publishers	Chemical technicians, machine operators
10. 2-Ethyl-1-hexanol	104-76-7	23,314	13%	C & A, textile mill products, rubber & miscellaneous plastic, health services	Machine operators, welders and cutters engineering technicians
11. 1-Octanol	111-87-5	16,536	29%	C & A, rubber & miscellaneous plastic, health services	Machine operators, chemical technicians, dentists
12. 1-Nonanol	143-08-8	1,557	18%	C & A	Machine operators
13. 1-Decanol	112-30-1	4,973	10%	C & A, health services	Machine operators, chemical technicians

[1]Numbers are taken from the National Occupational Exposure Survey (Seta et al., 1988). These are provisional data, as of October, 1988; estimates may increase as more trade-name products are resolved.
[2]C & A = Chemical and allied industries.

the percent of each population that is female, and the industries and occupations that have the largest number of exposed people. The two largest worker populations, exposed to isopropanol or ethanol, are approximately 50% female.

The general properties, biotransformation, and toxicity of the alcohols have been the subject of numerous reviews (e.g., von Oettingen, 1943; Rowe and McCollister, 1982; Wimer et al., 1983). In addition to the toxicity of the alcohols themselves, several alcohols have also been shown to potentiate the toxic effects of one another, of halogenated hydrocarbons, and of other industrial chemicals (e.g., Cornish and Adefuin, 1966; Strubelt, 1980; Hills and Venable, 1982; Hewitt et al., 1983). Ethanol has also been implicated in potentiating the teratogenicity of chemical agents such as glycol ethers (Nelson et al., 1982a and b; 1984), and physical agents, such as heat (Shiota et al., 1988).

Historically, some general observations on the toxicity of the alcohols are well established. As early as 1869, Richardson observed that, among the alcohols, toxicity to adult animals generally increased with chain length, up to about six carbons, after which toxicity decreased. This has become so well accepted that it is known as "Richardson's Law" (discussed by von Oettingen, 1943). As a nostalgic note, it is interesting that Richardson also cautioned that the term "alcohol" is not synonymous with "ethanol," an error that was apparently common in his day (and perhaps nearly as common today). In fact, he had the advantage of illustrating his point by referring to the alcohols (other than ethanol) which were burning in the lamps that provided light during his presentation at the meeting! He then proceeded to demonstrate some of the specific combustion properties of the different alcohols. He further demonstrated, using live guinea pigs, that butyl alcohol produced narcosis for a longer period of time than did ethyl alcohol, and described, for these two alcohols, the similar onset of symptoms including tremor, hypothermia, and subsequent death.

More recent studies have focused on potential mechanisms by which alcohols may exert effects. McCreery and Hunt (1978) tested some 60 alcohols for the ability to produce ataxia in rats, and related the behavioral effects to the physicochemical properties of the alcohols. Most of the alcohols which consist of up to 6 or 7 carbons in the primary chain produced a behavioral spectrum of intoxication virtually identical to that of ethanol. There was a high, inverse correlation between the effective dose that produced ataxia and the membrane/buffer partition coefficient, but there was no correlation with the concentration of alcohol in the non-aqueous phase of the animal, volume of the non-aqueous phase occupied, or thermodynamic activity. They concluded that intoxication is not induced by specific binding of a compound with a classically-defined receptor, but rather as a more non-specific interaction with some hydrophobic region of excitable membranes. Shoemaker (1981) discussed the acute, chronic, and fetal toxicity of alcohols, and noted that inhalation exposure to the alcohols produces effects similar to those induced by other routes of exposure.

The developmental toxicity of ethanol is well established (Abel, 1981), both in humans (Abel, 1982a) and experimental animals (Abel, 1982b). A publication by Jones et al. (1973) brought the Fetal Alcohol Syndrome to national and international focus. More recently, developmental toxicology evaluations have been completed for some other alcohols. Grant and Samson found strong similarities in microcephaly produced in the neonatal rat by ethanol and by tertiary-butanol (1982) and 1-propanol (1984). Daniel and Evans (1982) compared ethanol and tertiary-butanol for the ability to produce effects on the postnatal development of mice, and concluded that tert-butanol was five times more potent than ethanol in producing developmental impairments expressed later in postnatal performance. Mankes and colleagues evaluated the developmental toxicology of several "substituted ethanol" compounds. In an abstract reporting on this research (Mankes et al., 1985), they suggested that developmental toxicity increased with increasing lipid solubility. Only their report on 2-phenylethanol has been published to confirm this hypothesis (Mankes et al., 1983). Despite these isolated studies, the alcohols have not been systematically evaluated for developmental toxicity. Further, the relatively recent discovery of the developmental and reproductive toxicology of several structurally-related glycol ethers (Hardin, 1983; Nelson et al., 1984) suggested the potential for structure-activity relationships in other chemical series. The methyl and ethyl derivatives of ethylene glycol ethers and their acetates were found to produce developmental toxicity, as well as reproductive toxicity, at concentrations which were within the acceptable limits of exposure prevailing at that time. Investigations of structure-activity relationships are not uncommon in assessments of developmental toxicology. For example, within a decade after the discovery of the potent teratogenicity of thalidomide in humans, nearly 40 structurally related compounds were assessed for teratogenicity in rabbits (Jonsson, 1972). By 1981, at least 60 compounds related to thalidomide had been tested for their ability to produce teratogenicity in experimental animals; a small number were found to be teratogenic (Fabro, 1981). More recently, the teratogenicity of natural and synthetic retinoids has been under intense investigation. Some 40 congeners have been investigated for teratogenicity in the past few years; a large majority have been found to be teratogenic (Willhite et al., 1989). Those investigations using pharmaceutical agents, along with the interesting structure-activity relationships observed with the glycol ethers, prompted us to question if a pattern of adverse effects involving structure-activity relationships would be seen with the aliphatic alcohols at occupationally-relevant concentrations.

The need and justification for the present study, therefore, resulted from a combination of the factors discussed above: 1) A large and diverse exposure population, a significant proportion of which are female; 2) toxicity which was hypothesized to follow a predictable pattern of structure-activity relationships; 3) the potential for interactive effects with other chemicals; 4) established teratogenicity of ethanol both in animals and humans, as well as isolated reports

indicating teratogenic effects for other alcohols; and, 5) the recent discovery of teratogenic effects for structurally-related glycol ethers. Accordingly, we initiated a program of research to investigate the developmental toxicity of a series of aliphatic alcohols, focusing on the normal alcohols having primary carbon chain lengths from one to ten. Since postnatal functional deficits are important effects seen with prenatal ethanol exposure (e.g., Streissguth, 1983), as well as being reported or expected for other alcohols (Daniel and Evans, 1982; Grant and Samson, 1982, 1984), we included an evaluation of postnatal behavioral performance for a subset of these alcohols. In total, 13 alcohols were evaluated for developmental toxicology, and 4 of these were evaluated for behavioral teratology.

Results of individual studies have been published previously, including developmental toxicology investigations of methanol and ethanol (Nelson, et al., 1985), n-propanol and isopropanol (Nelson, et al., 1988a), 1-, 2-, and tertiary-butanol (Nelson, et al., 1989a), 1-pentanol, 1-hexanol, and 2-ethyl-1-hexanol (Nelson et al., 1989b), and 1-octanol, 1-nonanol, and 1-decanol (Nelson, et al., 1990a). Results have also been published of behavioral teratology investigations of ethanol (Nelson, et al., 1988b), 1-propanol (Nelson, et al., 1989c), 1-butanol (Nelson, et al., 1989d), and tertiary-butanol (Nelson, et al., 1990b). Finally, a report summarizing our experience in generating and monitoring vapor concentrations of the alcohols is in preparation (Khan et al., in preparation).

Purpose and Hypothesis

Our original hypothesis was based on "Richardson's Law," as discussed above, and on the observations of McCreery and Hunt (1978) that the general toxicity of the aliphatic alcohols increases as the length of the hydrocarbon skeleton increases. The alcohols selected for study are listed in Table 2. We focused on the straight chain alcohols, although some branched chain isomers were also tested. We hypothesized that the developmental toxicity of the alcohols would increase as carbon chain length increased, up to 6–8 carbons, after which it would decrease. Implicit in this hypothesis was that alcohols, as a class, would produce developmental toxicity when administered by inhalation, and that behavioral teratogenic effects would be observed at concentrations lower than those which produced embryotoxicity as assessed by more traditional means (e.g., malformations).

Since the volatility of alcohols decreases with increasing chain length, the maximal vapor concentrations that can be generated are inversely related to chain length. However, inhalation is a common route of occupational exposure, and we expected that embryotoxicity might occur at concentrations achievable for each alcohol. While cutaneous exposure is also an expected route of occupational exposure to the alcohols, and has been investigated to a limited extent (e.g., Blank, 1964), we elected to use inhalation exposures because of our previous experience with this route of exposure.

TABLE 2
Carbon Chain Skeletons of Alcohols Investigated for Developmental Toxicity

1. Methanol	C—O
2. Ethanol	C—C—O*
3. n-Propanol	C—C—C—O*
4. Isopropanol	O | C—C—C
5. n-Butanol	C—C—C—C—O*
6. 2-Butanol	O | C—C—C—C
7. tert-Butanol	C | C—C—O* | C
8. n-Pentanol	C—C—C—C—C—O
9. n-Hexanol	C—C—C—C—C—C—O
10. 2-Ethyl-1-hexanol	C | C | C—C—C—C—C—C—O
11. 1-Octanol	C—C—C—C—C—C—C—C—O
12. 1-Nonanol	C—C—C—C—C—C—C—C—C—O
13. 1-Decanol	C—C—C—C—C—C—C—C—C—C—O

*Also investigated for behavioral teratology

Results of Alcohol Exposures

Table 3 summarizes the maternal and fetal effects seen in our developmental toxicity evaluations, and presents, for comparison, the Permissible Exposure Limits (PELs) established by the Occupational Safety and Health Administration (29 CFR 1910.1000, as Revised [OSHA, 1989]). As may be seen in this table, very high concentrations of the short-chain alcohols, with the exception of ethanol, produced developmental toxicity as evidenced by resorptions, fetal weight reductions, and, in some cases, malformations. Methanol produced teratogenic effects (viz., exencephaly, skeletal malformations [primarily rudimentary cervical ribs], and a variety of visceral malformations) in the absence of detectable effects in the maternal animals. The other alcohols, however, produced developmental effects only in the presence of maternal effects. Ethanol was not teratogenic, even at concentrations which produced, in maternal animals, narcosis that persisted throughout the 7-hour exposure period. These results may be due to the low blood-alcohol levels achieved in our study (Nelson et al.,

TABLE 3
Summary of Maternal and Fetal Effects and PELs of Alcohols Investigated for Developmental Toxicology

Alcohol	PEL	Maternal Effects*	Fetal Effects**
Methanol	200 ppm (260 mg/m³; skin notation)		
5000 ppm		none	none
10,000		none	weights
20,000		none	weights, ext, skel, visc
Ethanol	1000 ppm (1900 mg/m³)		
10,000 ppm		none	none
16,000		none	weights (male)
20,000		narcosis, feed	weights (male)
1-Propanol	200 ppm (500 mg/m³)		
3500 ppm		none	none
7000		none	weights, skel
10,000		none	res, weights, ext, skel, visc
Isopropanol	400 ppm (980 mg/m³)		
3500 ppm		none	weights
7000		narcosis, feed, weight	weights, skel
10,000		narcosis, feed, weight	res, weights, skel
1-Butanol	50 ppm (150 mg/m³; ceiling; skin notation)		
3500 ppm		none	none
6000		feed	weights
8000		narcosis, feed	weights, skel
2-Butanol	100 ppm (300 mg/m³)		
3500 ppm		feed, weight	none
5000		narcosis, feed, weight	weights
7000		narcosis, feed, weight	res, weights
tert-Butanol	100 ppm (300 mg/m³)		
2000 ppm		narcosis	weights
3500		narcosis	weights
5000		narcosis, feed, weight	weights
1-Pentanol	none		
3900 ppm (14,000 mg/m³)		feed, weight	none
1-Hexanol	none		
840 ppm (3500 mg/m³)		none	res (slight)
2-Ethyl-1-hexanol	none		
200 ppm (850 mg/m³)		feed	none
1-Octanol	none		
65 ppm (350 mg/m³)		none	none
1-Nonanol	none		
25 ppm (150 mg/m³)		none	none
1-Decanol	none		
15 ppm (100 mg/m³)		none	none

*Narcosis (observed subjectively), feed (consumed significantly less than controls), weight (significantly less gestational gain than controls)

**Weights (significantly less than controls), ext (incidence of external malformations significantly increased from controls), skel (incidence of skeletal malformations significantly increased from controls), visc (incidence of visceral malformations significantly increased from controls), res (incidence of resorptions significantly increased from controls)

1985a and b). Both n-propanol and isopropanol showed developmental toxicity (i.e., external malformations such as ectrodactyly or missing tail, skeletal malformations [primarily rudimentary cervical ribs], and visceral malformations [primarily cardiovascular or urinary defects]), but only in the presence of maternal toxicity. In the series of butyl alcohols examined, only 1-butanol was teratogenic (viz., skeletal malformations, primarily rudimentary cervical ribs), in spite of maternal toxicity with all three isomers. In alcohols with carbon chains longer than four, vapors could not be generated at concentrations which produced detectable maternal toxicity. No developmental toxicity was evident with these longer-chain alcohols. In the short-chain alcohols which produced teratogenicity, these effects occurred at concentrations much higher than the permissible occupational exposure maxima for the respective alcohols.

The behavioral teratology investigations produced essentially negative results, with two exceptions of note. Administration of 7000 ppm 1-propanol for six weeks to male rats produced an apparently reversible infertility in the rats (Nelson et al., 1989c; only 2 of 18 exposed males produced litters). The other exception was the observation of neurochemical effects in offspring after maternal exposure to some alcohols (Nelson et al., 1988b; 1990b), despite a lack of behavioral effects.

Results of Control Group Comparisons

Over the five years of this research, we typically included one sham-exposed control group as a comparison group for the experimental animals exposed to two concentrations of a given alcohol (or to two alcohols if a single concentration was evaluated). Eleven control groups were used, and these groups provided data for comparison purposes. The rats were from the same supplier (Charles River Laboratories, generally from the Michigan facility), and were typically shipped in groups of 45 rats as needed. Consequently, we had shipments distributed throughout each year over this five-year period. Comparing the data from these 11 control groups, we found some variables which did not differ among groups, but some variables which did differ significantly among the groups. Those variables (including overall means of the individual study means [±SD] and ranges of the individual study means) that did not differ significantly among the control groups were: 1) Number of corpora lutea of pregnancy (15.0 [±0.8]; range 14–16); 2) number of resorptions (0.9 [±0.1]; range 0.2–1.5); 3) maternal weight gain (gestation day 20 minus gestation day 0) (110g [±5]; range 103–122g); 4) mean number of females per litter (7.1 [±0.1]; range 6.5–7.8) and mean number of males per litter (6.5 [±0.1]; range: 5.9–7.3) and, 5) fetal weights for females (3.15g [±0.02]; range 3.02–3.29g) and males (3.30g [±0.02]; range 3.17–3.45g).

The variables that did differ significantly among the control groups were: 1) Absolute maternal weights (e.g., day 0: 253g [±20]; range 219–287g; day 20: 364g [±16]; range 335–390g); 2) feed consumption (week 1: 125g [±13]; range 103–150g; week 2: 136g [±9]; range 124–150g; week 3: 127g [±7]; range 117–

137g); 3) water intake (week 1: 241g [±35]; range 204–304g; week 2: 266g [±29]; range 223–309g; week 3: 291g [±29]; range 246–364g); and, 4) malformations (based on the original five control groups for which the data had been previously entered into our computer system for analysis), including percent normal pups (99% [±1]; range 98–100%), percent of pups/litter with skeletal malformations (2% [±2]; range 0–3%), and visceral malformations (1% [±1]; range 0–3%); and, the percent of pups with skeletal variations (31% [±12]; range 12–41%) and visceral variations (13% [±6]; range 8–21%).

These control group comparisons proved useful for experimental design purposes. For example, because of difficulties in generating the final alcohol (1-decanol) assessed, we could not use the data from the control group as originally planned because nearly one year had elapsed between the time the control group was tested and the time the exposed group was assessed (Nelson et al., 1990a). By using historical control data from our prior research with other alcohols, the majority of the experimental data for the 1-decanol exposed group could be utilized (Nelson et al., 1990a). Also, we observed an apparent (i.e., a statistically significant) increase in resorptions after inhalation exposure to 1-hexanol (Nelson et al., 1989b). Close scrutiny of the control group, however, suggested that this particular control group had an unusually low incidence of resorptions (0.4), compared with the mean resorptions (0.9) of all control groups; the incidence of resorptions in the exposed group (1.3) fell within the range seen for other control groups, thus suggesting that there was no treatment effect on the number of resorptions.

Addressing the Hypotheses

Reviewing the data from this series of experiments, several statements can be made relative to the original hypothesis (viz., that the developmental toxicity of the alcohols would increase as carbon chain length increased to 6–8 carbons, after which toxicity would decrease). Although we observed that toxicity to maternal animals followed Richardson's Law (i.e., toxicity generally increased with increasing carbon chain length), we did not observe a similar pattern for developmental toxicity. Methanol was teratogenic at 10,000 and 20,000 ppm, and both propyl alcohol isomers were teratogenic at 7000 and 10,000 ppm. However, 1-butanol was the only butyl isomer that was teratogenic, and it increased skeletal malformations only slightly at 8000 ppm; no teratogenic effects were noted for butyl alcohol at 6000 ppm. Thus, the butyl series, which we had expected to be teratogenic at lower concentrations than the propyl series, did not fit the predicted pattern. Since sufficiently high vapor concentrations of longer chain alcohols could not be generated to produce toxicity in maternal animals or fetuses, these alcohols were not useful in evaluating this hypothesis.

An assumption implicit to this series of experiments was that alcohols, as a class, would produce developmental toxicity when administered by inhalation. For the methyl, propyl, and butyl alcohols we examined, this assumption was verified,

although we had anticipated finding effects in the conceptus at concentrations lower than those required to produce maternal toxicity. Except for methanol, this expectation was not verified. Once again, we could not generate concentrations of longer chain alcohols which produced either maternal or developmental toxicity.

A second assumption implicit in this experimental series was that behavioral teratogenic effects would be observed at concentrations lower than those which produced embryotoxic effects (e.g., malformations) as revealed by traditional assessments. This hypothesis was not verified. Although sporadic deviations in behavioral and/or neurochemical endpoints were observed with the alcohols, no pattern of effects was seen with any of the alcohols we examined. In the behavioral teratology investigation of 1-propanol, the highest concentration (7000 ppm) produced malformations as determined by standard teratology evaluations (Nelson et al., 1988a), and as evidenced by tail abnormalities in the behavioral teratology evaluation (Nelson et al., 1989c); yet, behavioral/neurochemical deviations were not seen consistently.

Summary and Conclusion

Both the Food and Drug Administration (Sobotka, 1989) and the Environmental Protection Agency (Sette, 1987; 1989), for example, employ structure-activity relationships to evaluate untested chemicals. Our research suggests caution when using structure-activity relationships to predict the potential teratogenicity of untested compounds, and that decisions based on structure-activity relationships require substantiation with considerable research data.

Several of the alcohols (methanol, 1-propanol, isopropanol, and 1-butanol) produced developmental toxicity in rats when administered by inhalation throughout gestation. When developmental toxicity was seen, however, it was at high concentrations, typically greater than 10 times the Permissible Exposure Limits, and generally in the presence of maternal toxicity. Thus, selective developmental toxicity was not apparent. We conclude that developmental toxicity would not be induced in rats by inhalation of the alcohol vapors we investigated at the concentrations presently permitted in the workplace. However, no-effect concentrations were not determined for 2-butanol (adult), isopropanol (fetus), 2-butanol (adult), tert-butanol (adult and fetus), 1-pentanol (adult), and 2-ethyl-1-hexanol (adult). The reproductive toxicity to male rats of high concentrations of 1-propanol should be investigated in future research.

While this series of studies evaluated several standard endpoints of developmental toxicity, other endpoints and research questions remain to be investigated. One area of potential concern not addressed by this research is the possibility that alcohols potentiate the toxicity of other chemicals. Earlier observations demonstrating that ethanol may potentiate both adult (e.g., Hills and Venable, 1982) and developmental (e.g., Nelson et al., 1984) toxicity suggest

the need for additional research determining interactive toxic effects of industrial alcohols when used in combination with other chemicals. A second area of research which needs addressing is potential teratogenicity by other routes of exposure, including percutaneous absorption, since this is another route of occupational exposure. A third area that should be investigated is the developmental toxicity of other structurally-related alcohols and/or substituted alcohol compounds.

Based on a research approach that is accepted currently throughout the industrialized world for evaluating pharmacologic, environmental, and occupational agents (e.g., Schardein, 1985), and given the considerations and limitations in extrapolating results from rodents to humans (e.g., Nau, 1986), we conclude that the large number of females occupationally exposed to alcohol vapors likely have a limited risk of alcohol-induced birth defects at exposures within current occupational exposure guidelines.

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