

# Teratogen Update: Toluene

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Toluene (methylbenzene) is an aromatic hydrocarbon widely used as an organic solvent in both industrial settings and common household products such as gasoline, glue and paint. (U.S. Public Health Service, '89; Verschueren, '77). Inhalation of air-borne toluene as a vapor is the most common route of human exposure. Approximately 80% of an initial inhaled dose is absorbed with decreasing absorption following continued exposure (Low et al., '88). A small amount of toluene is expired unchanged while most is metabolized by the liver (American College of Toxicology, '87; Low et al., '88). While other routes of exposure, such as ingestion following hazardous waste contamination, are possible, their relative contribution to the total load of toluene exposure is minimal (American College of Toxicology, '87; U.S. Environmental Protection Agency, '88).

Air-borne exposure to toluene vapor represents a significant concern to both industrial workers and consumers. Workers in the production and manufacturing of various industrial chemicals including benzene, toluene diisocyanate, phenol, benzyl, benzoic acid, toluene sulfates, nitrotoluenes, saccharin, and styrene face risks from chronic low-level exposure as well as industrial accidents. Current standards for a permissible exposure limit (PEL) for toluene have been established by U.S. Occupational Safety and Health Administration (OSHA) at 100 ppm (375 mg/mm<sup>3</sup>), calculated as a time weighted average over an 8-hour day (Donald et al., '91). Inadvertent, low-level consumer exposure occurs daily through household use of gasoline, glues, rubber cement, stain removers, paint thinners, fabric dyes, inks, and cigarette smoke (U.S. Public Health Service, '89).

Intentional toluene vapor exposure, known as "sniffing" or "huffing," remains a popular form of substance abuse. A sense of euphoria is generally achieved with exposures of at least 500 ppm, five times the OSHA Permissible Exposure Level (PEL). At 600–800 ppm, confusion, auditory and visual hallucinations, inhibition, and incoordination occur (Brozosky and Winkler, '65). In chronic abusers, levels of toluene exposure often reach 5,000 ppm, 50 times the OSHA PEL (Ron, '86).

As a drug of abuse, inhalation of toluene through the sniffing of gasoline, glue, and spray paints has been reported since the 1950s. The popularity of toluene abuse has been governed by its relative ease of accessibility, low cost, and misperceived lack of addictive qualities. In chronic abusers, both irreversible neurologic toxicity and reversible renal damage have been noted. Deaths have been attributed to long-standing

CNS and/or renal damage as well as to acute suffocation during inhalation. In the late 1980s, toluene abuse was a problem primarily among teenagers and young adults with 20% of recent high school students from various socioeconomic backgrounds acknowledging vapor abuse at least once (National Survey, '91). Data from the early 1980s documented occasional use in 10% and regular abuse in 4% of adolescents surveyed (Lowenstein, '85).

Regarding potential teratogenicity, as a lipid soluble compound, toluene readily crosses the placenta and has been recovered from various fetal tissues, amniotic fluid, and human neonates following documented in utero exposure (Goodwin, '88). In animals, approximately 10% of an inhaled dose rapidly crosses the placenta with organ distribution being gestational age dependent. Persistence of toluene in the fetal animal compartment can be documented for at least 24 hours. In mice, a greater accumulation in the liver with advancing gestational age has been reported (Ghantous and Danielsson, '86). In utero toluene exposure thus poses theoretical risks for both organ specific teratogenicity and overall fetotoxicity. To fully assess the impact of toluene exposure on the fetus, animal exposure studies (Donald et al., '91), available human studies, and a discussion of the confounders are considered in this review. The teratogenic effects of in utero toluene exposure may be influenced by maternal metabolic acidosis secondary to toluene-induced renal damage, the biologic variation in the metabolism of toluene, and the impact of concomitant drugs of abuse, particularly alcohol.

## ANIMAL STUDIES

### Exposure by inhalation

Only a few systematic studies have been reported as full publications (Hudak and Ungvary, '78; International Research and Development Corporation '85; Klimisch et al., '92; Litton Bionetics, '78; Ono et al., '95; Tatrai et al., '80; Ungvary and Tatrai, '85). One additional study has been described in abstract form (Shigeta et al., '81). In mice, levels of inhaled exposure have included 100 to 2,000 ppm at various times during

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TABLE 1. Inhalation studies of toluene in animal models<sup>1</sup>

Authors	Species	Exposure parameters (ppm) (days/gestation) (hrs/da)	Growth delay	Skeletal delay	Anomalies
Hudak and Ungvary ('78)	Mouse	133 or 399 ppm days 6-13 24 hr/day	Increase $\geq$ 133	No increase	NR
Shigeta et al. ('81)	Mouse	100 or 1,000 ppm days 1-17 6 hr/day	NR	NR	At 1,000
Ungvary and Tahrai ('85)	Mouse	133, 266, or 399 ppm days 6-15 3 $\times$ 4 hr/day	Increase $\geq$ 266	Increase $\geq$ 266	NR
Hudak and Ungvary ('78)	Rat	266 ppm days 1-21 8 hr/day	No increase	Increased	NR
Litton Bionetics ('78)	Rat	100 or 400 ppm days 6-15 6 hr/day	NR	No increase	No increase
		399 ppm days 1-8, 9-14 24 hr/day	Increased (days 1-8)	Increased	NR
Tatrai et al. ('80)	Rat	266 ppm days 7-14 24 hr/day	No increase	Increased	NR
International Research and Development Corp. ('85)	Rat	100, 500 or 2,000 ppm preconception - lactation 6 hr/day	NR	No increase	NR
Ono et al. ('95)	Rat	600, 2,000 ppm days 7-17 (6 hr/day)	Increase = 2,000	Increase = 2,000	No increase
Ungvary and Tatrai ('85)	Rabbit	133, 266 ppm	NR	No increase	NR
Klimisch et al. ('92)	Rabbit	30, 100, 300, 500 ppm	No increase	NR	No increase

<sup>1</sup>NR = not reported.

TABLE 2. Comparison of inhaled toluene exposures<sup>1</sup>

	PPM	mg/kg/d
OSHA permissible standard	100	34
Animal studies <sup>2</sup>		
N-O-E-L for fetotoxicity	500	127.5
Projected EPA RfD (reference dose)	3.3	1.125
Toluene abusers <sup>3</sup>		na
Euphoria, excitement	500	
Hallucinations, confusion	600-800	
Chronic abusers	5,000-12,000	

Legends: <sup>1</sup>ppm, parts per million; mg/kg/d, milligram/kilogram/day. na, total daily dose not calculated given variable lengths of exposure.

<sup>2</sup>Donald et al. ('91); U.S. Environmental Protection Agency, reference dose ('86).

<sup>3</sup>Brozosky and Winkler ('65); Ron ('86).

gestation as well as at various durations of exposure (6-24 hours/day) (Table 1). Growth and skeletal retardation were noted at lower levels (133 ppm and 266 ppm, respectively) when such exposures were of a 12- to 24-hour duration for at least half of the gestation period, (Ungvary and Tatrai, '85; Hudak and Ungvary, '78). Comparable human levels of inhaled exposure would be obtained by chronic abusers (Table 2). The only noted malformations were an increase in the frequency of 14th ribs, which was noted at 1,000 ppm on days 1-17 of gestation for 6 hours/day. This has been

the highest exposure studied in the mouse model and is comparable to the inhaled exposure which produces euphoria in humans (Table 2).

More extensive studies have been reported in the rat model (Table 1). Levels of inhaled exposure have ranged from 100-2,000 ppm at various times during gestation and for varied duration (6-24 hours/day). Increases in either growth or skeletal retardation have been noted at relatively low doses (266 and 399 ppm) with chronic (24 hours/day) exposures occurring during either a portion (7-14 days) or the entire gestation. Intermittent exposures (6-8 hours per day) produced growth and skeletal retardation only at higher levels (2,000 ppm). Exposures at this level would be comparable to that obtained during human inhalation to produce euphoria. Maternal malnourishment further increases these detrimental effects of toluene (Da Silva et al., '90). No increase in anomalies was noted at any of the exposures studied. No increase in either growth, skeletal retardation, or anomalies has been noted at low exposures (30-500 ppm) in the rabbit model (Table 2).

#### Exposure by gavage

Studies of gavage exposure are limited to an abstract of a mouse model (Nawrot and Staples, '79) and a more comprehensive study in rats (Gospe et al., '94). In mice, toluene by gavage was shown to decrease fetal weight (0.5 ml/kg) and increase the frequency of cleft palate

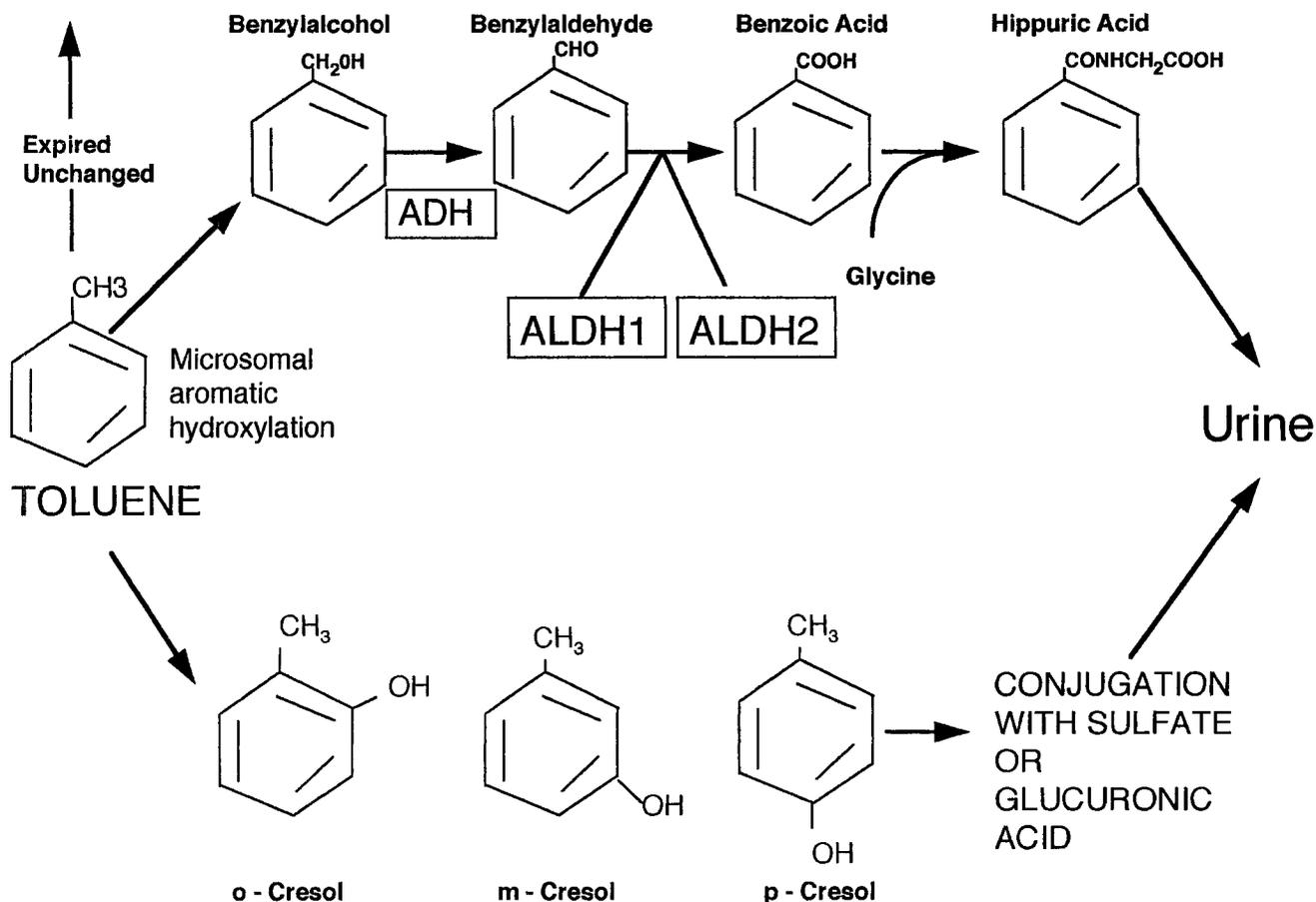


Fig. 1. Metabolism of toluene. ADH, alcohol dehydrogenase; ALDH, aldehyde dehydrogenase. Modified from Kawamoto et al. ('94).

(1.0 ml/kg). The latter dose is noted to achieve blood toluene levels comparable to 3 hours of exposure to 3,290 ppm. In humans, these blood levels would be expected following chronic toluene abuse. In the rat model, fetal weight was significantly reduced with 1.0 ml/kg toluene by gavage on days 6–19. However no increase in malformations was noted at this level of exposure.

Interactions between toluene and other drugs have been examined in various animal models. An interaction between acetylsalicylic acid (ASA) and toluene has received attention given the multiple therapeutic indications for ASA. Toluene, by lowering glycine, may result in higher levels of free salicylic acid, which may increase teratogenic and fetotoxic effects. In rats, exposure to 3,600 mg/m<sup>3</sup> inhaled toluene on days 10–13 in conjunction with varied levels of ASA produced greater maternal toxicity, fetotoxicity, and an increased incidence of rib anomalies (Ungvary et al., '83). A significant increase in maternal and embryonic salicylic concentrations above expected levels resulted in increased maternal toxicity, fetotoxicity, and minor anomalies. Supplemental glycine was shown to prevent these maternal and fetal effects supporting toluene in-

duced restriction of glycine as the mechanism of ASA mediated toxicity (Fig. 1) (Tatrai et al., '79; Ungvary et al., '83).

### HUMAN STUDIES

To put animal studies into perspective, similar levels of exposure have been documented in humans. In general, however, for occupational exposures, unknown levels of exposure and concomitant exposure to other solvents make accurate assessment difficult. Considering occupational exposures, a case/control study of pregnant women with prenatal chemical exposures disclosed a higher rate of anomalies. Exposure to aromatic solvents, most commonly toluene, was greatest among infants with urinary tract anomalies (McDonald et al., '87). In a retrospective case/control study of children with central nervous system defects, first trimester occupational organic solvent exposure was more frequent in the mothers of the affected group (Holmberg, '79). Conversely, one additional occupational exposure study found no increased risk of adverse outcome (Olsen, '83). The lack of information concerning exact exposure levels, timing of exposure

and durations precludes further assessment of these studies.

By contrast, the person who has used toluene by sniffing glue can achieve levels of exposure estimated at 500 to 12,000 ppm. Among the offspring of toluene-abusing women, a similar increase in nonspecific malformations has been observed. A "fetal solvent syndrome" was initially proposed to describe a child with facial features similar to those observed in the fetal alcohol syndrome. Prenatal history was significant for marked toluene abuse with relatively little alcohol exposure (Toutant and Lippman, '79). Other patients have been retrospectively ascertained from developmental clinics and/or perinatal units following documented prenatal exposure. Regardless of the mode of ascertainment, a recognizable pattern of craniofacial findings reminiscent of the fetal alcohol syndrome has been described: microcephaly, narrow bi-frontal diameter, short palpebral fissures, deep-set eyes, flat mid-face, flat nasal bridge, and small nose (Fig. 2). Digital hypoplasia and minor urinary tract anomalies have also been reported (Arnold et al., '94; Goodwin, '88; Hersch et al., '85; Hersch, '89; Pearson et al., '94). In the largest series of infants examined by a dysmorphologist (N = 18), 83% had craniofacial findings such as small palpebral fissures, thin upper lip, and midface hypoplasia, which are also more common in children with the fetal alcohol syndrome. In at least half of these infants, toluene was the only acknowledged teratogenic exposure (Pearson et al., '94). The risks for teratogenicity of toluene estimated from evaluation of these children is influenced by the variable quantity, duration and timing of exposure as well as the use of other potentially teratogenic drugs of abuse. Because of these variables, in conjunction with possible concomitant drug use, the magnitude of the risk of toluene as a teratogen remains unknown.

As has been the observation in animal studies, prenatal exposure to toluene in humans has been associated with an increased frequency of intrauterine growth retardation as compared to the general population (Table 3) (Arnold et al., '94; Goodwin, '88; Hersch et al., '85; Hersch, '89; Pearson et al., '94; Wilkins-Haug et al., '91). While determination of the extent and duration of exposure is difficult, women with a positive toluene screen and/or renal tubular acidosis had a greater risk of IUGR in offspring as compared to women who acknowledged exposure but who had no known medical complications (85 vs. 40%). Prenatal microcephaly was frequently observed in exposed children. In addition a substantial number of toluene-exposed children showed the postnatal onset of microcephaly. Developmental delays were common, irrespective of the means of ascertainment. Moreover, two-thirds of the children with greater prenatal exposure to toluene had persistence of developmental delay despite being placed in foster homes. In the latter case, the  $\frac{2}{3}$  rate of developmental delay is striking, as these children (with the exception of one) were all removed from the

original environment and raised in foster homes (Wilkins-Haug, '91).

A further confounding variable in humans is the potential concomitant exposure to other agents of abuse, especially alcohol. While in utero exposure to other potentially teratogenic drugs remains unknown, coabuse of other narcotics was denied by at least half of the women studied in the two largest clinical series (Wilkins-Haug, '91; Pearson et al., '94). Documentation of the lack of concomitant alcohol use during pregnancy was supported by the rare finding of positive alcohol toxicology screens at the time of testing for toluene (Wilkins-Haug, '91).

## CONFOUNDERS OF PRENATAL TOLUENE EXPOSURE

### Maternal toxicity and the role of metabolic acidosis

Chronic toluene abuse can produce a distal renal tubular acidosis, which is characterized by hyperchloremia, a normal "anion gap" and a decreased arterial pH in conjunction with an elevated urine pH. Significant hypokalemia can result in muscle paralysis and cardiac dysfunction. In addition, hypophosphatemia and hypobicarbonatemia are frequently present (Steicher et al., '81). Intermittent metabolic acidosis from toluene-induced renal tubular damage may further contribute either independently or synergistically to toluene fetotoxicity.

Based on animal and human studies, in the face of acute, short-term maternal acidosis, the fetus is able to maintain a normal acid base balance, although hypoxemia may occur (Blechner et al., '70). Fetal hypoxemia, due either to maternal hematological disease or high altitude habitation, has been associated with reduced fetal growth (Yip, '87). The contribution of toluene-induced fetal hypoxemia secondary to chronic renal tubular acidosis to fetal growth retardation in exposed pregnancies remains speculative. In addition, maternal acidosis, by decreasing uterine perfusion may result in fetal hypoperfusion and ischemia to the developing fetus, which may also contribute to poor growth in utero (Blechner, et al., '75).

Long-standing maternal metabolic acidosis may lead to direct fetal acidosis. Classic studies have shown maternal acidosis of greater than 4 hours can lower the fetal pH (Goodlin and Kaiser, '79). The possible teratogenic of fetal acidosis remain unclear. Decreased plasma pH in conjunction with increased carbon dioxide levels has been postulated to produce ectrodactyly (Weaver, '84).

### Gene polymorphisms in toluene metabolism pathway

Toluene metabolism occurs primarily in the liver through the microsomal aromatic hydroxylation pathways. Most inhaled toluene (80%) is metabolized by the enzymes alcohol dehydrogenase and aldehyde dehy-



**Fig. 2.** Facial appearance of children with in utero toluene exposure. Reproduced from Arnold et al. ('94) with permission of the publisher.

drogenase (ALDH) to benzoic acid. The addition of glycine produces hippuric acid, which is excreted in urine (Fig. 1). Genetic polymorphisms can result in a deficiency of ALDH2 with such polymorphisms known to occur with as high as a 50% prevalence among subgroups of Japanese and North American populations. Clinically, absolute deficiency of ALDH2 results

in intolerance to alcohol which is characterized by tachycardia, facial flushing, and hypotension (Harada, '89). DNA characterization of the mutation leading to ALDH2 deficiency allows for the identification of absolute deficiency of this enzyme (ALDH2-DD), heterozygosity (ALDH2-ND), and homozygosity for the normal allele (ALDH2-NN) (Hsu et al., '85).

**TABLE 3. Clinical growth features following in utero excessive chronic toluene exposure**

	Pearson et al. ('94)	Wilkins-Haug (91)	Total (%)
Prenatal			
Small for gestational age	6/18	13/18	18/36 (50)
Microcephaly	5/18	5/18	10/36 (28)
Postnatal			
Growth deficiency	3/9	8/13	11/21 (52)
Microcephaly	8/9	6/13	14/22 (64)
Developmental delay	5/6	6/13	11/21 (52)

As ALDH2 is an integral enzyme within the toluene metabolism pathway, and one for which a DNA polymorphism is known, implications for the effects of toluene in individuals deficient in ALDH2 have been proposed. Restriction fragment length analysis for the ALDH2 genotypes was undertaken in Japanese workers exposed to occupational toluene. The population distribution of ALDH2-NN (55.6%), ALDH2-ND (24.4%), and ALDH2-DD (13.3%) was not significantly different from a control population. Further analysis at various exposure levels as monitored by diffusion samplers of aerosolized levels and individual urinary hippuric acid determinations revealed a positive correlation within each genotype. An overall lowering of urinary hippuric acid determinations was noted for the DD genotypes at all exposure levels, reflecting lower rates of normal metabolism of toluene (Kawamoto et al., '94).

Furthermore, the impact of deficient ALDH2 on overall toluene kinetics is additionally mediated by the enzyme mechanics between the two isozymes of ALDH1 and -2. ALDH2 plays a more predominant role in the determination of the levels of toluene, and thus benzaldehyde. Individuals with polymorphic deficiency of ALDH2 would be expected to have higher benzaldehyde levels following the OSHA 100 ppm occupation exposure levels (Kawamoto et al., '94). This may likewise be true for exposures at the level of intentional abuse. The contribution of this enzyme deficiency to both the potential teratogenic effects of toluene requires further study.

### SUMMARY

Extrapolating from animal data, at the level at which well-controlled occupational exposure to toluene vapor is encountered, in utero exposure does not pose a significant fetal risk. However, following chronic and excessive industrial accidents or intentional abuse, toluene exposure several orders of magnitude greater exists, and at these levels in utero exposures in both animals and humans have been shown to produce significant delays in fetal growth. At these greater exposure levels, both dose and gestational timing relationships can be demonstrated in animal models. Of note, in both animals and humans, postnatal persistence of growth deficiency has been observed. A pattern of teratogenicity similar to that of the fetal alcohol

syndrome is prevalent in all human studies of excessive in utero exposure to toluene.

In humans, the effects of in utero toluene exposure among intentional abusers is confounded by such variables as general health and exposure to other teratogens. Chronic toluene abuse produces a renal tubular acidosis with maternal hypokalemia and profoundly lowered serum pH. Further evaluation of greater numbers of infants with respect to maternal renal tubular acidosis will be needed to fully assess the contribution of chronic acidosis. The contribution of maternal acidosis to fetal teratogenicity remains speculative. Coabuse of additional agents, in particular alcohol, may increase the teratogenic risks. The overlap of features following in utero toluene abuse with those of fetal alcohol syndrome suggests a possible common pathway of craniofacial teratogenesis.

Lastly, genetic variations that result in deficiency of ALDH2, an enzyme involved in toluene metabolism, may increase the risks of toluene teratogenicity in at-risk individuals at lower levels of exposure. Prospective studies of toluene-exposed pregnancies would provide more information on the fetal effects at these levels.

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