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## **Organic Solvents During Pregnancy: An Update on Occupational Exposure**

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Organic solvents are a diverse group of liquids that are used to dissolve other materials like oils, resins, and rubber (McMartin et al., 1998). Examples of organic solvents include: aliphatic hydrocarbons (mineral spirits, varnish, kerosene); aromatic hydrocarbons (benzene, toluene, xylene); halogenated hydrocarbons (carbon tetrachloride, trichloroethylene); aliphatic alcohols (methanol); glycols (ethylene glycol); and glycol ethers (methoxyethanol) (McMartin et al., 1998). While it is likely erroneous to make general statements about organic solvents due to their diverse nature, human reproductive studies have only studied organic solvents collectively. This newsletter will provide an updated review of these studies. See 1995 Risk Newsletter Volume 3(3) for the original newsletter.

Exposure to organic solvents occurs most frequently from inhalation or skin contact. Exposure is nearly unavoidable in the general population since organic solvents are present in many household products such as paints, aerosol sprays, spot removers, lighter fluids, inks, and gasoline (Koren 2005).

Household exposure is typically of a low level, episodic nature. This type of exposure is likely to be of little concern although conservative measures should include minimizing use, wearing protective clothing, such as gloves, making sure ventilation is adequate, or ideally having someone else use the product in the woman's absence. Occupational exposure is more of a concern because it typically involves higher dose, chronic exposure. Organic solvents are used in a wide range of industries such as dry cleaners, laboratories, paint manufacturers, chemical manufacturers of inks and plastics, beauty salons, carpentry, and funeral services (Koren, 2005). Moreover, some of these fields are female dominated.

### **Intentional Solvent Abuse**

Individuals may purposefully inhale organic solvent vapors to attain a feeling of euphoria by coating rags with spray paint and directly inhaling the rag as it covers their nose and mouth. Chronic toluene abuse (one-four 16 ounce cans per day) is associated with a myriad of toxic symptoms such as muscle weakness, neuropsychiatric disturbances, and renal tubular acidosis. (Pearson et al., 1994). Chronic abusers typically reach levels 50 x the Occupational Safety and Health Administration (OSHA) permissible levels (Wilkins-Haug, 1997).

Although causation is not proven, a congenital solvent syndrome from purposeful abuse of toluene or gasoline has been suggested by case series and uncontrolled cohorts. These reports have included premature delivery, low birth weight, microcephaly, developmental delay, growth retardation, and characteristic facial features similar to infants with fetal alcohol syndrome (Arnold et al., 1994; Pearson et al., 1994). While fetal alcohol syndrome was not ruled out, case reports have also described infants with renal tubular dysfunction which is associated with solvent and not alcohol abuse (Lindermann, 1991; Erramouspe et al., 1996). Additionally, some infants have smelled of solvents at birth (Koren, 2005).

Occupational Exposure Occupational exposures are difficult to assess for several reasons. First epidemiological reproductive data is typically sparse and high dose animal data is difficult to interpret to lower level human exposure. Secondly, the dose of exposure is also difficult to gauge unless specific airborne studies have been performed by an industrial hygienist. Odor is often an inaccurate way to assess the dosage of most organic solvents (McMartin et al, 1998).

Infrequently, organic solvents (such as toluene) can be monitored via blood or urine tests. Thirdly, occupational exposures typically include multiple exposures which confound outcome information for any one agent. In summary, available studies are limited by the lack of quantified measure of the exposure and the fact that exposures take place in diverse settings with different doses, durations, and combinations of chemicals.

### **Miscarriage and Major Malformations**

Occupational studies have yielded conflicting results on whether rates of miscarriage and congenital anomalies are increased following maternal exposure. McMartin et al. (1998) performed a meta-analysis of epidemiological studies on pregnancy outcomes following maternal organic solvent exposure. Five retrospective studies were included for spontaneous abortion (N= 2,899 patients) and five retrospective studies were utilized for major malformation analysis (N= 7,036 patients). While some prior studies have suggested an increased rate of miscarriage, the rate of spontaneous abortion was not significantly increased when analyzed in this meta-analysis. However, the rate of major malformations was significantly increased with an odds ratio of 1.64 (CI 1.16-2.30). Assuming a background risk of 3%, this study suggests the absolute risk for malformations would be 4.9%.

Limitations of the McMartin et al. (1998) meta-analysis include that the studies analyzed were looking at different organic solvents, unknown dosages, and wide durations of exposure in a wide range of occupational environments. Despite these limitations, the authors supported the current recommendation that pregnant women should limit their exposure to organic solvents as much as possible. The authors also pointed out that these risks should be further investigated in a prospective study. Khattak S et al. (1999) prospectively followed 125 pregnant women who were occupationally exposed to organic solvents. All women worked for at least the entire first trimester.

Hours were not documented. The majority of women were factory workers, laboratory technicians, artists, chemists, painters, and printers. The most commonly reported organic solvent exposures were aliphatic and aromatic hydrocarbons, phenol, trichloroethylene, vinyl chloride, and acetone. The exposed group had a significantly higher rate of malformations compared to the control group. There were 13 major malformations in the exposed group compared to only one malformation in the control group. While the control group had an unusually low rate of malformations, the exposed rate was still greater than historic controls. Additionally, a dose response relationship was suggested in that at least 12/13 of the infants with malformations occurred in women who reported work-related illness such as irritation of the eyes or respiratory system, headaches, and breathing difficulties.

There was no pattern to the malformations to suggest cause and effect. Malformations included ventricular septal defect, clubfoot, laryngomalacia, diaphragmatic hernia, neural tube defect, congenital deafness, micropenis, cloacal extrophy, left inguinal hernia, congenital hydronephrosis, neuronal migration defect, and hemivertebrae. However, the authors argued that diverse exposures should not be expected to create a homogenous pattern. The authors concluded that additional studies are needed to confirm their findings but in the interim it is prudent to minimize women's exposure to organic solvents and particularly to take precaution to avoid symptomatic exposure.

### **Neurological effects**

Organic solvents like toluene are considered neurotoxins since acute exposures have documented effects on the central nervous system in adult workers. A subset of adults with a long history of

occupational exposure have cognitive deficits and women with purposeful abuse have delivered infants with developmental delay (Koren, 2005). Therefore, fetal exposure raises a significant concern for adverse cognitive function following exposure to known neurotoxins. Similar to major malformations and miscarriage, results however have been inconsistent.

Eskenzai et al. (1988) assessed neurocognitive functioning and growth in 41 children age 3-4 years old whose mothers had been occupationally exposed to organic solvents. Using maternal reports and the McCarthy Scales of General Abilities, no differences in neurobehavioral development or growth were identified in the exposed versus control group.

Till et al. (2001a) also evaluated long-term cognitive and behavioral functioning of 28 children ages 3-7 years old who were exposed to a wide range of organic solvents in utero. No group differences were observed on measures of attention, visuo-spatial ability, or fine-motor ability. However, exposed children scored significantly lower on receptive language, expressive language, and graphomotor ability, suggesting detrimental effects on selective cognitive functions.

Laslo-Baker et al. (2004) examined the long-term neurodevelopment effects of 32 children age 3-9 years old whose mothers had been exposed to organic solvents at work during their pregnancy. Mothers reported exposures to a total of 78 different organic solvents for 1-40 hours per week (mean, 24 hours) and for 8-40 weeks (mean, 32 weeks) during their pregnancy. Exposed mothers reported a high level of protective equipment. Occupations listed were diverse including painter, laboratory technician, factory worker, hair stylist, graphic designer, funeral embalmer, and science teacher. After controlling for demographic variables and maternal IQ and education, there were no significant differences in global, verbal, or performance IQ. The authors however reported differences in more subtle areas of neurodevelopment. Exposed children had lower test scores in subtests of recall, attention, and language. No dose relationship (which would further causation) was found between the length and total hours of exposure and any of neurodevelopmental scores.

### **Visual impairments**

Noting that impairment of color vision discrimination can be altered by certain solvent exposures in adult workers, Till et al. (2001b, 2005) conducted two studies to examine visual impairments in infants and children whose maternal parents were occupationally exposed to organic solvents during pregnancy.

Till et al. (2001b) measured color vision and visual acuity in 32 exposed children whose mothers worked in diverse occupations with multiple exposures during their pregnancies. Overall, results showed that exposed children had significantly higher error scores on color discrimination and visual acuity. Three of the 32 exposed children suffered from clinical red-green color vision loss compared to none of the control children. The authors commented that these visual deficits are of concern because they may have implications for higher level cognitive functioning, such as learning to read. A dose response relationship, which would argue for causation, was not found.

In 2005, Till et al. tested 21 exposed infants in which maternal qualitative exposure levels were gathered prospectively. This study found a significant decrease in contrast sensitivity as well as grating acuity (dependant upon the level of exposure) in exposed infants compared to controls. Regarding color vision, 26.3% of exposed infants showed abnormal red-green color vision compared to 0% of controls. These findings suggest that prenatal solvent exposure is associated with selective visual deficits.

### **Summary**

Maternal intentional abuse of organic solvents has suggested that a congenital solvent syndrome, similar to fetal alcohol syndrome, may exist. Effects of doses not toxic to the mother warrant further investigation. Available occupational exposure studies are severely limited in that they study multiple diverse exposures together and that there is no quantified measure of the exposures.

Not surprising, the available data is inconsistent. There is some evidence of an increased risk for congenital anomalies, particularly in women who reported symptoms related to their occupational exposure. Initial data suggests that there may be detrimental effects on subtle cognitive functions or visual color acuity. Given the inconclusive but concerning information, occupational exposure to known neurotoxins should be minimized or ideally avoided. If air monitoring is available, OSHA dose standards that are established for adult health, and may or may not adequately protect fetal health, should not be exceeded. Mothers are encouraged to limit the time they are exposed to organic solvents and to wear protective clothing, such as solvent resistant gloves and splash-proof eye goggles. Respirators need to be specifically approved for organic solvents and individuals would need to be assessed and fitted to use them. Engineering controls, such as a chemical hood, which would contain chemicals in their own ventilation system are preferred.

## References

- Arnold GL, Kirby RS, Langendoerfer S, Wilkins-Haug L (1994). Toluene embryopathy: clinical delineation and developmental follow-up. *Pediatrics* 93(2):216-20.
- Erramouspe J, Balvez R, Fischel D (1996) Newborn renal tubular acidosis associated with prenatal maternal toluene sniffing. *J Psych Drugs* 28:201-4.
- Eskenazi B, Gaylord L, Bracken MB, Brown D (1988) In utero exposure to organic solvents and human neurodevelopment. *Dev Med Child Neurol* 30(4):492-501.
- Khattak S, K-Moghtader G, McMartin K, Barrera M, Kennedy D, Koren G (1999) Pregnancy outcome following gestational exposure to organic solvents: a prospective controlled study. *JAMA* 281:1106-1109.
- Koren G (2005) Occupational toxicology of organic solvents-the reproductive context. 18th International Conference of Organization of Teratology Information Services.
- Laslo-Baker D, Barrera M, Knittel-Keren D, Kozer E, Wolpin J, Khattak S, Hackman R, Rovet J, Koren G (2004) Child neurodevelopment outcome and maternal occupational exposure to solvents. *Arch Pediatr Adolesc* 128:956-961.
- Lindermann R (1991) Congenital renal tubular dysfunction associated with maternal sniffing of organic solvents. *Acta Paediatr Scand* 80(8-9):882-4.
- McMartin KI, Chu M, Kopecky E, Einarson TR, Koren G (1998) Pregnancy outcome following maternal organic solvent exposure: a meta-analysis of epidemiologic studies. *Amer J Indust Med*, 34:228-292.
- Pearson MA, Hoyme HE, Seaver LH, Rimsza ME (1994) Toluene embryopathy: delineation of the phenotype and comparison with fetal alcohol syndrome. *Pediatrics* 93(2):211-215.
- Till C, Koren G, Rovet JF (2001) Prenatal exposure to organic solvents and child neurobehavioral performance. *Neurotoxicol Teratol* 23(3):235-45.
- Till C, Westall CA, Rovet JF, Koren G (2001) Effects of maternal occupational exposure to organic solvents on offspring visual functioning: a prospective controlled study. *Teratology* 64(3):134-41.
- Till C, Westall CA, Koren G, Nuiman I, Rovet JF (2005) Vision abnormalities in young children exposed prenatally to organic solvents. *Neurotoxicology* 26(4):599-613.
- Wilkins-Haug L (1997) Teratogen Update:Toluene. *Teratology* 55:145-151.
- Wilkins-Haug L and Gabow PA (1991) Toluene abuse during pregnancy: obstetric complications and perinatal outcomes. *Obstet Gynecol* 77:504-9.

## Contributors

Lauren Bowling, BS

Genetic Counseling Intern

Mara Gaudette, MS, CGC

Coordinator, Illinois Teratogen Information Service

Eugene Pergament, MD, PhD, FACMG

Northwestern Reproductive Genetics, Inc.