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## **Non-Prescription Allergy Medications and Inhalers**

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During this time of year, the Illinois Teratogen Information Service receives many telephone calls regarding the use of common, over-the-counter, allergy medications and inhalers. Most of these medications contain more than one chemical and many of these chemicals are found in more than one medication. This RISK||NEWSLETTER will discuss the teratogenic effects of the chemicals found in these medications. A listing of the chemicals found in common medications is also included.

This newsletter will cover in detail only those chemicals that may be contraindicated in pregnancy. Chemicals that have not been associated with adverse pregnancy outcomes are acetaminophen, chlorpheniramine, dextromethorphan, doxycycline, pseudoephedrine and pseudoephedrine. The remaining drugs are divided into three categories: antihistamines, expectorants, and sympathomimetics. Inhalers will be covered separately.

### **Antihistamines**

Dexbrompheniramine and brompheniramine are chemically related in that dexbrompheniramine is the d-isomer of brompheniramine. Neither has been studied thoroughly, but brompheniramine has been studied more extensively. According to the Collaborative Perinatal Project, prenatal exposure to brompheniramine in the first trimester has a relative risk of 2.34 for congenital malformations. This risk is based on only 65 infants, however, and 10 had minor malformations. When the same study assessed brompheniramine use anytime during pregnancy, no increased risk was found. In addition, the Boston Collaborative Drug Surveillance Program studied 270 women exposed to brompheniramine in the first trimester and did not find an increased frequency of malformations (Teris; Jick 1981).

Most studies of diphenhydramine have not found an association between prenatal exposure to this drug and an increased risk of malformations. One case control study found a significant association between first trimester use and oral clefting. The risk of oral clefts is probably less than 1%. Diphenhydramine withdrawal has been reported in one infant whose mother had taken 150 mg/day throughout pregnancy.

Clemastine has an undetermined teratogenic risk based on the fact that no epidemiological studies in humans have been reported. No animal studies have been reported either. The chemical is related to diphenhydramine and, therefore, those risks may apply.

There is some concern about antihistamines compromising the physiological role of histamine in the fetus. Histamine is felt to be important in the cardiovascular response to stress in the neonate. Infants and young children given antihistamines may convulse after these drugs are administered, and there is a

concern that third trimester use of these agents may cause non-teratogenic effects, yet to be clearly defined.

**Expectorants**

Guaifenesin was associated with an increased incidence of inguinal hernias when taken in the first trimester, according to one study of 197 offspring. In this same study, there was no significant increase in malformations in the 1336 offspring exposed anytime in pregnancy (Collaborative Perinatal Project, Heinonen 1977; Reprotox). Two separate studies of 241 and 925 women with exposure in the first trimester found no increased incidence of birth defects in their offspring (Aselton, 1985; Reprotox; Boston Collaborative Drug Surveillance Program; Jick, 1981). Overall, the risk to a conception is estimated not to be increased after exposure.

**Sympathomimetics**

Sympathomimetics as a group are considered to have a “none” to “minimal” risk of birth defects. An increased incidence of minor malformations such as inguinal hernias and clubfoot has been found in some studies (Collaborative Perinatal Project, 1977; Berkowitz, 1986). Pseudoephedrine is a drug of choice in this class.

Phenylephrine was associated with a slight increase in the incidence of minor anomalies, mostly eye and ear malformations in one study of 1249 women exposed in the first trimester (Collaborative Perinatal Project, 1977). A smaller sized study did not find this association (Boston Collaborative Drug Surveillance Program; Jick, 1981; Aselton, 1985). A case control study of 390 children with congenital heart disease found a preponderance of maternal exposure to phenylephrine in these children (Rothman, 1979), as did a study of 298 children with congenital heart disease (Zierler & Rothman, 1985). A third cohort study did not find this increased incidence (Heinonen, 1977). Another area for concern is the potential for phenylephrine and other alpha-adrenergic antagonists to induce maternal hypertension and to decrease uterine blood flow. Uterine blood vessels contain alpha-adrenergic receptors that constrict when stimulated. In pregnant ewes, uterine blood flow decreased by 40% upon receiving a dose of phenylephrine equivalent to one cold tablet (Cottel, 1982).

Phenylpropanolamine has also been found to increase the incidence of minor anomalies when taken in the first trimester. These include hypospadias, eye and ear malformations, polydactyly, and pectus excavatum. The Collaborative Perinatal Project assigned a relative risk of 1.67 for minor anomalies as a group and a 4.04 relative risk for eye and ear malformations, specifically to the prenatal use of phenylpropanolamine. This is only based on a small number of malformations, however. Other studies did not find an increased incidence of any anomalies following prenatal exposure to phenylpropanolamine (Boston Collaborative Drug Surveillance Program; Jick, 1981; Werler, 1992).

**COMON ALLERGY MEDICATIONS AND THEIR CHEMICAL COMPOSITIONS**

	Bena dryl	Brom fed	Chlor trimeton	Com trex	Con tac	Cori cidin	Dime tane	Dris tan	Drix oral	Ny quil	Robi tussin	Suda fed	Tavist
aceta- minophen				x	x	x		x	x	x			
alcohol	x									x	x		
brom-		x					x						

pheniramine									
chlor-pheniramine		X		X	X	X		X	
clemastine									X
dexbrom-pheniramine								X	
dextro-methorphan				X	X				X
diphen-hydramine	X								
doxycylamine								X	
guaifenesin									X
phenyl-ephine								X	
phenyl-propanolamine					X	X			
pseudo-ephedrine		X	X		X	X		X	X
pseudo-epinephrine								X	

**Inhalers**

Beclomethasone, an adrenal hormone used for asthma treatment and present in the medications, Beclovent and Vancenase, has not been found to be associated with an increase in birth defects. Low birth weight and premature delivery, however, have been associated with prenatal use of Beclomethasone. Albuterol (Proventil, Ventolin) is a beta-sympathomimetic used for bronchodilation and arresting of premature labor. It is not thought to be teratogenic in rats or rabbits. Teratogenic effects have been seen in mice, primarily oral clefts. No epidemiological studies have been reported for human pregnancies. Three case studies of women inhaling albuterol beginning in the second trimester did not find any increase in malformations (Lind, 1980; Addis, 1981; and, Edmonds and Letchworth, 1982). Albuterol treatment late in pregnancy produces fetal tachycardia but does not cause any significant neonatal problems. Pirbuterol is an analog of albuterol and is found in MaxAir. It is not teratogenic in mice or rabbits. High doses administered to rats was associated with fetal growth impairment and high doses administered to rabbits was associated with abortion. Human reproductive effects have not been reported. Flunisolide (AeroBid) is a synthetic glucocorticoid. In mice and rats, it is associated with an increase in oral clefting and other anomalies at 5 and 2.5 the human therapeutic dose, respectively. Lower doses did not cause a teratogenic effect. No reports are available on human use during pregnancy. Flunisolide is related to beclomethasone. Theophylline (Theo-Dur) is a methylxanthine stimulant used as a diuretic, cardiac stimulant, and bronchodilator. It has a “none” to “minimal” risk of birth defects. No human studies of prenatal exposure to theophylline have found an association with an increased incidence of birth defects. A potential risk of neural tube defects exists based on the fact that theophylline depresses lipid synthesis in the developing neural system, but has not been reported following exposure. Tachycardia and jitteriness have been noted in neonates exposed in-utero.

**SUMMARY**

Allergy medications contain a wide variety of chemicals, most are not associated with an increased risk for birth defects. Medications containing acetaminophen, chlorpheniramine, dextromethorphan, doxycyclamine, pseudoephedrine and pseudoepinephrine have not been associated with adverse pregnancy outcomes. From the enclosed table it is apparent that these are the chemicals in many over-the-counter medications.

Inhalers are primarily used by asthmatics, and information regarding teratogenic effects and these products, limited as it may be, suggests that most have not been associated with birth defects.