

INACTIVE PHARMACEUTICAL INGREDIENTS: IMPLICATIONS FOR PREGNANCY

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Administration of pharmaceutical agents to pregnant women is a concern, because of safety issues to both mother and fetus. However, all medication formulations contain many other inactive ingredients in addition to the active drug.

In contrast to the extensive research on the safety of active pharmaceutical ingredients in pregnant patients, the fetal safety of the inactive ingredients has been largely ignored. This is likely due to the fact that the inactive ingredients are considered to be in “small amounts” and are believed to be “inert”. However, this is often not the case. Most pharmaceutical preparations will typically contain 5 to 10 times more inactive ingredients in terms of weight versus the actual active ingredients. Therefore, most tablets, for example, are mainly made up of inactive ingredients.

It is common for a medicine to have a dozen or so inactive ingredients within its formulation acting as lubricants, fillers, binders, disintegrating agents, stabilizers or silica flow conditioners. Also, there are numerous oral liquid or syrup drugs that contain 15-20% of ethanol, the most widespread human teratogen. For instance, a patient taking 2 teaspoons of Cholelyl elixir 4 times daily will absorb 8g of alcohol. This is equal to the amount of ethanol in one bottle of beer. The Kaletra (oral solution of lopinavir /ritonavir) contains a surprising 42.4% of ethanol (Table 1).

As this review highlights, many chemicals that are commonly used as inactive ingredients in drugs have adverse effects on reproductions. These inactive ingredients have been described

in variety of models, and most often the No-Observed-Adverse-Effect-Level (NOAEL) in humans has not yet been established. Given these examples, a manufacturer should employ a great deal of prudence while formulating drugs that contain ethanol or other unstudied alcohols destined to be consumed by pregnant women. Hence, it seems logical that rather than risking fetal safety, the use of such compounds as inactive ingredients should be restricted or banned.

We propose that to study the safety of medications in pregnancy, one should apply the principles of teratology not only to the active ingredients, but also to the ingredients termed in-active.

The basic principles of evaluating teratogenic potential have been articulated by scores of different authors and include the following:

1. Biological plausibility for teratogenic potential, including mechanism of action, periods of greatest sensitivity, and genetic susceptibility.
2. Analysis of dose-response relationships and pharmacokinetics in an animal model and in humans.
3. Analysis and interpretation of human epidemiologic studies.
4. The examination of the relationship between the secular trend of birth defects and the population exposure to drugs.

The aim of this review is to present the existing animal and human data on the reproductive toxicology of the most common inactive ingredients used in pharmaceutical formulations.

TABLE 1 Ethanol-containing Medications. Source Canadian Compendium of Pharmaceuticals & Specialties (CPS)

Preparation	Drug	Alcohol as inactive ingredients (CPS)	OTC / Prescription
Allernix Elixir (Rougier- Pharma)	Diphenhydramine	Yes (between 10 to 20%)	OTC
Benlylin DM-E Syrup	Dextromethorphan	Yes (Between 1 to 10%)	OTC
Balminil DM Nighttime	Guaifenesin	Yes	OTC
Benadryl Elixir	Diphenhydramine	Yes (Between 10 to 20%)	OTC
Fermentol liquid	Pepsin	Yes (Between 1 to 10%)	OTC
Robitussin Cough and Cold	Guaifenesin	Yes (Between 1 to 10%)	OTC
Senokot Syrup	Senna Concentrate	Yes (Between 1 to 10%)	OTC
Tylenol with Codeine Elixir	Codeine / acetaminophen	Yes (Between 1 to 10%)	OTC
Zantac oral solution	Ranitidine	Yes (7.5%)	OTC
Choledyl Elixir	Oxtriphylline	Yes (20%)	PRESCRIPTION
Kaletra	Lopinavir / ritonavir	Yes (42.4%)	PRESCRIPTION
Phenobarbital elixir	Phenobarbital	Yes (20%)	PRESCRIPTION
Gravol IV	Dimenhydrinate	Yes (20%)	PRESCRIPTION
Prograf IV	Tacrolimus	Yes (45%)	PRESCRIPTION
Sandimmunne IV	Cyclosporine	Yes (30%)	PRESCRIPTION
Septra	Trimethoprim - Sulfamethoxazole	Yes (20%)	PRESCRIPTION

Acetone

Acetone is a solvent in topical preparations, found in tablets with water-sensitive active ingredients, or found in a wet granulation process. Acetone has also been used in the formulation of microspheres to enhance drug release. Acetone is produced in the human body as a consequence of free fatty acid metabolism. Levels of endogenous acetone have been shown to vary widely. Mean blood acetone concentration in adults is approximately 3 mg/l (95th percentile = 80 mg/l). Concentrations in children and adolescents tend to be higher than in adults due to higher energy expenditure, with levels as high as 140 mg/l reported in neonates.⁹⁶ Exposure to less than 8.7 mg/kg/day has been proposed as developmentally safe, based on the no-observed-adverse-effect level (NOAEL) reported in studies of pregnant rats, adjusted by an uncertainty factor of 30 (3 for interspecies extrapolation and 10 for human variability).⁹⁶ On this basis, exposure to acetone dose lower than 8.7 mg/kg/day is expected to be safe during pregnancy. This dose is expected to produce plasma levels several times lower than the lowest level associated with toxicity in humans (>200 mg/l).⁹⁶

Aluminum

Aluminum (Al) and its salts are commonly used food and drug additives.²¹ Aluminum-containing aspirins and antacids are also commonly used medications in pregnancy. It appears that 12% to 31% of the orally administered aluminum is absorbed systemically,^{21,22} crosses the placenta and accumulates in the fetus.²³⁻²⁵ In rats aluminum exposure has caused fetal death and resorptions,²⁶ malformations,²⁷ abnormal skeletal growth,^{27,28} and neurobehavioral deficits.^{24,29,30} In animal studies, malformations were shown mostly with parenterally administered aluminum.^{24,28,30,31} Male mice injected intraperitoneally with high dose aluminum developed testicular toxicity.³² A case of a 9 year-old with a fatal neurodegenerative disorder was reported.³³ His mother had taken an average of 75 antacid tablets (containing 200 mg of aluminum hydroxide per tablet) each day throughout the entire pregnancy.

Postmortem analysis of the child revealed high tissue aluminum.³³ Aluminum contaminating intravenous solutions, formula, and soy formulas, may cause intoxication in premature newborns, as

well as neurologic symptoms and osteopenia.³⁴⁻³⁶ Aluminum salts have also been used in some vaginal douches with potential fetal exposure.²¹

Benzoic Acid

Benzoic acid is a common preservative and antifungal. Sodium benzoate, was shown to be teratogenic in rats.³⁷

Benzyl Alcohol

Benzyl alcohol is an antimicrobial preservative used in oral and parenteral preparations, at concentrations up to 2.0% v/v. Benzyl alcohol has been associated with fatal reactions in exposed neonates.¹¹⁰ Presently, there is no available data regarding the effects of benzyl alcohol on pregnancy outcome. In animals, reduced offspring birth weight has been observed only at doses that produced severe toxicity in the mother (over 700 mg/kg/day). The NOAEL in mice was defined at 550 mg/kg. Based on the NOAEL, the acceptable daily intake of benzoyl alcohol was set at 5 mg/kg/day in humans by the World Health Organization (WHO).¹¹¹ Under the light of the WHO recommendation a parenteral solution of with 2% benzyl alcohol could be administered up to a volume of 0.25 ml/kg/day without exceeding the maximum acceptable dose.

Boric Acid

Boric acid is used as an antibacterial agent in nonprescription products, and as an insecticide. The salt orthoborate and the sodium salt borax are used as detergents. Only 0.5% of topically applied boric acid or borax are absorbed systemically.³⁸ Most animal studies have failed to show teratogenic potential except for very high doses.³⁹⁻⁴⁹ It has been hypothesized that fetal toxicity of boric acid is due to riboflavin depletion.⁴² The needed trough levels are substantially higher than those achieved following typical food and water ingestion by pregnant women.⁵⁰ In 253 pregnancies with early embryonic exposure to boric acid there was no significant increase in the incidence of birth defects.

Cetyl Alcohol

Cetyl alcohol is a constituent of numerous pharmaceutical formulations including suppositories, modified-release solid dosage forms, emulsions, lotions, creams, and ointments.

There are no published studies evaluating the potential impact of this compound on human pregnancies. No reproductive toxicity studies in animals are reported in the literature. Toxic doses in animal studies were quite high (in grams/kg range).¹¹² It is assumed to be practically non-toxic to humans (probable human oral lethal dose above 15 g/kg).¹¹³

Chlorobutanol

Chlorobutanol is used in ophthalmic and parenteral preparation as an antimicrobial preservative. Chlorobutanol crosses the placenta in animals¹¹⁶ and produces human embryotoxicity.¹¹⁷ Based on these limited data, systemic preparations containing chlorobutanol should be used with caution during pregnancy. Repeated administration, in particular, should be avoided due to the long terminal half life of chlorobutanol (about 10 days) that may lead to accumulation in the fetus.¹¹⁶

Diethanolamine

Diethanolamine is used as a buffering agent. In pharmaceuticals it is used as a pH adjuster. Animal studies observed reproductive toxicity of diethanolamine only at doses that produced overt maternal toxicity.¹¹⁴ One study observed reduced postnatal growth and survival, but no malformations, in rats, after gestational exposure to diethanolamine (at doses that produced maternal toxicity), with a NOAEL of 50 mg/kg/day.¹¹⁵ Human chronic environmental exposure level has been established at 5 mg/m³ in many countries.

Dimethyl Phthalate

Dimethyl phthalate is used in pharmaceutical applications as a solvent and plasticizer for film-coatings such as hydroxypropyl methylcellulose, cellulose acetate and cellulose acetate-butyrate mixtures. In addition to a number of industrial applications, dimethyl phthalate is also widely used as an insect repellent with topical preparations typically applied as a 40% cream or lotion; it has also been applied as a tent fabric treatment. Similarly to Diethyl Phthalate (see above), Dimethyl Phthalate is a ubiquitous

chemical of the phthalate family. Some members of this family have been associated with reproductive toxicity, but dimethyl phthalate seems to be among the safest in its class.^{118,119} There is little, if any evidence of reproductive toxicity of dimethyl phthalate from animal studies.^{120,121}

Ethanol

Ethanol and aqueous ethanol solutions of various concentrations are constituents of many medications. Ethanol is used as a solvent. Ethanol has also been used in transdermal preparations in combination with Labrasol as a co-surfactant. There are over 130 preparations, containing ethanol, listed in the Canadian Compendium of Pharmaceuticals & Specialties (CPS). Ethanol is a known human teratogen and neurotoxicant. A dose-dependant malformation risk has been repeatedly proven in animal experiments.⁹⁷⁻⁹⁹ Clear evidence of dose-dependent toxicity has also been obtained from epidemiological studies in humans, with babies of heavy-drinking mothers having a higher risk for fetal alcohol syndrome and neurotoxicity than babies of moderate drinkers.¹⁰⁰⁻¹⁰² A clear threshold for the deleterious effect of ethanol consumption on the fetus has not been defined so far.^{103,104}

It has been suggested, on the basis of animal studies, that the threshold may be at very low levels of exposure, particularly for CNS toxicity.¹⁰⁴ According to animal studies, blood ethanol level seems to be the best marker for risk of fetal toxicity and teratogenicity. On the other hand, definition of a no-observed-adverse-effect level (NOAEL) must be based on the most sensitive indicator of toxicity, the brain. Unfortunately, direct measurements of alcohol concentrations in the human fetal brain and correlation with neurotoxicity are not feasible, which prevents a precise estimation of dose-related risk.¹⁰⁴ Nevertheless, most of the above-mentioned data and conclusions are based on evidence coming from fetal ethanol exposures in the context of alcohol drinking mothers. This may not be applicable or relevant to the low blood alcohol concentrations resulting from the direct use of consumer products containing ethanol.^{105,106}

Small quantities of ethanol are rapidly metabolized, unlike the medium-to-large quantities of ethanol ingested with beverages that saturate the metabolizing enzymes and lead to high blood concentrations.¹⁰⁷⁻¹⁰⁹ Experiments in primates have established a NOAEL blood concentration of 400 mg/l (40 mg/dl).¹⁰⁵ This level is quite above the expected exposure produced by ethanol-containing medications. Even elixir formulations taken in adult doses (i.e. 80ml of Benadryl elixir per day, with 15% ethanol) would rarely exceed exposure level higher than a single average drink (9-14 grams of ethanol), which produces ethanol serum levels of about 150 mg/l (15 mg/dl), well below the NOAEL threshold. Ethanol in topical preparations is expected to have negligible absorption.¹⁰⁵

In conclusion, most medical, industrial and domestic uses of ethanol-containing products are likely to be safe during pregnancy. Adult doses of some elixirs with high ethanol concentrations may produce blood levels closer to those observed following a single alcoholic drink consumption, a level considered safe by many authors.¹⁰⁵

Ethanolamine

Ethanolamine is used in the production of hair waving solutions. Pregnant Wistar rats were administered monoethanolamine (MEA) and gavage (450 mg MEA/kg/day), which resulted in maternal toxicity including decreased food consumption and decreases in mean maternal body weight. There was no evidence of maternal toxicity at 40 or 120 mg/kg/day of MEA. Despite the maternal effects observed at 450 mg/kg/day, no significant fetal effects were observed at this or any dose level tested, nor were there any indications of a treatment-related effect on postnatal growth or on the viability of the offspring.⁶³ Of interest, female fetuses recovered faster and repaired chemical-induced damage better.⁶⁴ In mice, a dose of 850 mg/kg/d decreased the viable litters. However, maternal mortality was high.⁶⁴

Glucose (Dextrose)

Abnormally high blood glucose may cause abnormal embryo development in diabetic pregnancies. Glucose (dextrose) is a hexose, abundantly found in all cells. Vigilance towards

the effects of glucose on embryogenesis stem from the fact that infants of diabetic women have more congenital anomalies. In hamsters, small amounts of glucose in the medium inhibit in vitro development.^{9,10} In rat embryos, high glucose concentrations result in anomalies, particularly in the brain.¹¹⁻¹³ Animal experiments suggest that osmotic effects may play a role in producing these defects.¹⁴

While solutions containing glucose may be administered during labor, if the rate of administration is too rapid, maternal hyperglycemia may lead to neonatal hypoglycaemia, hyponatremia and metabolic acidosis.^{15,16} Placental growth hormone (PGH) progressively replaces pituitary growth hormone in the maternal circulation from mid-gestation onwards in human pregnancy. Investigators studied the response of maternal serum PGH to oral glucose loading in pregnant women who demonstrated normal glucose tolerance at a mean gestation of 29 weeks. No suppression of PGH was noted at one, two or three hours after a 75 g oral glucose load. Similarly, no changes were noted in growth hormone binding protein or in calculated free PGH over the course of the glucose tolerance test. The authors concluded that PGH concentrations in maternal serum are not suppressed by oral glucose loading in non-diabetic mothers.¹⁷

Glycerin

Glycerin (glycerol) is 1,2,3-propanetriol, an alcohol used as a diuretic or a laxative. Glycerin is produced naturally in the blood of mammals by hydrolysis of triglycerides in adipose tissue. A rat study reported that glycerin exposure altered the chromosomes of bone marrow and male germ cells.¹ Glycerin crosses the placenta in small amounts.² Immediately after birth, glycerin and free fatty acids in the plasma increase.^{3,4}

Glycerin is widely used in the cryopreservation of human sperm⁵ and glycerin-containing vaginal lubricants may impair sperm motility.⁶ At a dose of up to 100 mg/kg, glycerin had no effect on fertility in male rats.⁷ In a study testing the effects of glucagon on contractility of the uterine muscle, the authors alternatively found that it was a diluent solution containing glycerine that actually affected the uterine contractions. Glycerine, especially in combination with mannitol and urea are known to relax vascular

smooth muscle. Due to glycerins high osmolarity, it has been hypothesized that it can cause hyperpolarization of the cell membrane, resulting in smooth muscle relaxation. As a result, this may cause relaxation of uterine muscle during contractions, which may be harmful to the pregnant patient.⁸

Kaolin (Kaopectate, Attapulgit, Pectin)

Kaolin is used as a treatment for diarrhea. It was originally a mixture of kaolin and pectin but it is now an attapulgit mixture with pectin. Rats given a 20% kaolin diet before and during pregnancy become anemic and gave birth to low birth weight pups.¹⁸ When an iron supplement was administered along with the kaolin diet, rats did not develop anemia and gave birth to normal weight pups.¹⁸ In humans, maternal anemia increases the risk of prematurity and perinatal mortality.¹⁹ These effects do not manifest when Kaopectate is used as an antidiarrheal.

Many commonly used antidiarrheal medications include kaolin and pectin, bismuth subsalicylate, loperamide, and atropine/diphenoxylate. Experimental evidence has only proven thus far that kaolin and pectin preparations are not absorbed across the placenta. Thus, while there have been possible associations between the ingestion of clays containing kaolin and the development of iron deficiency anemia, they may be the safest of the antidiarrheal medications, especially in combination with iron supplements. The use of bismuth subsalicylate can result in absorption of salicylate and should be avoided in pregnancy.²⁰

Lactic Acid

Lactic acid is a by-product of anaerobic glycolysis. Lactate crosses the human placenta by both diffusion and active transport.^{51,52} The use of fetal lactate levels has been proposed as a means of monitoring fetal well-being.⁵³ Mice gavaged with 570 mg per kg of lactate during organogenesis did not have an increase in congenital defects, but a delay in fetal ossification was observed.⁵⁴

Methylcellulose

Methylcellulose is used as a vehicle to administer medications. A rat study showed that methylcellulose given to pregnant rats result in diaphragm anomalies in the offspring.⁵⁵

Methylparaben

Methyl hydroxybenzoate (methylparaben) is added as a bacteriostatic agent to pharmaceuticals and cosmetics.⁵⁶ It suppresses DNA and RNA synthesis in bacteria,⁵⁷⁻⁶⁰ and has weak estrogenic activity.⁵⁶ Even though no epidemiological studies have been conducted in humans, no teratogenic effects of methylparaben were observed in animal studies in rats, mice, hamsters and rabbits.^{61,62}

Norflurane (Tetrafluoroethane)

Norflurane is used as an anesthetic, a refrigerant, and the propellant in metered-dose inhalers. No adverse effects on reproductive performance in rats exposed to levels between 2500 and 50,000 ppm daily throughout pregnancy was found.⁶⁹ Inhalation doses of 40,000 ppm in rabbits and doses of 100,000 ppm in rats (1,2) caused maternal toxicity and embryofetal toxicity in the rat pups.⁷⁰⁻⁷² Based on experimental animal studies, norflurane exposure is not expected to increase the risk of birth defects.

Phenol

Phenol is widely used in numerous nonprescription products. It is part of many disinfectants. At 5% or higher, phenol causes caustic damage. Phenol is readily absorbed by all routes of administration even when applied topically. Phenol has been shown to cross the placenta in rats.⁶⁵ Phenol did not cause malformations in rats or mice exposed during gestation.⁶⁵⁻⁶⁸ In studies in rats, no malformations were observed, but dose-related fetal toxicity was seen.⁶⁸

Phenylmercuric Salts (Borate, Nitrate)

Phenylmercuric salts are used as antimicrobial preservatives mainly in ophthalmic preparations, but are also used in cosmetics, parenteral, and topical pharmaceutical formulations. Phenylmercuric salts are active against bacteria and fungi over a wide pH range, and are usually used in neutral to alkaline solutions. In acidic formulations, phenylmercuric nitrate may be preferred to phenylmercuric acetate or phenylmercuric borate as it does not precipitate. Phenylmercuric nitrate is also an effective spermicide, although its use in vaginal contraceptives is no longer recommended.

Phenylmercuric borate is used as an alternative antimicrobial preservative to phenylmercuric acetate or phenylmercuric nitrate. It is more soluble than phenylmercuric nitrate and has also been reported to be less of an irritant than either phenylmercuric acetate or phenylmercuric nitrate. When employed as a preservative in eye drops, a concentration of 0.002% is usually used; in injection solutions, the concentration is usually 0.001%.

Concern with the toxicity of mercury compounds may preclude the use of phenylmercuric salts under certain circumstances. Subacute and chronic exposure to toxic doses of phenylmercuric salts produce intoxication syndromes indistinguishable from those induced by inorganic mercury.¹¹³ Safe inorganic mercury concentrations in drinking water have been set at about 2 microg/l in many countries. Oral reference dose has been defined by EPA at 0.008 mg/kg/d, based on a maximum recommended daily exposure of inorganic mercury of 0.1 mg/kg.¹²²

Polyethylene Glycols

Polyethylene glycols exhibit low toxicity. Polyethylene glycol 200 causes congenital defects in mice including skull, paws, and thoracic skeleton effects.⁷⁷ In rabbits, polyethylene glycol 300 or 400 caused maternal toxicity but not teratogenic effects.⁷⁸ A 90-d oral toxicity study, doses of PEG-75 of 230 mg/kg/d caused testicular toxicity and oligospermia.⁷⁹ Large molecular weight polyethylene glycols (PG4000) have been suggested for the treatment of constipation during pregnancy (6-38 weeks).⁸⁰ In contrast, polyethylene glycol 8000 in the diet of Min mice increased the number of colon tumors.⁸¹ In the case of low molecular weight polyethylene glycol, a potential mutagenic and genotoxic risk for polyethylene glycol derivatives has been suggested.⁸²

Polysorbate

Polyoxyethylene-sorbitan-20-monooleate is a solubilizing agent ubiquitously used in ointments, lotions, and multiple medical preparations (e.g., vitamin oils, vaccines, and anticancer agents) and as an additive in tablets. Injection of Tween 80 in chick eggs has not been found to be teratogenic.⁸⁸ Addition of Tween 80 at 0.5 but not 0.1 volume% in rat whole embryo culture resulted in growth

inhibition and dysmorphogenesis.⁸⁹ In mice, Tween 20 administered during pregnancy produced multiple defects suggestive to the authors of thalidomide embryopathy.⁹⁰ One study in neonatal rats reported an indication of estrogenic effects associated with Tween 80 administration.⁹¹ Feeding of Tween 20, 60, or 80 to pregnant rats at more than 7 g/kg/d did not produce signs of fetal toxicity or increased birth defects,⁹²⁻⁹⁴ leading some investigators to recommend these agents as vehicles for intravenous reproduction studies.^{93,94} Rabbits dosed intravenously with 10 mg/kg/d Tween 80 during days 6 to 18 of gestation did not show signs of fetal toxicity or an increased incidence of developmental defects.⁹⁵

Thimerosal

Thimerosal (merthiolate; thiomersal) is a widely used anti-infective and preservative in biologics and vaccines.⁷³ Thimerosal contains 49.6% mercury and is metabolized to ethyl mercury and thiosalicylate. Because of the developmental neurotoxicity of mercury, the American Academy of Pediatrics and the US Public Health Service have recommended stopping the use of thimerosal-containing vaccines.⁷⁴ Yet, post-vaccination mercury levels in infants probably do not exceed safe levels.^{75,76}

In summary, thimerosal preparations should be avoided in pregnancy and infants due to their mercury content. Occasional exposure to thimerosal-containing products does not result in absorption of mercury and inadvertent pregnancy exposure has not been shown to increase the risk for malformations.

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