

AMERICAN ACADEMY OF PEDIATRICS

Committee on Drugs

The Transfer of Drugs and Other Chemicals Into Human Milk

ABSTRACT. The American Academy of Pediatrics places emphasis on increasing breastfeeding in the United States. A common reason for the cessation of breastfeeding is the use of medication by the nursing mother and advice by her physician to stop nursing. Such advice may not be warranted. This statement is intended to supply the pediatrician, obstetrician, and family physician with data, if known, concerning the excretion of drugs into human milk. Most drugs likely to be prescribed to the nursing mother should have no effect on milk supply or on infant well-being. This information is important not only to protect nursing infants from untoward effects of maternal medication but also to allow effective pharmacologic treatment of breastfeeding mothers. Nicotine, psychotropic drugs, and silicone implants are 3 important topics reviewed in this statement.

INTRODUCTION

A statement on the transfer of drugs and chemicals into human milk was first published in 1983,¹ with revisions in 1989² and 1994.³ Information continues to become available. The current statement is intended to revise the lists of agents transferred into human milk and describe their possible effects on the infant or on lactation, if known (Tables 1-7). If a pharmacologic or chemical agent does not appear in the tables, it does not mean that it is not transferred into human milk or that it does not have an effect on the infant; it only indicates that there were no reports found in the literature. These tables should assist the physician in counseling a nursing mother regarding breastfeeding when the mother has a condition for which a drug is medically indicated.

BREASTFEEDING AND SMOKING

In the previous edition of this statement, the Committee on Drugs placed nicotine (smoking) in Table 2, "Drugs of Abuse-Contraindicated During Breastfeeding." The reasons for placing nicotine and, thus, smoking in Table 2 were documented decrease in milk production and weight gain in the infant of the smoking mother and exposure of the infant to environmental tobacco smoke as demonstrated by the presence of nicotine and its primary metabolite, cotinine, in human milk.⁴⁻¹² There is controversy regarding the effects of nicotine on infant size at 1 year of age.^{13,14} There are hundreds of compounds in tobacco smoke; however, nicotine and its metabolite acotinine are most often used as markers of tobacco

exposure. Nicotine is not necessarily the only component that might cause an increase in respiratory illnesses (including otitis media) in the nursing infant attributable to both transmammary secretion of compounds and environmental exposure. Nicotine is present in milk in concentrations between 1.5 and 3.0 times the simultaneous maternal plasma concentration,¹⁵ and elimination half-life is similar—60 to 90 minutes in milk and plasma.⁷ There is no evidence to document whether this amount of nicotine presents a health risk to the nursing infant.

The Committee on Drugs wishes to support the emphasis of the American Academy of Pediatrics on increasing breastfeeding in the United States. Pregnancy and lactation are ideal occasions for physicians to urge cessation of smoking. It is recognized that there are women who are unable to stop smoking cigarettes. One study reported that, among women who continue to smoke throughout breastfeeding, the incidence of acute respiratory illness is decreased among their infants, compared with infants of smoking mothers who are bottle fed.¹⁶ It may be that breastfeeding and smoking is less detrimental to the child than bottle feeding and smoking. The Committee on Drugs awaits more data on this issue. The Committee on Drugs therefore has not placed nicotine (and thus smoking) in any of the Tables but hopes that the interest in breastfeeding by a smoking woman will serve as a point of discussion about smoking cessation between the pediatrician and the prospective lactating woman or nursing mother. Alternate (oral, transcutaneous) sources of nicotine to assist with smoking cessation, however, have not been studied sufficiently for the Committee on Drugs to make a recommendation for or against them in breastfeeding women.

PSYCHOTROPIC DRUGS

Anti-anxiety drugs, antidepressants, and neuroleptic drugs have been placed in Table 4, "Drugs for Which the Effect on Nursing Infants is Unknown but May Be of Concern." These drugs appear in low concentrations (usually with a milk-to-plasma ratio of 0.5-1.0) in milk after maternal ingestion. Because of the long half-life of these compounds and some of their metabolites, nursing infants may have measurable amounts in their plasma and tissues, such as the brain. This is particularly important in infants during the first few months of life, with immature hepatic and renal function. Nursing mothers should be informed that if they take one of these drugs, the infant will be exposed to it. Because these drugs affect neurotransmitter function in the developing central

The recommendations in this statement do not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.
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nervous system, it may not be possible to predict long-term neurodevelopmental effects.

SILICONE BREAST IMPLANTS AND BREASTFEEDING

Approximately 800 000 to 1 million women in the United States have received breast implants containing silicone (elemental silicon with chemical bonds to oxygen) in the implant envelope or in the envelope and the interior gel. Concern has been raised about the possible effects to the nursing infant if mothers with implants breastfeed. This concern was initially raised in reports that described esophageal dysfunction in 11 children whose mothers had implants.^{17,18} This finding has not been confirmed by other reports. Silicone chemistry is extremely complex; the polymer involved in the covering and the interior of the breast implant consists of a polymer of alternating silicon and oxygen atoms with methyl groups attached to the oxygen groups (methyl polydimethylsiloxane).¹⁹ The length of the polymer determines whether it is a solid, gel, or liquid. There are only a few instances of the polymer being assayed in the milk of women with implants; the concentrations are not elevated over control samples.²⁰ There is no evidence at the present time that this polymer is directly toxic to human tissues; however, concern also exists that toxicity may be mediated through an immunologic mechanism. This has yet to be confirmed in humans. Except for the study cited above, there have been no other reports of clinical problems in infants of mothers with silicone breast implants.²¹ It is unlikely that elemental silicon causes difficulty, because silicon is present in higher concentrations in cow milk and formula than in milk of humans with implants.²² The anticolic compound simethicone is a silicone and has a structure very similar to the methyl polydimethylsiloxane in breast implants. Simethicone has been used for decades in this country and Europe without any evidence of toxicity to infants. The Committee on Drugs does not feel that the evidence currently justifies classifying silicone implants as a contraindication to breastfeeding.

DRUG THERAPY OF THE LACTATING WOMAN

The following should be considered before prescribing drugs to lactating women:

1. Is drug therapy really necessary? If drugs are required, consultation between the pediatrician and the mother's physician can be most useful in determining what options to choose.
2. The safest drug should be chosen, for example, acetaminophen rather than aspirin for analgesia.
3. If there is a possibility that a drug may present a risk to the infant, consideration should be given to measurement of blood concentrations in the nursing infant.
4. Drug exposure to the nursing infant may be minimized by having the mother take the medication just after she has breastfed the infant or just before the infant is due to have a lengthy sleep period.

Data have been obtained from a search of the medical literature. Because methodologies used to

quantitate drugs in milk continue to improve, this information will require frequent updating. Drugs cited in Tables 1 through 7 are listed in alphabetical order by generic name; brand names are available from the current *Physicians' Desk Reference*,²³ *USP DI 2001: Drug Information for the Health Care Professional, Volume 1*,²⁴ and *USP Dictionary of USAN and International Drug Names*.²⁵ The reference list is not inclusive of all articles published on the topic.

Physicians who encounter adverse effects in infants who have been receiving drug-contaminated human milk are urged to document these effects in a communication to the Food and Drug Administration (<http://www.fda.gov/medwatch/index.html>) and to the Committee on Drugs. This communication should include the generic and brand names of the drug, the maternal dose and mode of administration, the concentration of the drug in milk and maternal and infant blood in relation to the time of ingestion, the method used for laboratory identification, the age of the infant, and the adverse effects. Such reports may substantially increase the pediatric community's fund of knowledge regarding drug transfer into human milk and the potential or actual risk to the infant.

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TABLE 1. Cytotoxic Drugs That May Interfere With Cellular Metabolism of the Nursing Infant

Drug	Reason for Concern, Reported Sign or Symptom in Infant, or Effect on Lactation	Reference No.
Cyclophosphamide	Possible immune suppression; unknown effect on growth or association with carcinogenesis; neutropenia	26, 27
Cyclosporine	Possible immune suppression; unknown effect on growth or association with carcinogenesis	28, 29
Doxorubicin*	Possible immune suppression; unknown effect on growth or association with carcinogenesis	30
Methotrexate	Possible immune suppression; unknown effect on growth or association with carcinogenesis; neutropenia	31

* Drug is concentrated in human milk.

TABLE 2. Drugs of Abuse for Which Adverse Effects on the Infant During Breastfeeding Have Been Reported*

Drug	Reported Effect or Reasons for Concern	Reference No.
Amphetaminet	Irritability, poor sleeping pattern	32
Cocaine	Cocaine intoxication: irritability, vomiting, diarrhea, tremulousness, seizures	33
Heroin	Tremors, restlessness, vomiting, poor feeding	34
Marijuana	Only 1 report in literature; no effect mentioned; very long half-life for some components	35
Phencyclidine	Potent hallucinogen	36

* The Committee on Drugs strongly believes that nursing mothers should not ingest drugs of abuse, because they are hazardous to the nursing infant and to the health of the mother.

† Drug is concentrated in human milk.

TABLE 3. Radioactive Compounds That Require Temporary Cessation of Breastfeeding*

Compound	Recommended Time for Cessation of Breastfeeding	Reference No.
Copper 64 (^{64}Cu)	Radioactivity in milk present at 50 h	37
Gallium 67 (^{67}Ga)	Radioactivity in milk present for 2 wk	38
Indium 111 (^{111}In)	Very small amount present at 20 h	39
Iodine 123 (^{123}I)	Radioactivity in milk present up to 36 h	40, 41
Iodine 125 (^{125}I)	Radioactivity in milk present for 12 d	42
Iodine 131 (^{131}I)	Radioactivity in milk present 2-14 d, depending on study	43-46
Iodine 131	If used for treatment of thyroid cancer, high radioactivity may prolong exposure to infant	47, 48
Radioactive sodium	Radioactivity in milk present 96 h	49
Technetium 99m (^{99m}Tc), ^{99m}Tc macroaggregates, $^{99m}\text{Tc O}_4$	Radioactivity in milk present 15 h to 3 d	41, 50-55

* Consult nuclear medicine physician before performing diagnostic study so that radionuclide that has the shortest excretion time in breast milk can be used. Before study, the mother should pump her breast and store enough milk in the freezer for feeding the infant; after study, the mother should pump her breast to maintain milk production but discard all milk pumped for the required time that radioactivity is present in milk. Milk samples can be screened by radiology departments for radioactivity before resumption of nursing.

TABLE 4. Drugs for Which the Effect on Nursing Infants Is Unknown but May Be of Concern*

Drug	Reported or Possible Effect	Reference No.
Anti-anxiety		
Alprazolam	None	57
Diazepam	None	58-62
Lorazepam	None	63
Midazolam	—	64
Perphenazine	None	65
Prazepam†	None	66
Quazepam	None	67
Temazepam	—	68
Antidepressants		
Amitriptyline	None	69, 70
Amoxapine	None	71
Bupropion	None	72
Clomipramine	None	73
Desipramine	None	74, 75
Dothiepin	None	76, 77
Doxepin	None	78
Fluoxetine	Colic, irritability, feeding and sleep disorders, slow weight gain	79-87
Fluvoxamine	—	88
Imipramine	None	74
Nortriptyline	None	89, 90
Paroxetine	None	91
Sertraline†	None	92, 93
Trazodone	None	94
Antipsychotic		
Chlorpromazine	Galactorrhea in mother; drowsiness and lethargy in infant; decline in developmental scores	95-98
Chlorprothixene	None	99
Clozapine†	None	100
Haloperidol	Decline in developmental scores	101-104
Mesoridazine	None	105
Trifluoperazine	None	104
OTHERS		
Amiodarone	Possible hypothyroidism	106
Chloramphenicol	Possible idiosyncratic bone marrow suppression	107, 108
Clofazimine	Potential for transfer of high percentage of maternal dose; possible increase in skin pigmentation	109
Lamotrigine	Potential therapeutic serum concentrations in infant	110
Metoclopramide†	None described; dopaminergic blocking agent	111, 112
Metronidazole	In vitro mutagen; may discontinue breastfeeding for 12-24 h to allow excretion of dose when single-dose therapy given to mother	113, 114
Tinidazole	See metronidazole	115

* Psychotropic drugs, the compounds listed under anti-anxiety, antidepressant, and antipsychotic categories, are of special concern when given to nursing mothers for long periods. Although there are very few case reports of adverse effects in breastfeeding infants, these drugs do appear in human milk and, thus, could conceivably alter short-term and long-term central nervous system function.³⁶ See discussion in text of psychotropic drugs.

† Drug is concentrated in human milk relative to simultaneous maternal plasma concentrations.

TABLE 5. Drugs That Have Been Associated With Significant Effects on Some Nursing Infants and Should Be Given to Nursing Mothers With Caution*

Drug	Reported Effect	Reference No.
Acebutolol	Hypotension; bradycardia; tachypnea	116
5-Aminosalicylic acid	Diarrhea (1 case)	117-119
Atenolol	Cyanosis; bradycardia	120-124
Bromocriptine	Suppresses lactation; may be hazardous to the mother	125, 126
Aspirin (salicylates)	Metabolic acidosis (1 case)	127-129
Clemastine	Drowsiness, irritability, refusal to feed, high-pitched cry, neck stiffness (1 case)	130
Ergotamine	Vomiting, diarrhea, convulsions (doses used in migraine medications)	131
Lithium	One-third to one-half therapeutic blood concentration in infants	132-134
Phenindione	Anticoagulant: increased prothrombin and partial thromboplastin time in 1 infant; not used in United States	135
Phenobarbital	Sedation; infantile spasms after weaning from milk containing phenobarbital, methemoglobinemia (1 case)	136-140
Primidone	Sedation, feeding problems	136, 137
Sulfasalazine (salicylazosulfapyridine)	Bloody diarrhea (1 case)	141

* Blood concentration in the infant may be of clinical importance.

TABLE 6. Maternal Medication Usually Compatible With Breastfeeding*

Drug	Reported Sign or Symptom in Infant or Effect on Lactation	Reference No.
Acetaminophen	None	142-144
Acetazolamide	None	145
Acitretin	—	146
Acyclovir†	None	147, 148
Alcohol (ethanol)	With large amounts, drowsiness, diaphoresis, deep sleep, weakness, decrease in linear growth, abnormal weight gain; maternal ingestion of 1 g/kg daily decreases milk ejection reflex	4, 149-152
Allopurinol	—	153
Amoxicillin	None	154
Antimony	—	155
Atropine	None	156
Azapropazone (apazone)	—	157
Aztreonam	None	158
B ₁ (thiamin)	None	159
B ₆ (pyridoxine)	None	160-162
B ₁₂	None	163
Baclofen	None	164
Barbiturate	See Table 5	
Bendroflumethiazide	Suppresses lactation	165
Bishydroxycoumarin (dicumarol)	None	166
Bromide	Rash, weakness, absence of cry with maternal intake of 5.4 g/d	167
Butorphanol	None	168
Caffeine	Irritability, poor sleeping pattern, excreted slowly; no effect with moderate intake of caffeinated beverages (2-3 cups per day)	169-174
Captopril	None	175
Carbamazepine	None	176, 177
Carbetocin	None	178
Carbimazole	Golter	83, 179, 180
Cascara	None	181
Cefadroxil	None	182
Cefazolin	None	182
Cefotaxime	None	183
Cefoxitin	None	183
Cefprozil	—	184
Ceftazidime	None	185
Ceftriaxone	None	186
Chloral hydrate	Sleepiness	187
Chloroform	None	188
Chloroquine	None	189-191
Chlorothiazide	None	192, 193
Chlorthalidone	Excreted slowly	194
Cimetidine†	None	195, 196
Ciprofloxacin	None	197, 198
Cisapride	None	199
Cisplatin	Not found in milk	30
Clindamycin	None	200
Clogestone	None	201
Codeine	None	144, 156, 202
Colchicine	—	203-205
Contraceptive pill with estrogen/progesterone	Rare breast enlargement; decrease in milk production and protein content (not confirmed in several studies)	206-213
Cycloserine	None	214
D (vitamin)	None; follow up infant's serum calcium level if mother receives pharmacologic doses	215-217
Danthron	Increased bowel activity	218
Dapsone	None; sulfonamide detected in infant's urine	191, 219
Dexbrompheniramine maleate with <i>d</i> -isopropylamine	Crying, poor sleeping patterns, irritability	220
Diatrizoate	None	221
Digoxin	None	222, 223
Diltiazem	None	224
Dipyrrone	None	225
Disopyramide	None	226, 227
Domperidone	None	228
Dyphyllinet	None	229
Enalapril	—	230
Erythromycin†	None	231
Estradiol	Withdrawal, vaginal bleeding	232
Ethambutol	None	234
Ethanol (cf. alcohol)	—	

TABLE 6. Continued

Drug	Reported Sign or Symptom in Infant or Effect on Lactation	Reference No.
Ethosuximide	None, drug appears in infant serum*	176, 233
Fentanyl	—	234
Fexofenadine	None	235
Flecainide	—	236, 237
Fleroxacin	One 400-mg dose given to nursing mothers; infants not given breast milk for 48 h	238
Fluconazole	None	239
Flufenamic acid	None	240
Fluorescein	—	241
Folic acid	None	242
Gadopentetic (Gadolinium)	None	243
Gentamicin	None	244
Gold salts	None	245-249
Halothane	None	250
Hydralazine	None	251
Hydrochlorothiazide	—	192, 193
Hydroxychloroquine†	None	252, 253
Ibuprofen	None	254, 255
Indomethacin	Seizure (1 case)	256-258
Iodides	May affect thyroid activity; see iodine	259
Iodine	Goiter	259
Iodine (povidone-iodine, eg, in a vaginal douche)	Elevated iodine levels in breast milk, odor of iodine on infant's skin	259
Iohexol	None	97
Iopanoic acid	None	260
Isoniazid	None; acetyl (hepatotoxic) metabolite secreted but no hepatotoxicity reported in infants	214, 261
Interferon- α	—	262
Ivermectin	None	263, 264
K ₁ (vitamin)	None	265, 266
Kanamycin	None	214
Ketoconazole	None	267
Ketorolac	—	268
Labetalol	None	269, 270
Levonorgestrel	—	271-274
Levothyroxine	None	275
Lidocaine	None	276
Loperamide	—	277
Loratadine	None	278
Magnesium sulfate	None	279
Medroxyprogesterone	None	201, 280
Mefenamic acid	None	281
Meperidine	None	61, 282
Methadone	None	283-287
Methimazole (active metabolite of carbimazole)	None	288, 289
Methohexital	None	61
Methyldopa	None	290
Methypylon	Drowsiness	291
Metoprolol†	None	120
Metrizamide	None	292
Metrizoate	None	97
Mexiletine	None	293, 294
Minoxidil	None	295
Morphine	None; infant may have measurable blood concentration	282, 296-298
Moxalactam	None	299
Nadolol†	None	300
Nalidixic acid	Hemolysis in infant with glucose-6-phosphate dehydrogenase (G-6-PD) deficiency	301
Naproxen	—	302
Nefopam	None	303
Nifedipine †	—	304
Nitrofurantoin	Hemolysis in infant with G-6-PD deficiency	305
Norethynodrel	None	306
Norsteroids	None	307
Noscapine	None	308
Ofloxacin	None	198
Oxprenolol	None	309, 310
Phenylbutazone	None	311
Phenytoin	Methemoglobinemia (1 case)	138, 176, 312
Piroxicam	None	313
Prednisolone	None	314, 315
Prednisone	None	316

TABLE 6. Continued

Drug	Reported Sign or Symptom in Infant or Effect on Lactation	Reference No.
Procainamide	None	317
Progesterone	None	318
Propoxyphene	None	319
Propranolol	None	320-322
Propylthiouracil	None	323
Pseudoephedrine†	None	324
Pyridostigmine	None	325
Pyrimethamine	None	326
Quinidine	None	191, 327
Quinine	None	296
Riboflavin	None	159
Rifampin	None	214
Scopolamine	—	156
Secobarbital	None	328
Senna	None	329
Sotalol	—	237, 330
Spirolactone	None	331
Streptomycin	None	214
Sulbactam	None	332
Sulfapyridine	Caution in infant with jaundice or G-6-PD deficiency and ill, stressed, or premature infant; appears in infant's milk	333, 334
Sulfisoxazole	Caution in infant with jaundice or G-6-PD deficiency and ill, stressed, or premature infant; appears in infant's milk	333
Sumatriptan	None	336
Suprofen	None	337
Terbutaline	None	338
Terfenadine	None	235
Tetracycline	None; negligible absorption by infant	339, 340
Theophylline	Irritability	169, 341
Thiopental	None	139, 342
Thiouracil	None mentioned; drug not used in United States	343
Ticarcillin	None	344
Timolol	None	310
Tolbutamide	Possible jaundice	345
Tolmetin	None	346
Trimethoprim/sulfamethoxazole	None	347, 348
Tripolidine	None	324
Valproic acid	None	176, 349, 350
Verapamil	None	351
Warfarin	None	352
Zolpidem	None	353

* Drugs listed have been reported in the literature as having the effects listed or no effect. The word "none" means that no observable change was seen in the nursing infant while the mother was ingesting the compound. Dashes indicate no mention of clinical effect on the infant. It is emphasized that many of the literature citations concern single case reports or small series of infants.

† Drug is concentrated in human milk.

TABLE 7. Food and Environmental Agents: Effects on Breastfeeding

Agent	Reported Sign or Symptom in Infant or Effect on Lactation	Reference No.
Aflatoxin	None	354-356
Aspartame	Caution if mother or infant has phenylketonuria	357
Bromide (photographic laboratory)	Potential absorption and bromide transfer into milk; see Table 6	358
Cadmium	None reported	359
Chlordane	None reported	360
Chocolate (theobromine)	Irritability or increased bowel activity if excess amounts (≥ 16 oz/d) consumed by mother	169, 361
DDT, benzene hexachlorides, dieldrin, aldrin, heptachlorepoxyde	None	362-370
Fava beans	Hemolysis in patient with G-6-PD deficiency	371
Fluorides	None	372, 373
Hexachlorobenzene	Skin rash, diarrhea, vomiting, dark urine, neurotoxicity, death	374, 375
Hexachlorophene	None; possible contamination of milk from nipple washing	376
Lead	Possible neurotoxicity	377-380
Mercury, methylmercury	May affect neurodevelopment	381-383
Methylmethacrylate	None	384
Monosodium glutamate	None	385
Polychlorinated biphenyls and polybrominated biphenyls	Lack of endurance, hypotonia, sullen, expressionless facies	386-390
Silicone	Esophageal dysmotility	17-22
Tetrachloroethylene cleaning fluid (perchloroethylene)	Obstructive jaundice, dark urine	391
Vegetarian diet	Signs of B ₁₂ deficiency	392