Imported food risk advice

Medicines or drugs of abuse in human milk and human milk products

Context of this risk advice

- Human milk means expressed milk collected from lactating women to be fed to infants that are not the biological infants of the women supplying the milk.
- Human milk products means products derived from human milk that have been specially formulated to meet the specific nutritional needs of infants such as fortifiers and formula.
- The level of risk for this hazard in human milk and human milk products was determined assuming that the most vulnerable category of infants (preterm infants in hospital neonatal intensive care units) would be receiving the products.

Nature of the hazard

Medications

The safety of medications in human milk or human milk products is determined by the hazard of the medication, the maternal/infant dose and the health condition of the infant.

Most medications that are commonly consumed by lactating women are relatively safe for breastfed babies because the total exposure of an infant to the medicine is usually much less than the maternal dose (Anderson et al. 2016; Ito et al. 1993; Soussan et al. 2014).

Only rarely does the amount of a medicine transfer from maternal plasma into milk at levels likely to provide clinically relevant doses to the infant (Hotham and Hotham 2015). These include iodine containing drugs (e.g. amiodarone) and some highly lipid soluble drugs with central nervous system effects (e.g. meperidine).

Drugs of abuse

Many legal (e.g. alcohol) or illicit (e.g. marijuana, cocaine and heroin) drugs of abuse used by nursing mothers are detectable in milk (D'Apolito 2013; Keim et al. 2015). Unlike medications, drugs of abuse provide no medical benefit to weigh against potential risk to the infant.

Presence in human milk

Most medicines are transferred from maternal plasma into human milk by passive diffusion with the degree of equilibrium dependent upon several factors including molecular weight, charge, lipid solubility, volume of distribution and maternal serum protein binding (Sachs 2013).

Medications with a high pKa, such as barbiturates, are retained in the milk due to the lower pH of milk compared to maternal plasma. The high lipid solubility of central nervous system drugs may also result in higher levels of transfer from maternal plasma to milk. For iodides there exists active systems that pump iodides into maternal milk and this may result in unacceptably high infant intakes.

Conversely, highly protein-bound medicines such as ibuprofen or warfarin are unable to diffuse into human milk in significant amounts (Hotham and Hotham 2015). Medicines with a high volume of distribution (e.g. sertraline) have a lower concentration in milk (Hotham and Hotham 2015), and high molecular weight substances such as heparins or insulin enter the milk much less easily than low molecular weight compounds such as ethanol or caffeine (Hotham and Hotham 2015).

Maternal genetic polymorphisms can also influence the levels of medicines in human milk. Individuals who have an ultra-rapid metaboliser cytochrome P450 (CYP) 2D6 phenotype show increased production of morphine from codeine, which can result in high levels of morphine in milk (Madadi et al. 2007).

Adverse health effects

Medicines

In general, it is considered that the majority of lactating women take few medications and that most maternal medications do not cause serious adverse effects in breastfeeding infants (Anderson et al. 2016; Hale 2003; Ito et al. 1993; Soussan et al. 2014).

However a small number of medicines such as codeine, meperidine, iodine-containing compounds, gold salts and some antineoplastic agents have been reported to cause adverse effects in breastfed infants and some are contraindicated during breastfeeding.

These medications, together with some additional examples of medications reported to cause adverse effects in review articles (Anderson et al. 2016; Davanzo et al. 2013; Hale 2003; Sachs 2013), grouped by drug class, are listed in Table 1 of Appendix 1 together with their *'Hale's Medications and Mothers' Milk'* (Hale 2019) lactation risk categories.

The lactation risk categories range from compatible with breastfeeding (L1) to hazardous and contraindicated for breastfeeding mothers (L5). L5 is defined as *"Studies in breastfeeding mothers have demonstrated that there is significant and documented risk to the infant based on human experience, or it is a medication that has a high risk of causing significant damage to an infant. The risk of using the drug in breastfeeding women clearly outweighs any possible benefit from breastfeeding. The drug is contraindicated in women who are breastfeeding an infant."*

The Hale reference should be consulted for a complete list of medications classified as L5.

Drugs of abuse

Many drugs of abuse used by nursing mothers can be detected in milk (D'Apolito 2013; Keim et al. 2015). A number are psychoactive, raising concerns regarding exposure to the developing infant. Adverse effects on the breastfeeding infant have been associated with several drugs of abuse including alcohol, cocaine, heroin and marijuana (Sachs 2013).

Examples of substances of abuse for which adverse effects on breastfeeding infants and/or concerns have been reported are listed in Table 2, Appendix 1. These include drugs classified as L5 such as cocaine, heroin, LSD and methamphetamine.

Risk mitigation

International guidelines for milk banks recommend screening donors by asking questions regarding the use of medications or substances of abuse.

- Australian guidelines for operation of donor milk banks state that donors should be asked questions regarding the use of prescription medications (Hartmann et al. 2007). British guidelines indicate that donors should be asked if they are currently taking any medication or undergoing any other medical therapy (NICE 2010).
- US guidelines include a list of specific medications permitted during the donation of milk (HMBANA 2015); see Appendix 1, Table 3). Daily use of over-the-counter medications or systemic prescription medicines not listed as permitted during the donation of milk is one of the Exclusion Criteria listed by the Human Milk Banking Association of North America (HMBANA).
- The HMBANA guidelines note that other medications may be acceptable on a temporary basis if an appropriate deferral period is followed. For most drugs the deferral period would be five times the half-life of the medication, while for radiopharmaceuticals (e.g. radio-iodine) and live-virus vaccines, deferral periods of two months are recommended. Use of illegal drugs within the past 12 months and daily use of more than

a specified amount of alcohol are also triggers to exclude potential donors. A full list of substances listed in the HMBANA Exclusion Criteria is set out in Appendix 1, Table 4.

- The American Academy of Pediatrics notes that the pooling process with donor milk makes it very unlikely that non-infectious contaminants such as medications will represent a significant exposure risk (Committee on Nutrition, Section on Breastfeeding, Committee on Fetus and Newborn 2017). Pooling of human milk from multiple donors is common practice amongst many human milk banks, however some milk banks only pool milk from individual donors (Haiden and Ziegler 2016). The Australian Red Cross milk bank pasteurises human milk in single donor batches (Australian Red Cross 2018).

Evaluation of uncertainty

A literature search identified few published studies investigating levels of medicines or drugs of abuse in human milk or human milk products.

Three studies of milk samples provided to human milk banks (436 samples in total from a milk bank in Spain) or purchased over the internet (102 samples purchased online in the USA) did not detect illegal drugs or caffeine (Escuder-Vieco et al. 2014; Escuder-Vieco et al. 2016; Keim et al. 2015). Nicotine was detected in one sample (Escuder-Vieco et al. 2014). A further study of tobacco metabolites in 102 milk samples purchased online identified four samples from donors who were active smokers (Geraghty et al. 2015). Three of these donors had specifically stated they were 'smoke free'.

There is also uncertainty around the extent to which premature or neonatal infants may be more sensitive to low levels of medications or drugs of concern than older infants. Premature and newborn infants are considered to be at somewhat greater risk, while older infants are at somewhat lower risk due to their higher metabolic capacity (Hale 2019).

Risk characterisation

Medications

Most medications that are commonly consumed by lactating women are relatively safe for breastfed babies because the total exposure of an infant to the medicine is usually much less than the maternal dose.

However some medications have been associated with significant and documented risk to the infant based on human experience and are contraindicated during breastfeeding, such as those medications classified as lactation risk category L5. In the absence of risk mitigation measures such as donor screening and pooling processes for donor milk, these medicines are considered to be of medium to high risk in human milk and human milk products.

Drugs of abuse

Some drugs of abuse have also been associated with adverse effects in breastfeeding infants and, unlike medicines, provide no medical benefit that may be weighed against the potential risk to the infant. In the absence of risk mitigation measures, drugs of abuse that are categorised as contraindicated during breastfeeding, such as those listed as lactation risk category L5, are considered to be of medium to high risk in human milk and human milk products.

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Appendix 1

Table 1 Examples of medications for which adverse effects on the breastfeeding infant have been reported[#]

Medication	Reported effects/concerns	References	Lactation Risk Category (Hale 2019)
Analgesics			
Codeine	Associated with several reports of CNS depression, bradycardia, apnea, cyanosis, sedation and respiratory arrest in breastfeeding infants. A case of fatality was reported in an infant of a mother with ultrarapid CYP2D6 metabolism of codeine, due to the presence of a higher proportion of morphine from codeine metabolism in the milk than would normally be expected.	(Anderson et al. 2016; Madadi et al. 2008)	L4
Meperidine	Decreased alertness and respiratory depression	(Hale 2003; Wittels et al. 1997)	L4
Antidepressants, anxiolytics and antipsychotics			
Ethosuximide	Large RID (31.4 – 73.5%); considered potentially dangerous during lactation	(Davanzo et al. 2013)	L4
Zonisamide	Considered contraindicated during breastfeeding based on large RID (28.9 – 36.8%)	(Davanzo et al. 2013)	L4
Herbal products			
Borage	Contains hepatotoxic pyrrolizidine alkaloids (PAs)	(Hale 2019)	L5
Blue cohosh	Congestive heart failure in neonatal infant following maternal prenatal consumption	(Jones and Lawson 1998)	L5
Comfrey	Contains PAs; liver toxicity in experimental animals and humans; transfer of PAs into rat milk	(Hale 2019)	L5
Yohimbe	Fatalities	(Sachs 2013)	Not listed
Iodine containing compounds			
Iodine	Abnormal thyroid function tests; hypothyroidism	(Anderson et al. 2016; Hotham and Hotham 2015; National Library of Medicine (US) 2006)	L4
Amiodarone	Long half-life, hypothyroidism in one case involving exposure in utero and via milk	(Hotham and Hotham 2015; Plomp et al. 1992)	L5
Radiolabelled iodinated products	Concentrated in developing thyroid; radioactivity persists after imaging	(Sachs 2013)	L5
Other medications			
Radioactive compounds for diagnostic imaging	Breastfeeding should be interrupted to avoid infant exposures greater than 1 mSv. Recommended time periods range from none to greater than 3 weeks.	(Sachs 2013)	L2/L3/L4/L5
Antineoplastics	Leukopenia, bone marrow suppression	(Hotham and Hotham 2015)	L3/L4/L5
Gold salts	Rash, nephritis, haematological abnormalities	(Hotham and Hotham 2015)	L5

[#] In Australia not all these products are registered or are registered under a different name. For current registration status and tradenames, Australian consumers should consult the Australian Register of Therapeutic Goods (ARTG) of the Therapeutic Goods Administration (TGA) website at https://www.tga.gov.au/artg.

- L1 'Compatible': A drug that has been taken by a large number of breastfeeding mothers without any observed increase in adverse effects in the infant. Controlled studies in breastfeeding women fail to demonstrate a risk to the infant and the possibility of harm to the breastfeeding infant is remote, or the product is not orally bioavailable in an infant.
- L2 'Probably Compatible': A drug that has been studied in a limited number of breastfeeding women without an increase in adverse effects in the infant and/or the evidence of a demonstrated risk that is likely to follow use of this medication in a breastfeeding woman is remote.
- L3 'Probably Compatible': There are no controlled studies in breastfeeding women; however, the risk of untoward effects to a breastfed infant is possible, or controlled studies show only minimal non-threatening adverse effects. Drugs should be given only if the potential benefit justifies the potential risk to the infant. New medications that have absolutely no published data are automatically categorized in this category, regardless of how safe they may be.
- L4 'Potentially Hazardous': There is positive evidence of risk to a breastfed infant or to breast milk production, but the benefits from use in breastfeeding mothers may be acceptable despite the risk to the infant (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).
- L5 'Hazardous': Studies in breastfeeding mothers have demonstrated that there is significant and documented risk to the infant based on human experience, or it is a medication that has a high risk of causing significant damage to an infant. The risk of using the drug in breastfeeding women clearly outweighs any possible benefit from breastfeeding. The drug is contraindicated in women who are breastfeeding an infant.

Table 2 Examples of drugs of abuse for which adverse effects on breastfeeding infants have been reported

Drug	Reported effects/concerns	References	Lactation Risk Category (Hale 2019)
Alcohol	Sleep disturbances, reduced milk intake, impaired motor development, reduced postnatal growth, lower weight and verbal IQ	(Backstrand et al. 2004; Little et al. 2002; May et al. 2016; Mennella 2001; Mennella and Garcia-Gomez 2001)	L4
Cocaine	Seizures, hypertension, tachycardia, irritability, vomiting and diarrhoea	(Chaney et al. 1988; Chasnoff et al. 1987; Cressman et al. 2012; Winecker et al. 2001)	L5
Heroin	Lethargy, irritability, sleeplessness, restlessness hypertonia, increased respiration and heart rate, vomiting, poor feeding and weight gain, fever, convulsions, withdrawal symptoms	(Cobrinik et al. 1959; vande Velde et al. 2007)	L5
LSD	Potent hallucinogen	(Hale 2003; Sachs 2013)	L5
Marijuana	Decreased motor development, sedation, lethargy, less frequent and shorter feeding times. Infants may eliminate drug in urine for weeks after exposure. Insufficient data to evaluate effects on infant during lactation and breastfeeding	(ACGOG 2017; Astley and Little 1990; Bertrand et al. 2018; Garry et al. 2009; Sachs 2013)	L4
Methamphetamine	Possible fatality due to cardiopulmonary failure; presence in human milk for up to 48 hours after use	(Ariagno et al. 1995; Bartu et al. 2009)	L5
Phencyclidine	Potent hallucinogen; significant concentrations would likely transfer to infant.	(Hale 2003; Sachs 2013)	L5

Table 3 HMBANA guideline list of medications for which prospective donors do not need deferral[#]

Medications not requiring deferral (HMBANA 2015)		
Topical medications applied to the skin away from the breast*	Eye drops	Selected human immune globulin products: - Intravenous immunoglobulin - Rhogam - Tetanus - Rabies
Drugs given orally to mothers that are not absorbed (e.g. aluminium, calcium or magnesium antacids, stool softeners, fibres, simethicone)	Selected birth control methods: - Spermicides - Copper IUDs - Progestin-only or low-dose estrogen (<25 µg)	Selected supplements: - Vitamins - Minerals - Fish oil - Omega-3-fatty acids - Lecithin - Probiotics
Inhaled drugs for asthma, colds and allergies	Hormonal replacement drugs that are normally found in milk: - Thyroid replacement - Hydrocortisone - Insulin	
Non-sedating antihistamines: - Allegra® (fenofenadine) - Clarinex® (desloratadine) - Claritin® (loratidine) - Zyrtec® (cetirizine)	Inactivated vaccines, intranasal influenza vaccine, toxoids and allergy shots	

[#] In Australia not all these products are registered or are registered under a different name. For current registration status and tradenames, Australian consumers should consult the Australian Register of Therapeutic Goods (ARTG) of the Therapeutic Goods Administration (TGA) website at https://www.tga.gov.au/artg.
* Topical medications applied to breast should be washed off before expressing milk for donation

Table 4 Substances listed in HMBANA donor exclusion criteria

HMBANA exclusion criteria – substances (HMBANA 2015)	
Daily use of more than 1.5 ounces (approximately 44 mL) of hard liquor, 12 ounces (approximately 455 mL) of beer, 5 ounces (approximately 148 mL) of wine or 10 ounces (approximately 296 mL) of wine cooler in 24 hours*	Daily use of over-the-counter medications or systemic prescriptions not permitted for donor milk
Current use of marijuana for medical or casual use	Regular use of mega-dose vitamins (at least 20 times the recommended daily allowance) and/or herbal products used as medication, including vitamin/herb combinations
Use of tobacco or nicotine products including gum, patches or e-cigarettes. This includes casual or occasional smokers.	Use of illegal drugs within the past 12 months

* Milk banks will have a chart on specific elimination times per type of alcohol based on data from the US Centers for Disease Control and Prevention