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Caffeine Concentrations in Human Milk Donated to a Human Milk Bank in Japan

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Abstract

Background: Human milk banks have been established to provide human milk to preterm infants who are unable to obtain milk from their mothers. Donor screening methods vary, and prospective donors are commonly screened for drug and recreational substance use through behavioral screening. Although the risk of illegal drug consumption in Japan is extremely low, caffeine may be consumed unknowingly and can be found in human milk. To date, only a few reports have been conducted on the concentration of caffeine in donor milk.

Research Aim: This study aimed to examine the pre-pasteurization levels of caffeine in human milk donated to a milk bank in Japan.

Methods: This was a cross-sectional, observational study of caffeine concentrations in human milk donated to a human milk bank in Japan. Caffeine concentration in the donor milk was measured using high-performance liquid chromatography.

Results: Caffeine was detected in 70% of the donor milk samples ($N = 350$). The median (range) of caffeine concentration was 0.46 [< 0.10, 7.54] mg/L, and 64.0% of the samples had less than 1 mg/L of caffeine. The caffeine concentration varied widely among as well as within individuals.

Conclusion: The average caffeine concentration in Japanese donor milk samples was higher than that previously reported in samples from Spain, but the range was similar. Donors should be informed that caffeine intake should be within a moderate range, to further increase the safety of donor milk.

Keywords

breastfeeding, caffeine, donor milk, human milk banking, observational study

Background

Human milk banks are integral to the standard of care for medically fragile preterm neonates (Moro, 2018). In Japan, the first human milk bank was established in 2014, and two human milk banks (the Japan Human Milk Bank Association and the Nippon Foundation Human Milk Bank) are currently in operation (Mizuno et al., 2020). The Japan Pediatric Society recently recommended that donor human milk should be used as an alternative to mother's own milk (milk produced by a parent for their own infant) for preterm and very low birth weight infants if the supply of maternal milk is inadequate, despite receiving adequate support from medical staff for effective expression, or if the mother's milk cannot be given to the infant for any reason.

Donor selection and milk management are important because human milk delivered from a milk bank must be safe for infant consumption. Donor selection and screening methods vary among countries with different types of milk banks. Human milk banks screen and conduct serological tests for communicable diseases (e.g., human immune deficiency virus, Hepatitis B and C, syphilis, human T-lymphotropic virus Type I and II, and Creutzfeldt-Jakob disease; PATH, 2019). Prospective donors are also commonly screened for drug and recreational substance use through behavioral screening. However, donated milk is not routinely tested for contamination with pharmaceuticals and other drug substances (Palmquist et al., 2019). The standard operating procedure for human milk banks in Japan is based on the international guidelines (Mizuno et al., 2020). Mothers who register as donors should undergo medical check-ups and serum screening tests for viruses and are taught how to express, preserve, and deliver milk. In Japan, donation to milk banks is an act of complete goodwill and is not rewarded. As illegal drug intake is extremely rare in Japan compared with other countries, the likelihood of illegal drugs entering donor human milk is low (Japan Ministry of Health, Labour and Welfare, 2018).

Caffeine, a central nervous system stimulant, is present in coffee (ground coffee 60 mg/150 ml, instant coffee (66 mg/150 ml), green tea (bags 34 mg/250 ml, leaf 41 mg/250 ml), chocolates (bitter chocolate 67 mg/100 g, milk chocolate 21 mg/100 g), cacao (5 mg/250 ml), cola-like drinks (25 mg/250 ml), and energy drinks (80 mg/250 ml; Błaszczyk-Bębenek et al., 2018; Willson, 2018). Therefore, unlike nicotine and alcohol, mothers may ingest caffeine unintentionally. Recommendations regarding caffeine intake for breastfeeding women are limited. Further, they are inconclusive and of limited quality (McCreedy et al., 2018). However, care must be taken regarding caffeine concentration in mother's milk, since a high dose causes irritability in infants, and the half-life of caffeine in early infants is much longer than that in adults (Nehlig, 2018). In neonates, caffeine plasma half-life is prolonged and reaches 65 to 103 hr. Caffeine is used as a treatment for apnea in preterm infants; hence, if there is already caffeine in the milk they are consuming, it is necessary to be wary of caffeine overdosage. While it is important to know how much caffeine is in the milk provided by milk banks, only a few studies—all from Spain—have reported on caffeine levels (Escuder-Vieco et al., 2014; Marchei et al., 2011). As there may be variations in caffeine intake by country and caffeine levels in human milk, this study aimed to examine the pre-pasteurization levels of caffeine in human milk donated to a milk bank in Japan.

Key Messages

- No prior research has been conducted to detect caffeine concentrations in human milk donated to milk banks in Japan.
- We examined the pre-pasteurization levels of caffeine in human milk donated to a milk bank in Japan.
- Caffeine was detected in 70% of the donor milk samples.
- Donors should be informed to consume caffeine within a moderate range.

Methods

Research Design

This was a prospective cross-sectional observational study of caffeine in human milk donated to a human milk bank in Japan prior to the pasteurization process. The design enabled us to investigate the current caffeine concentration in donor milk in Japan. The study protocol was approved by the Institutional Review Board of Kagawa University (approval number 2020055).

Setting and Relevant Context

In many countries, human milk banks have been established and institutionalized to increase the availability and accessibility of donor human milk for preterm infants. The number of these banks is growing worldwide (Moro, 2018; Palmquist et al., 2019). In Japan, the first human milk bank for preterm infants was opened in 2014 at the Showa University Koto Toyosu Hospital. In 2017, the Japanese Human Milk Bank Association was established, which began supplying human donor milk to facilities throughout the country. To ensure the safety of infants, human milk banks conduct a bacterial culture test of donated human milk to confirm the absence of pathogens. The samples are pasteurized at 62.5 °C for 30 minutes, followed by another bacterial culture test. After confirming that no bacteria of any type are present, the samples are frozen and stored for babies in need before being delivered nationwide. The donor's drug history, smoking status, alcohol consumption, various viral antibody tests, and life history are thoroughly assessed to ensure safety. Donors are bona fide volunteers, and no money is exchanged for milk donation. The donors also report their physical condition, drug usage, and other such factors at the time of expression.

Sample

The donors who registered at the Japan Human Milk Bank Association and donated their milk from June to October 2020 were included in the study. In Japan, term donors typically self-register through human milk bank websites, while preterm donors are typically referred by medical staff in neonatal intensive care units (NICUs).

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Donor health conditions were confirmed through a health checklist, and donors underwent screening which included a detailed medical history review, physical examinations, and laboratory assessments, all in accordance with the Guidelines for the Establishment and Operation of a Donor Human Milk Bank (Mizuno et al., 2020). However, caffeine intake was not recorded during this study period. Donors who did not meet the eligibility criteria were excluded from donating milk. The exclusion criteria included inappropriate delivery of donor milk (maintained at room temperature [$n=17$] or refrigerated milk [$n=11$]).

Donor milk was stored in approximately 100 ml milk storage bags and then transported in a frozen state to the milk banks. The milk donated by mothers was sampled from each milk storage bag prior to pasteurization. The frozen donated milk was refrigerated and defrosted. Subsequently, the thawed milk was stirred well by hand. After transferring the human milk from the milk bags to a bottle for pasteurization, 200 µl of the human milk remaining in the bags was placed in a microtube and frozen by the technical staff of the Human Milk Bank Association until caffeine level measurement took place.

To distinguish the milk from each donor and to track the number of milk samples per individual participant, each milk sample was assigned a donor identification number. Even if the milk was divided into two milk bags for each expression session, only one sample was collected. Typically, in Japan, if a milk donation has a very large number of bacteria, it is used for research purposes only until firm measures to reduce bacteria are established. In this study, we sampled both rejected and non-rejected human milk. The human milk rejected as donor milk was stored in the freezer in bags until caffeine levels were measured.

In total, there were 350 human milk samples from 43 donor samples. Published studies of caffeine concentration in donated human milk included 36 to 400 milk samples from 34 to 63 donors (Escuder-Vieco et al., 2014; Marchei et al., 2011). The paper published by Escuder-Vieco et al. in 2014 had the highest number of milk samples among those published to this point; those 400 milk samples were provided by 63 mothers. Our study's sample size was consistent with the literature and achieved data saturation.

Measurement

The collected information from the participants included the gestation and source of donor registration (referred by a NICU doctor or through the Internet). We calculated the number of milk samples obtained from each donor.

Caffeine was assayed using a previously reported high-performance liquid chromatography (HPLC) method (Berlin et al., 1984). The sample fluid of 200 µl was stirred with 2 ml acetonitrile and shaken for 5 minutes. After centrifugation at 606 g, 20 µl of the supernatant was injected into the reversed-phase HPLC system, which consisted of an LC20AB pump (Shimadzu, Kyoto, Japan) and SIL20AC autosampler (Shimadzu, Kyoto, Japan). A Kinetex C18 column (5 µm, 150 × 4.5 mm) (Phenomenex, California, USA) and a CTO20AC column oven (Shimadzu, Kyoto, Japan) were used. The flow rate was 1.0 ml/minute, and a mixture of 90% 0.1 M sodium acetate buffer (pH 4.0) and 10% acetonitrile was used. Further, 8-chlorotheophyline was used as the internal standard. The detector was SPD20A (Shimadzu) and monitoring was done at 280 nm.

Standard curves were constructed using caffeine concentrations of 0 to 5.0 mg/L in the sample fluid. The limit of detection was 0.1 mg/L. The recovery rate was 10.6%, repeatability (percent relative standard deviation) was 8.1%, and intermediate precision (percent relative standard deviation) was 0.64%.

Data Collection

Data were collected from June 2020 to October 2020. During the donor registration process, staff from the Human Milk Bank Association informed all donors about the usage of their donated milk for research. The purpose of this study and the details of the research were presented online in an opt-out format. Written, informed consent for the use of human milk and information for the research was obtained from all Human Milk Bank Association donors before data collection.

To maintain confidentiality, the milk bank staff allocated a unique number to each donor, and other researchers were unaware of any personal identifying information. Moreover, the Japan Human Milk Bank Association data were stored on a personal computer that was never connected to the internet. The milk samples were obtained at the Japan Human Milk Bank Association, and the experiment was performed in the research laboratory of the Department of Pediatrics, Kagawa University. The anonymized donor information and caffeine levels in the samples were analyzed at the Department of Pediatrics, Kagawa University.

Data Analysis

Demographic variables of donor samples, such as the samples per mother or gestation and source of registration are described using numbers and percentages. Demographic variables of the milk samples are also presented in numbers and percentages. Caffeine concentrations in human milk are described using medians and ranges. Because the caffeine concentration data were not normally distributed, the sample numbers were plotted using a histogram to show the distribution. Therefore, the Wilcoxon signed-rank test was used to compare the data directly. The number of samples for each donor was different; therefore, the interquartile range was represented by a box-and-whisker diagram to show the distribution for each donor. Pearson's $\chi 2$ test was used to examine the differences in categorical data. Data were analyzed using JMP Pro software (Version 16.1.0, SAS).

Table 1. Characteristics of Donor Samples (N = 43) and Donor Human Milk Samples (N = 350).

Characteristics	Donor Samples *n* (%)	Milk Samples *n* (%)
Samples per participant		
1	13 (30)	13 (4)
2-9	19 (44)	78 (22)
10-50	10 (23)	187 (53)
> 50	1 (2)	72 (20)
Participants and their infants		
Gestation		
preterm	11 (26)	101 (29)
term	32 (74)	249 (71)
Source of donor registration		
NICU[a]	15 (35)	141 (40)
Community[b]	29 (67)	209 (60)

Note. [a]The donors' infants were admitted to the NICU. [b]The participant applied through the Internet.

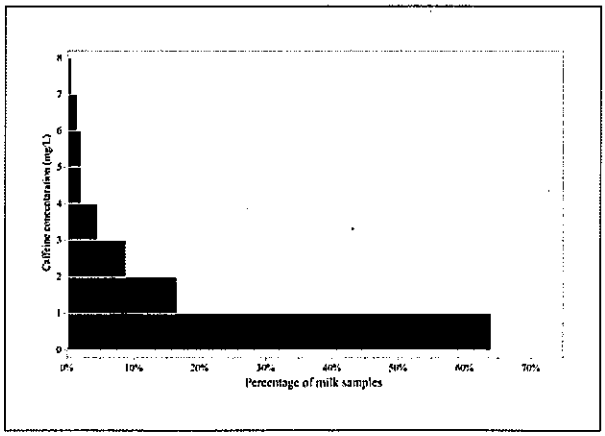

Figure 1. Distribution of Caffeine Concentration in Donated Human Milk (N = 350).

Results

Sample Characteristics

The characteristics of the participants and the donated milk are presented in Table 1. In total, 350 human milk samples were collected from 43 participants. A total of 172 samples (49%) were deemed unsuitable for use as donor milk, while 178 (51%) samples were considered suitable. Human milk identified as suitable for donation was sent for pasteurization after the collection of samples for caffeine content testing, whereas milk unsuitable for donation was exclusively utilized for this study.

Analysis of the Caffeine Concentration in Human Milk

Caffeine was detected in 70% (n = 245) of donor milk samples, with large variability (median 0.46, range [< 0.1, 7.54] mg/L). Further, 64.0% of milk samples had less than 1 mg/L of caffeine (Figure 1). The range of caffeine concentrations in human milk varied between participants (Figure 2). Especially in the case of Donor No. 28, who had the widest range of concentrations, caffeine concentrations ranged from 0.19 mg/L to 7.54 mg/L.

There were no significant differences in the median caffeine levels found in donor milk, regardless of donor registration source (NICU, median 0.51 mg/L, range [< 0.1, 7.16]; community, median 0.46 mg/L [< 0.1, 7.54]), or whether the milk came from participants who had given birth to preterm or term infants (median mg/L 0.5, range [< 0.1, 7.16]; median 0.46 mg/L, range [< 0.1, 7.54]). Human milk that was determined to be unsuitable as donor milk, owing to previous higher bacterial counts than permitted by the criteria in the preliminary bacterial test, had more samples with human milk caffeine concentrations above 5 mg/L than human milk that went to pasteurization as donor milk: 12/172 and 2/178 respectively, $p < 0.0052$, $\chi 2$ (1) = 7.804.

Discussion

The administration of caffeine to preterm infants may impact clinical symptoms, and it is essential to be aware of the caffeine intake from donor milk. This knowledge is crucial to enhance the safety of human milk provided by milk banks. Our study reported a higher proportion of caffeine-containing milk samples (70%) than did previous studies, with a higher average level. Only three studies, all of them conducted in Spain, have reported caffeine levels in donor milk (Table 2; Escuder-Vieco et al., 2014; Marchei et al., 2011). The authors used validated reversed-phase liquid chromatography-tandem mass spectrometry to determine the concentration of caffeine in the milk samples.

Escuder-Vieco et al. (2014) reported that caffeine was detected in 45.3% of donor milk. There are no reports of Japanese people consuming more caffeine, as coffee consumption in this population is low. Further, Japanese people often prefer leaf tea and consume it daily; hence, it is possible that they unintentionally consume caffeine from other food sources. The median caffeine concentration in human milk in Japan is lower than the average in our study. We also confirmed that the range of caffeine concentration is similar to that reported in Spain, although with a larger standard deviation (*SD*).

There were also inter- and intra-individual differences in caffeine concentrations in our human milk samples. Upon consumption, caffeine is quickly absorbed from the gastrointestinal tract. After 60 to 120 min, it reaches the maximum level in human milk, with a half-life of 4.9 hr in adults (Hale, 2022). Daily caffeine intake and the time between caffeine intake and expression may be responsible for the difference

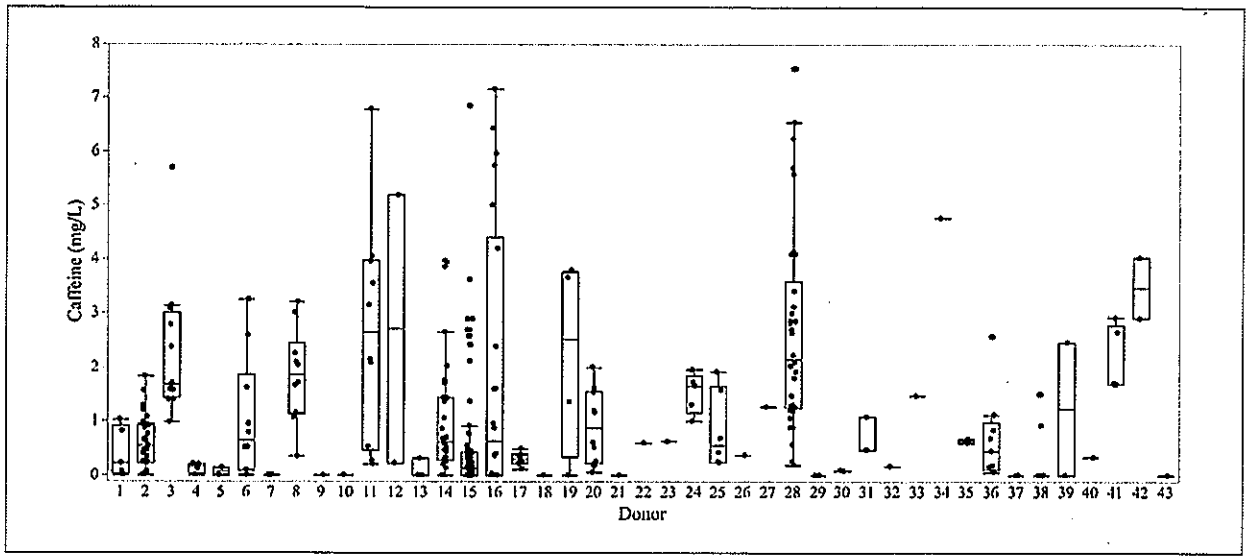

Figure 2. Variation in Individual Milk Caffeine Concentrations.

Table 2. Comparison of Caffeine Concentrations in Donor Milk.

	Caffeine Concentration (mg/L)				
Milk Samples (*n*)	mean (*SD*)	median	range	Country	Reference
-	-	-	ND-2.12	Spain	Marchei et al. (2011)
400	0.45 (0.78)	-	ND-7.56	Spain	Escuder-Vieco et al. (2014)
36	0.27 (0.56)	-	ND-2.24	Spain	Escuder-Vieco et al. (2016)
350	1.10 (1.49)	0.46	ND-7.54	Japan	our study

Note. ND = not detected.

in caffeine levels in human milk. However, this was unclear because the intake of caffeine-containing foods and beverages was not considered in this study.

We previously conducted a study of human milk caffeine concentrations at one month postpartum (mean 0.47, *SD* = 0.69; median 0.14. range [< 0.1, 2.39]; Kozai et al., 2019), and the concentrations were lower than those observed in this study. Donor registration is possible one month postpartum, and many donors are several months postpartum. A study of 100 lactating women in Poland reported higher caffeine concentrations during the later postpartum period (Purkiewicz et al., 2022). We believe that the donors in our study were more likely to have increased caffeine intake because of the number of postpartum days. Purkiewicz et al. reported that factors such as place of residence, level of education, age, and stage of lactation influenced the nutritional choices of breastfeeding women, which, in turn, had an effect on the levels of caffeine and its metabolites in human milk (Purkiewicz et al., 2022). It has also been reported that there is potential interindividual variability in caffeine metabolism (Nehlig, 2018).

These high concentrations were similar to those reported in samples from Spain (Escuder-Vieco et al., 2014). The authors of the paper from Spain reported that, based on the concentrations found in the milk, including the highest concentrations, the potential exposure of an infant to caffeine ingested through human milk is not of concern. Caffeine is also used as a treatment for apnea in preterm infants. The recommended loading dose of caffeine citrate for apnea of prematurity is 20 mg/kg, followed by 5 to 10 mg/kg/d maintenance. In other words, the loading dose for anhydrous caffeine is 10 mg/kg, and the maintenance dose is used at 2.5 to 5 mg/kg/d. If an infant drinks 150 ml/kg/d of human milk, it would ingest 1.1 mg/kg/d of caffeine from human milk at the highest caffeine concentration in the human milk (7.5 mg/L). Only two of the 178 human milk samples, with concentrations greater than 5 mg/L, were considered suitable as donor milk in the prior bacterial screening, compared with 12 of 172 unsuitable samples. The higher caffeine concentration in milk from donors with higher bacterial counts might be related to the participant's behavioral patterns.

Purkiewicz studied a detailed 3-day caffeine intake history and reported that higher reported caffeine intake corresponded to higher caffeine concentration in human milk (Purkiewicz et al., 2022). In contrast, Escuder-Vieco et al. (2014) reported that a lifestyle questionnaire is reliable for the assessment of illicit drug use by donors to a human milk bank; however, there are certain limitations regarding the disclosure of the consumption of caffeinated beverages. Furthermore, they investigated caffeine levels in human milk and hair samples from donors (Escuder-Vieco et al., 2016). They stated that almost all donors consumed caffeinated beverages, and it might be advisable for professionals from human milk banks to remind donors to reduce their consumption of caffeinated beverages.

We recommend that donors should be asked about caffeine intake and informed that caffeine intake should be within a moderate range to further increase the safety of donor milk. In response to the findings of this research, the Japan Human Milk Bank Association added a warning to the donor registration process about the consumption of caffeine-containing beverages, not limited to coffee. In the future, we aim to investigate whether the awareness campaign will lead to a decrease in caffeine concentrations in donor milk.

Limitations

This study has several limitations. We did not have access to detailed donor information, such as caffeine intake history, residence, postpartum duration, and parity. The caffeine concentration in human milk is related to the amount of caffeine ingested by the parent. Caffeine intake is regional in nature—this study's results do not reflect the trends of Japan as a whole, as there may be more donors from areas near the Japan Human Milk Bank Association. At a constant amount of ingested caffeine, the longer the time between ingestion and expression, the lower the caffeine concentration in human milk. Primiparas parents and those early in the postpartum period may be more concerned about caffeine intake; however, we did not have this information for the study. Therefore, we were unable to fully discuss the differences in caffeine concentrations.

The number of bacteria may have affected the concentration of caffeine. It is known that some bacteria can decompose and metabolize caffeine (Lin et al., 2023); therefore, if such bacteria were present, the concentration of caffeine may have been lower. In this study, we did not conduct detailed examinations, such as the number and recent types of bacteria in human milk, nor did we pre-examine the extent to which bacteria may influence caffeine concentration. Furthermore, we did not use pasteurized human milk in this study because it needed to be handled as cleanly as possible after pasteurization. Since human milk delivered to preterm infants is post-pasteurization, it should be measured in the state in which it is actually used. We suggested that future studies use pasteurized milk.

Conclusion

The average concentrations in this study were higher than those previously reported; however, the highest concentrations were similar across studies. Although the highest concentrations of caffeine in this study would not significantly affect infants, we should inform donors that caffeine intake should be within a moderate range to further increase the safety of donor milk.

Author Contributions

Shoko Kozai: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Writing – original draft; Writing – review & editing.
Ikuko Kato: Conceptualization; Formal analysis; Funding acquisition; Investigation; Project administration; Writing – original draft; Writing – review & editing.
Noriko Mizuno: Investigation; Methodology; Writing – review & editing.
Naho Nakamura: Investigation; Methodology; Writing – review & editing.
Hitoshi Okada: Investigation; Methodology; Writing – review & editing.
Katsumi Mizuno: Conceptualization; Writing – review & editing.
Takashi Kusaka: Conceptualization; Supervision; Writing – review & editing.

Disclosures and Conflicts of Interest

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: KM received consulting fees from the Japan Human Milk Bank Association. NM and NN are employed by the Japanese Human Milk Bank Association.

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References

Berlin, C. M., Jr., Denson, H. M., Daniel, C. H., & Ward, R. M. (1984). Disposition of dietary caffeine in milk, saliva, and plasma of lactating women. *Pediatrics, 73*(1), 59–63.

Błaszczyk-Bębenek, E., Piórecka, B., Kopytko, M., Chadzińska, Z., Jagielski, P., & Schlegel-Zawadzka, M. (2018). Evaluation of caffeine consumption among pregnant women from Southern Poland. *International Journal of Environmental Research and*

Public Health, *15*(11), Article 2373. https://doi.org/10.3390/ijerph15112373

Escuder-Vieco, D., Garcia-Algar, O., Joya, X., Marchei, E., Pichini, S., Pacifici, R., & Pallas-Alonso, C. R. (2016). Breast milk and hair testing to detect illegal drugs, nicotine, and caffeine in donors to a human milk bank. *Journal of Human Lactation*, *32*(3), 542–545. https://doi.org/10.1177/0890334416648110

Escuder-Vieco, D., Garcia-Algar, O., Pichini, S., Pacifici, R., Garcia-Lara, N. R., & Pallas-Alonso, C. R. (2014). Validation of a screening questionnaire for a human milk bank to determine the presence of illegal drugs, nicotine, and caffeine. *The Journal of Pediatrics*, *164*(4), 811–814. https://doi.org/10.1016/j.jpeds.2013.11.043

Hale, T. W. (2022). *Hale's medications & mothers' milk 2023: A manual of lactational pharmacology* (T. W. Hale & K. Krutsch, Eds.; 20th ed.). Springer.

Japan Ministry of Health, Labour and Welfare. (2018). *Lifetime experience rates by drug in major countries*. https://www.mhlw.go.jp/bunya/iyakuhin/yakubuturanyou/torikumi/dl/index-05.pdf

Kozai, S., Kato, I., Tanaka, A., Kawanishi, K., Okada, H., & Kusaka, T. (2019). 授乳期における母親のカフェイン摂取の意識調査と母乳中のカフェイン濃度について [Maternal attitudes toward caffeine intake and caffeine concentration in breastmilk during lactation]. 日本小児臨床薬理学会雑誌 [*Journal of the Japanese Society of Pediatric Clinical Pharmacology*], *32*(1), 33–38.

Lin, Z., Wei, J., Hu, Y., Pi, D., Jiang, M., & Lang, T. (2023). Caffeine synthesis and its mechanism and application by microbial degradation, a review. *Foods*, *12*(14), Article 2721. https://doi.org/10.3390/foods12142721

Marchei, E., Escuder, D., Pallas, C. R., Garcia-Algar, O., Gomez, A., Friguls, B., Pellegrini, M., & Pichini, S. (2011). Simultaneous analysis of frequently used licit and illicit psychoactive drugs in breast milk by liquid chromatography tandem mass spectrometry. *Journal of Pharmaceutical and Biomedical Analysis*, *55*(2), 309–316. https://doi.org/10.1016/j.jpba.2011.01.028

McCreedy, A., Bird, S., Brown, L. J., Shaw-Stewart, J., & Chen, Y. F. (2018). Effects of maternal caffeine consumption on the breastfed child: A systematic review. *Swiss Medical Weekly*, *148*, Article w14665. https://doi.org/smw.2018.1466510.4414/smw.2018.14665

Mizuno, K., Shimizu, T., Ida, S., Ito, S., Inokuchi, M., Ohura, T., Okumura, A., Kawai, M., Kikuchi, T., Sakurai, M., Sugihara, S., Suzuki, M., Takitani, K., Tanaka, D., Mushiake, S., Yoshiike, N., Kodama, H., Okada, K., Tsutsumi, C., . . .Sugiyama, A. (2020). Policy statement of enteral nutrition for preterm and very low birthweight infants. *Pediatrics International*, *62*(2), 124–127. https://doi.org/10.1111/ped.14067

Moro, G. E. (2018). History of milk banking: From origin to present time. *Breastfeeding Medicine*, *13*(S1), S16–S17. https://doi.org/10.1089/bfm.2018.29077.gem

Nehlig, A. (2018). Interindividual differences in caffeine metabolism and factors driving caffeine consumption. *Pharmacological Reviews*, *70*(2), 384–411. https://doi.org/10.1124/pr.117.014407

Palmquist, A. E. L., Perrin, M. T., Cassar-Uhl, D., Gribble, K. D., Bond, A. B., & Cassidy, T. (2019). Current trends in research on human milk exchange for infant feeding. *Journal of Human Lactation*, *35*(3), 453–477. https://doi.org/10.1177/0890334419850820

PATH. (2019). *Strengthening human milk banking: A resource toolkit for establishing and integrating human milk bank programs—A global implementation framework*. (Version 2.0). https://www.path.org/programs/maternal-newborn-child-health-and-nutrition/strengthening-human-milk-banking-resource-toolkit-0/

Purkiewicz, A., Pietrzak-Fiećko, R., Sörgel, F., & Kinzig, M. (2022). Caffeine, paraxanthine, theophylline, and theobromine content in human milk. *Nutrients*, *14*(11), Article 2196. https://doi.org/10.3390/nu14112196

Willson, C. (2018). The clinical toxicology of caffeine: A review and case study. *Toxicology Reports*, *5*, 1140–1152. https://doi.org/10.1016/j.toxrep.2018.11.002