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Predicted Mercury Concentrations in Hair From Infant Immunizations: Cause for Concern☆

Lyn Redwood*, Sallie Bernard, David Brown

Coalition for Safe Minds, 14 Commerce Drive, Cranford, NJ 07016, USA

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Abstract

Mercury (Hg) is considered one of the worlds most toxic metals. Current thinking suggests that exposure to mercury occurs primarily from seafood contamination and rare catastrophic events. Recently, another common source of exposure has been identified. Thimerosal (TMS), a preservative found in many infant vaccines, contains 49.6% ethyl mercury (EtHg) by weight and typically contributes 25 μg. of EtHg per dose of infant vaccine. As part of an ongoing review, the Food and Drug Administration (FDA) announced in 1999 that infants who received multiple TMS-preserved vaccines may have been exposed to cumulative Hg in excess of Federal safety guidelines. According to the centers for disease control (CDC) recommended immunization schedule, infants may have been exposed to 12.5 μg Hg at birth, 62.5 μg EtHg at 2 months, 50 μg EtHg at 4 months, 62.5 μg EtHg at 6 months, and 50 μg EtHg at approximately 18 months, for a total of 237.5 μg EtHg during the first 18 months of life, if all TMS-containing vaccines were administered. Neurobehavioral alterations, especially to the more susceptible fetus and infant, are known to occur after relatively low dose exposures to organic mercury compounds. In effort, to further elucidate the levels of ethyl mercury resulting from exposure to vaccinal TMS, we estimated hair Hg concentrations expected to result from the recommended CDC schedule utilizing a one compartment pharmacokinetic model. This model was developed to predict hair concentrations from acute exposure to methymercury (MeHg) in fish. Modeled hair Hg concentrations in infants exposed to vaccinal TMS are in excess of the Environmental Protection Agency (EPA) safety guidelines of 1 ppm for up to 365 days, with several peak concentrations within this period. More sensitive individuals and those with additional sources of exposure would have higher Hg concentrations. Given that exposure to low levels of mercury during critical stages of development has been associated with neurological disorders in children, including ADD, learning difficulties, and speech delays, the predicted hair Hg concentration resulting from childhood immunizations is cause for concern. Based on these findings, the impact which vaccinal mercury has had on the health of American children warrants further investigation.

Keywords: Mercury; Vaccine; Neurotoxicity; Thimerosal; Learning disabilities

INTRODUCTION

Mercury is a potent human toxicant that has long been the source of serious health problems. Toxicologic manifestations of mercury exposure have become known through hundreds of years of medicinal applications, industrial uses, and environmental tragedies. After exposure to mercury, deposition has been found in all body tissue. Therefore, it is not surprising that the clinical manifestations of mercury toxicity involve multiple organ systems with variable features and intensity. These manifestations vary by the route of exposure, the chemical form of mercury involved, the acuity of the intoxication, and the age at exposure (Goldfrank et al., 1998). Also, a mercury dose given acutely may produce toxic effects whereas the same dose distributed over a period of time may give no evidence of toxicity (Koos and Longo, 1976).

☆Modeled hair mercury concentrations arising from exposure to mercury-containing infant vaccines show elevations in excess of Federal safety guidelines for extended periods and with several peaks. Elevations over guidelines occur during critical stages of infant development. Predicted Hg levels are cause for concern, and further research is warranted.

* Corresponding author. Tel.:+1-908-276-8032; fax: +1-908-276-1301.
E-mail address: tlredwood@mindspring.com (L. Redwood).

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Both adult and fetal brains are susceptible to Hg toxicity, but the developing nervous system appears to be much more sensitive (NAS, 2000). The structure of the central nervous system is more complex than any other organ, and it is subject to continual changes during maturation. This maturation takes place not only during the prenatal period, but postnatally as well (Gilbert and Grant-Webster, 1995). Therefore, birth does not constitute a significant event in the development of the brain. Exposures to mercury during these critical periods of development appear to interfere with the growth and migration of neurons, with the potential to cause irreversible damage to the central nervous system (EPA, 1997).

Recent investigations in human populations have identified adverse effects on development associated with levels of mercury exposure that had previously been considered safe. Neurodevelopmental effects in children, particularly in the domains of language, attention, and memory, were documented to occur from low-level prenatal exposures (Grandjean et al., 1998). Based on these and similar findings in exposed populations, the NAS recently confirmed the EPA reference daily dose (RfD) of 0.1 μg/Hg/kilogram of body weight per day, as being scientifically justifiable for the protection of public health (NAS, 2000).

Current Hg investigations have focused primarily on methyl mercury from fish contamination and from rare occupational or catastrophic events. Recently, another source of exposure has been identified. Thimerosal, a preservative utilized in the production of biological and pharmaceutical products including infant vaccines, contains 49.6% ethyl mercury by weight. The amount of thimerosal typically utilized in a single dose of infant vaccines varies from 25 to 50 mcg, which results in a 12.5–25 mcg ethyl mercury exposure per dose of vaccine. It is currently recommended that several infant vacines be administered at one visit. Therefore, it is possible for infants to be exposed to acute bolus exposures from 50 to 62.5 mcg of ethyl mercury at 2, 4, and 6 months of age from vaccine administration with a cummulative maximun exposure of 187.5 mcg of ethyl mercury the first 6 months of life, in the event that all thimerosal preserved vaccines were administered. Additionally, this exposure to ethyl mercury from vaccine administration results in intermittent bolus exposures, rather than small daily exposures over a longer period of time, which may result in increased toxicity.

Like MeHg, EtHg is an organic mercury compound, considered by some researchers to have similar toxic properties to MeHg (Magos et al., 1985). Unfortunately, there is a paucity of data on the metabolism, excretion and toxicity of ethyl mercury although there have been limited case reports of toxicity and death following massive inadvertant exposures.

As part of an ongoing review of health products required by the FDA Modernization Act of 1997, cumulative exposure to ethyl mercury from pediatric vaccines was determined. From this review, the FDA determined that infants who received multiple TMS-containing vaccines in the first 6 months of life were exposed to cumulative Hg in excess of the EPA RfD of 0.1 μg/Hg/kg per day (Halsey, 1999).

The EPA guidelines were derived from contaminated fish or grain eating populations in which the actual Hg intake was difficult to establish. To determine the benchmark RfD, an observed biomarker, maternal hair Hg concentrations in the effected populations, was converted into an oral daily Hg intake with a pharmacokinetic model incorporating a chronic exposure scenario. In the case of ethyl mercury exposure from vaccines, the Hg intake levels and timing are known, based on manufacturers' product formulation data and the CDC immunization schedule.

Thus, to assess the potential impact of Hg from pediatric vaccines, we have taken the known EtHg intake as established by manufacturers and the CDC immunization schedule and have estimated the resulting hair Hg concentrations utilizing a pharmacokinetic model incorporating repeated, acute exposures. The purpose was to determine if the resulting key biomarker, hair mercury concentrations, would be predicted to exceed EPA action levels and if so, for what time period.

MATERIALS AND METHODS

The Ginsberg model (Ginsberg and Toal, 2000) was utilized to predict infant hair Hg concentrations after exposure to bolus doses of ethyl mercury following vaccinal TMS exposure. The one compartment biokinetic model is a useful tool for exploring how a key biomarker, hair, may be affected by intermittent acute dosing exposures of Hg. This model simulates Hg uptake, distribution and elimination according to first order (nonsaturable) kinetic processes. This model was run in Excel™ for acute and repeated dosing scenarios, with the resulting body burden residual added to each additional exposure. Although the two compartment model may be more appropriate to simulate Hg concentrations in blood following acute exposures, hair mercury, a longer term indicator of dose exposure, has

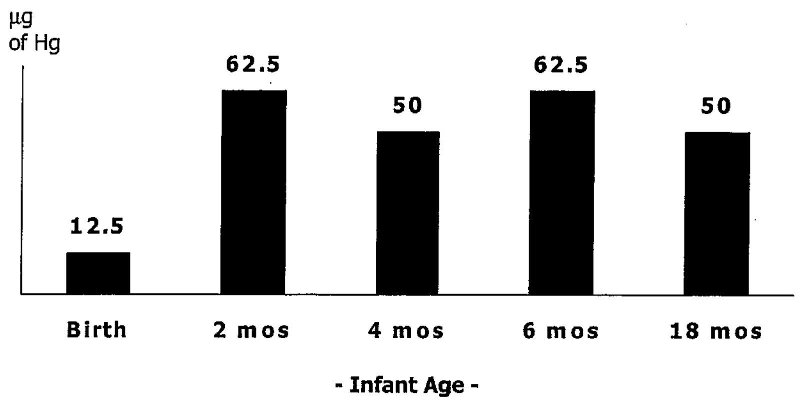

Fig. 1. Mercury exposure by age of child from thimerosal-containing vaccines (DTP/DtaP, HiB, Hepatitis B) based on the CDC recommended schedule in place in 1999. Cumulative Hg at 6 months is 187.5 µg and at 18 months is 237.5 µg. Source: Vaccine Safety Institute.

been the traditional model used in epidemiological studies of neurodevelopmental effects. Therefore, it was selected as the appropriate biomarker. In previous evaluations, the model's predictiveness has been confirmed against appropriate datasets (Ginsberg and Toal, 2000).

The CDCs 1999 recommended vaccine schedule was used to determine the timing of vaccine administration for the first 2 years of life. Levels of exposure to ethyl mercury from TMS in the recommended vaccines were established from the PDR and published vaccine manufacturers' data and assumed TMS-containing formulations were administered. The vaccines involved, the amount of Hg given, and the timing of exposure are shown in Fig. 1 (Halsey, 1999). Two sets of scenarios were modeled. One set assumed normal adult Hg excretion rates with a half life of 50 days (NAS, 2000). The other set assumed no excretion for the first 6 months of life and then normal adult rates after this point. Several studies have suggested that neonates up to 6 months of age have low or no Hg excretion due to immature hepatic function, low bile production, and insufficient bile glutathione which binds the mercury (Thomas et al., 1982; Ballatori and Clarkson, 1982; Rowland et al., 1980). All scenarios were modeled based on the weight of children at birth and at 2, 4, 6, 12, and 18 months of age for the 5th, 50th and 95th weight percentiles obtained from the Department of Health, Education and Welfare standardized growth charts. For the no excretion scenarios up to 6 months of age, the effect of not factoring in interim body weights would be to reduce the downward slope of the post-injection curves by a maximum of 20%. For the adult excretion scenarios as well as the data for the no excretion scenarios after 6 months of age, the effect would be a shift in the downward slope by less than 1% in most cases and in all cases by no more than 5%. Other variables used for the modeled scenarios were (a) blood volumes of 65 cc per kg of body weight as published in Nelson's Textbook of Pediatrics; (b) complete (100%) absorption of the EtHg due to injection; and (c) hair to blood concentration ratio of 250:1 and 5% of dose distributed to blood (as described by NAS, 2000, p.108).

The analysis of the data addresses only the known exposure source, TMS from vaccines. There was no attempt to factor into the model other sources of exposure, either environmental (pre- or postnatal) or through dietary exposure in the mother's milk.

RESULTS

The results of the model calculations are given in graphic form in Figs. 2–7. Figs. 2–4 represent the "no excretion" scenarios for infants in the 5th, 50th, and 95th percentile weight categories. Figs. 5–7 represent the "adult excretion" scenarios for the same weight percentiles.

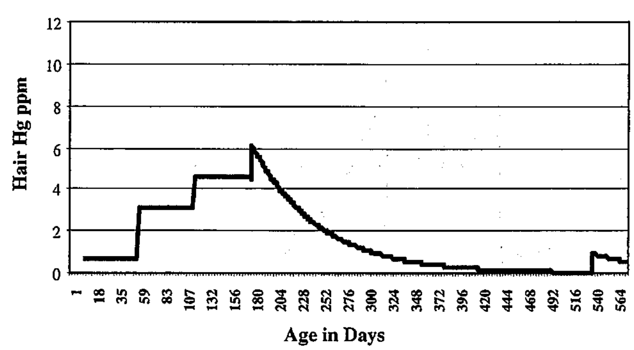

Fig. 2. Infant/child of 95th percentile body weight (no excretion first 6 months).

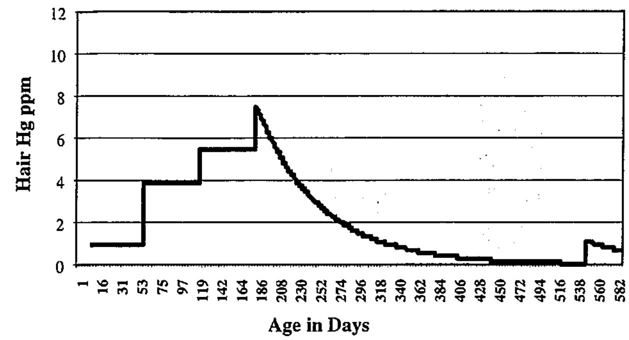

Fig. 3. Child/infant of 50th percentile body weight (no excretion first 6 months).

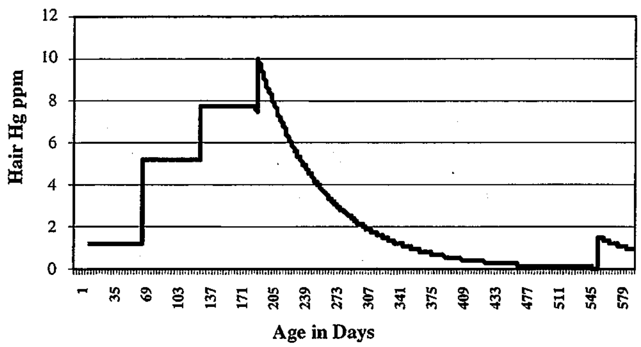

Fig. 4. Infant/child of 5th percentile body weight (no excretion first 6 months).

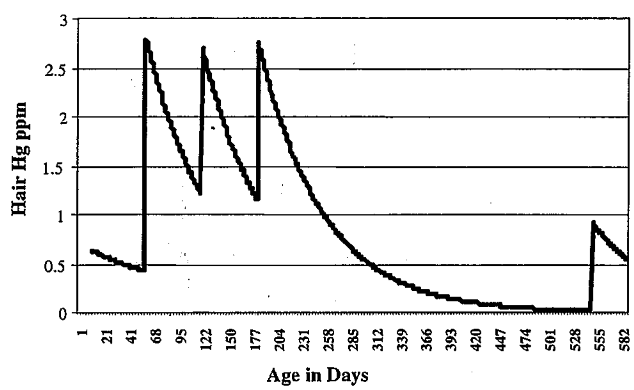

Fig. 5. Infant/child of 95th percentile body weight (adult excretion).

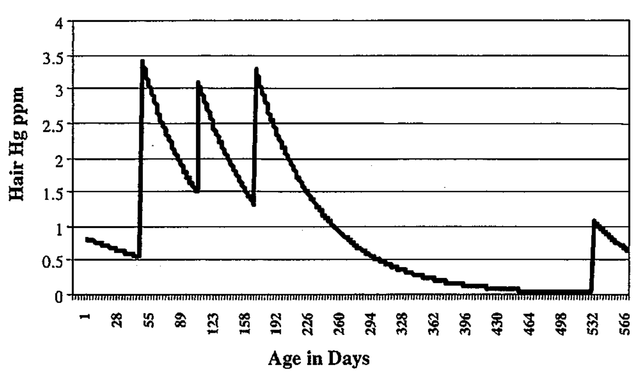

Fig. 6. Infant/child of 50th percentile body weight (adult excretion).

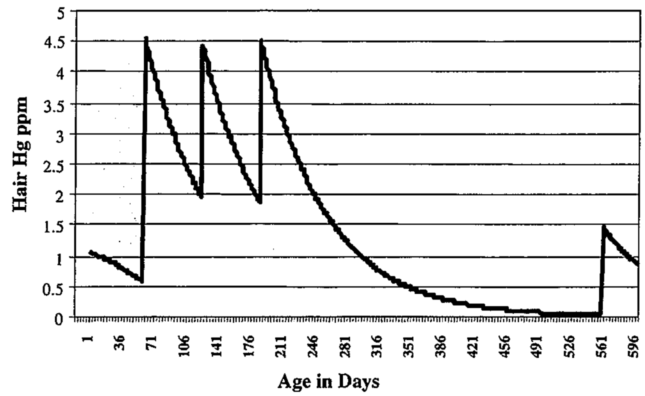

Fig. 7. Infant/child of 5th percentile body weight (adult excretion).

No Excretion Scenarios

For the 95th percentile weight babies, hair Hg concentrations exceed 3 ppm at age 60 days, reflecting the multiple immunizations given at 2 months. A peak concentration of 6 ppm is reached at day 180 (6 months immunizations). After this point, Hg levels gradually decline, falling below 1 ppm at day 300. There is a slight increase in Hg concentration at day 540, reflecting the 50 μg given at 18 months of age.

Hair Hg levels for medium weight infants (50th percentile) are predicted to reach the 1 ppm mark at birth from the 12.5 μg given at that time, and they do not fall below this mark until day 318. The slight increase at age 18 months also reaches the 1 ppm level. Several peak concentrations are observed: of 4 ppm on day 60, of over 5 ppm on day 120, and of nearly 8 ppm on day 180.

Predicted Hg concentrations for the smallest babies (5th percentile) are the highest. Levels slightly exceed 1 ppm from birth, exceed 5 ppm at day 60, and reach a peak concentration of 10 ppm at day 180. Elevations do not fall below 1 ppm until day 365. The 18 month vaccinations raise Hg concentrations slightly over 1 ppm.

Adult Excretion Scenarios

Estimated hair Hg levels exceed 2 ppm at day 60 for the heaviest infants (95th percentile). Peak elevations over 2 ppm also occur at days 120 and 180. Levels fall below 1 ppm at day 250. The 18 month immunizations do not raise concentrations over 1 ppm.

For average weight infants, the highest peak concentration occurs at day 60, with levels of approximately 3.5 ppm. Peaks of just over 3 ppm occur at days 120 and 180. Levels drop below 1 ppm at day 260, and rise again to 1 ppm at 18 months.

Table 1
Duration of hair Hg concentrations over EPA/NAS guidelines and highest peak Hg concentration for each modeled scenario

Infant weight	# Days Hg levels above 1 ppm		Highest peak Hg concentration (ppm)	
	No excretion	Adult excretion	No excretion	Adult excretion
95th percentile	240	190	6	2.5
50^{th} percentile	318	200	8	3.0
5th percentile	365	310	10	4.5

Hair concentrations in the 5th percentile weight babies reach 1 ppm at birth and show a peak elevation of 4.5 ppm at 2 months of age. Similar peaks occur at 4 and 6 months of age. Concentrations are predicted to fall below 1 ppm on day 310. The 18 month vaccines are modeled to raise Hg elevations to over 1 ppm.

The predicted hair levels of mercury resulting from postnatal vaccinal TMS exposure are concerning in that they exceed the EPA safety guideline of 1 ppm for a significant period of time, with several peak concentrations occurring during the first 6 months of life. The extended elevations over 1 ppm and the multiple peaks occurred for all infant weight categories and for both no excretion and adult excretion scenarios. The duration of the elevation over 1 ppm, as well as the highest peak concentration, are summarized for the six scenarios in Table 1. The shortest duration was 190 days and the longest was 365 days. The lowest peak was 2.5 ppm and the highest was 10 ppm, depending on the scenario modeled. In the Faröe Islands study, Grandjean et al. (1998) found neurological deficits, particularly in the areas of attention, memory, and language, in children of mothers with maternal hair Hg concentrations of 10–20 ppm. Katz and Katz (1992) have suggested that a maternal hair level of 5 ppm is indicative of toxicity. We assert that levels above 5 ppm are even more of a concern in developing infants.

DISCUSSION

There are a number of issues that deserve discussion as they relate to the ability to accurately predict mercury levels resulting from vaccinal TMS exposure based on the currently available information. The first issue to consider in evaluating this model is whether vaccines have been shown clinically to raise hair Hg concentrations. While no formal hair analyses have been published, Stajich et al. (2000) measured blood Hg levels in newborns administered the Hepatitis B vaccine, containing 12.5 μg ethyl mercury, and found elevated post-immunization concentrations relative to pre-immunization levels in all neonates studied. Levels of blood mercury after exposure in low birth weight infants were 7.36 (±4.99) μg/l. One infant was found to have mercury levels of 23.6 μg/l after exposure, which supports the inter-individual variability of mercury intoxication. Interestingly, the study subjects had measurable blood Hg concentrations prior to immunization, indicating that cumulative risk from other mercury and non-vaccinal TMS sources is real.

A second issue is whether this model, which was developed and validated for Hg effects on the fetus from maternal exposure, is appropriate for assessing Hg effects in infants from direct exposure. Since the pharmacokinetic models used for Hg risk assessment assume that maternal Hg concentrations reflect blood Hg concentrations that in turn represent the degree of organ and tissue accumulations of Hg in both fetus and mother, and since, as noted previously, infant brain development is a continuum of fetal brain development, we feel the use of the Ginsberg model is appropriate.

The third issue is whether a model developed for methyl mercury ingested with food can be applied to an assessment of ethyl mercury injected with vaccines. While both mercury compounds are organic and appear to have similar toxic properties, as noted previously (Magos et al., 1985), researchers have noted some differences in their effects. There is a need for more thorough investigations of the biokinetics of ethyl mercury itself, as well as possible synergistic relationships between EtHg and other components in vaccines, including attenuated or killed viruses, aluminum hydroxide, aluminum phosphate, and formaldehyde. For example, Cheek, in studying acrodynia, a severe disorder of childhood and infancy caused by mercury, found a synergistic effect between the low doses of Hg in calomel, given to infants in teething powders and other health remedies, and "stress" caused by concurrent viral infections, other environmental factors, and internal physiological states (Cheek et al., 1959; Cheek, 1951).

The question also arises as to which scenario modeled is more valid, the no excretion or adult excretion.

There is much uncertainty involving excretion of mercury in infants and elimination kinetics relative to adults are not known. Data from animal studies indicate that distribution, retention, and clearance of mercury are influenced by the age of exposure. Thomas et al. (1982) found that neonatal rats exposed to inorganic Hg displayed a different pattern of tissue distribution than similarly exposed adult rats. Neonatal rats treated with MeHg displayed an initially high whole body retention of Hg and then an abrupt onset of clearance at 17 or 18 days of age. Similar mechanisms may also occur in newborn infants. Alterations in the excretion of glutathione in bile (Ballatori and Clarkson, 1982) and in the flora of the gastrointestinal tract (Rowland et al., 1980) may be important associated excretion factors in infants well. Therefore, the scenarios assuming adult excretion are probably an overestimate of excretion, whereas the no excretion scenarios may somewhat understate actual Hg excretion in infants.

CONCLUSIONS

According to our modeled findings, predicted hair mercury concentrations from TMS exposure in infant vaccines administered following to the CDC immunization schedule, (assuming that all vaccines administered contained TMS) has the potential to raise hair Hg concentrations in infants to levels in excess of EPA guidelines for extended periods. Peak concentrations are predicted to reach levels that have elicited concern over adverse neurodevelopmental outcomes by many researchers.

The concern that the hair Hg concentrations predicted from vaccinal TMS may contribute to adverse neurodevelopmental outcomes is compounded by the recognition that even relatively minor effects can have profound societal impacts when amortized across the entire population and life span (Rice and Barone, 2000). These concerns are heightened by a recent report that found statistically significant associations between cumulative exposure to TMS-containing vaccines at 2 months of age and unspecified developmental delay; cumulative TMS exposure at 3 months of age and tics; cumulative exposure at 1, 3, and 6 months of age and speech and language delay; cumulative exposure at 1, 3, and 6 months and neurodevelopmental delays in general; and cumulative exposure at 6 months of age and attention deficit disorder (Stehr-Green, 2000).

Current thinking suggests that there are "windows of vulnerability" to Hg during neurological development and that specific types of developmental outcomes may have separate windows of vulnerability (NAS, 2000). These critical periods for Hg effects have not been established and may be relatively short in duration. That TMS from vaccines has the potential, based on a standard model, to raise hair Hg concentrations over the 1 ppm EPA action level for the first year of life means that "windows of vulnerability" may be impacted.

Based on these findings, every effort should be made to reduce or eliminate this unnecessary exposure. Since there are currently TMS-free vaccines available that can be utilized without altering the current CDC schedule, preference should be given to those preparations. Further, neurodevelopmental investigations of infants exposed to vaccinal TMS during the first 6 months of life, and who later exhibit neurodevelopmental delay, are warranted. Other health products which contain TMS, like immune globulins administered during pregnancy or ear and eye drops which might be given to pregnant women or infants, should also undergo scrutiny.

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