FATTY ACID ETHYL ESTERS (FAEE); COMPARATIVE ACCUMULATION IN HUMAN AND GUINEA PIG HAIR AS A BIOMARKER FOR PRENATAL ALCOHOL EXPOSURE

VIVIAN KULAGA1, DANIELA CAPRARA1, UMAR IQBAL2, BHUSHAN KAPUR1, JULIA KLEIN1, JAMES REYNOLDS2, JAMES BRIEN2 and GIDEON KOREN1*

1Division of Clinical Pharmacology and Toxicology, The Hospital for Sick Children, Toronto, Canada MSG 1X8 and 2Department of Pharmacology and Toxicology, Faculty of Health Sciences, Queen’s University, Kingston, Canada K7L 3N6

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Abstract — Aims: To compare the incorporation rate (ICR) of fatty acid ethyl esters (FAEE) in hair between guinea pigs and humans, and to assess the relationship between ethanol exposure and FAEE concentrations in hair. Methods: Published data from pregnant guinea pigs and humans were obtained from published data (26.2 and 24 mg/dl/h, respectively).

Results: Total and individual FAEE ICRs, defined as the ratio of hair FAEE to the area under the BEC-time curve (total systemic ethanol exposure), were found to be on average an order of magnitude lower in the guinea pig than in the human. The profiles of ester incorporation also differed slightly between species, with ethyl stearate being highly incorporated in guinea pig hair and less so in human hair. The results may reflect in the human greater FAEE production, greater FAEE deposition in hair, slower FAEE catabolism, differential sebum production and composition, or a combination thereof. Also, ethyl oleate was found to correlate with total systemic ethanol exposure for both guinea pigs and humans, correlation coefficients equalling 0.67 (P < 0.05) and 0.49 (P < 0.05), respectively. No other ethyl esters, nor total FAEE, were found to correlate with systemic ethanol exposure. Conclusion: When extrapolating FAEE concentrations in hair from guinea pigs to humans, an order of magnitude difference should be considered, with humans incorporating more FAEE per unit of ethanol exposure. Also, the results suggest caution should be taken when interpreting values of single esters because of their differential incorporation among species. Lastly, our findings suggest ethyl oleate may be of keen interest in FAEE hair analysis, particularly across species.

INTRODUCTION

Fatty acid ethyl esters (FAEE) are direct biomarkers of ethanol exposure. FAEE are formed during non-oxidative metabolism of ethanol by the conjugation of ethanol to endogenous free fatty acids and fatty acyl-CoA. FAEE formation can be spontaneous but is most often catalyzed by microsomal acyl-CoA:ethanol O-acyltransferase (AEAT), which utilizes ethanol and acyl-CoA as its substrates, or cytosolic FAEE synthase that is found ubiquitously throughout the body, which uses ethanol and free fatty acids as its substrates (Laposata, 1998; Laposata and Lange, 1986). FAEE can be detected in hair, meconium, blood, and various organs (Laposata and Lange, 1986; Doyle et al., 1994, 1996; Klein et al., 1999, 2002; Auwärter et al., 2001; Pragst et al., 2001; Wurst et al., 2004). However, it is the ability to measure FAEE in hair as a means of assessing chronic or long-term ethanol exposure that is of most interest to our group.

The ability to assess ethanol exposure by FAEE hair analysis is a remarkable tool with the potential for a variety of applications. First developed by Pragst et al. (2001), the FAEE hair test is useful for forensic purposes because it provides an unbiased means of assessing long-term alcohol usage and potential alcohol status. The test is also useful in toxicological settings, with particular promise for use in paediatric patients to assess prenatal exposure to ethanol, a well known teratogen (Klein et al., 2002; Caprara et al., 2005a). The potential to use hair FAEE to screen for infants at high risk for fetal-alcohol-associated effects would revolutionize care for such patients who are often either misdiagnosed or not diagnosed at all (Streissguth et al., 1996; Williams et al., 1999).

Therefore, our laboratory’s goal is to further develop the hair test in order to be able to reliably quantify FAEE concentrations in neonatal hair assessing in utero ethanol exposure.

The guinea pig has been our choice of experimental animal for recent studies of FAEE as a biomarker of fetal ethanol exposure (Brien et al., 2004; Caprara et al., 2005) because of the guinea pig’s long history as a validated animal model for fetal alcohol syndrome (FAS) (Reynolds and Brien, 1995; Kimura et al., 2000; Cudd, 2005), and most critically because the guinea pig is the only small mammalian born with neonatal hair. Unlike the rat or mouse, the guinea pig undergoes substantive prenatal brain development that closely mimics that of the human (Dobbing and Sands, 1979). Furthermore, the manifestations of ethanol neurobehavioural teratogenicity in the guinea pig are similar to the brain dysfunction and dysmorphology of fetal-alcohol-affected humans (Reynolds and Brien, 1995; Kimura et al., 2000). Recently, it has been shown that in pregnant guinea pigs treated with ethanol throughout gestation total FAEE concentrations in fetal meconium, neonatal hair, and maternal hair were significantly higher than isocaloric-sucrose/pair-fed nutritional control (Brien et al., 2004; Caprara et al., 2005). However, before we can accurately interpret how FAEE concentrations in guinea pig hair relate to concentrations found in humans, it is important to know whether a difference exists in the FAEE hair incorporation rate (ICR) between the two species, i.e. the ratio of total hair FAEE to total systemic exposure to ethanol. Therefore, the objective of the present study is to utilize recently published data to compare FAEE ICRs into hair between guinea pigs and humans as well as to assess the relationship between systemic ethanol exposure and FAEE concentrations.

*Author to whom correspondence should be addressed: Gideon Koren FACMT, FRCPC, The Hospital for Sick Children, 555 University Avenue, Toronto, Ontario, M5G 1X8, Canada. Tel: +416 813 5781; Fax: +416 813 7562; E-mail: gkoren@sickkids.ca

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Guinea pigs

Published data from female Dunkin–Hartley strain Albino guinea pigs (n = 9) were used (Caprara et al., 2005b). The pregnant guinea pigs received chronic oral administration of 4 g ethanol/kg maternal body weight/day from gestational day (GD) 0, defined as the last day of full vaginal membrane opening, until GD 67. Maternal hair samples of full fur length, weighing ~20 mg were obtained on GD 57 and 65, were quantitatively analysed for ethyl myristate (E14), ethyl palmitate (E16), ethyl oleate (E18:1), and ethyl stearate (E18). Analytical methods are described in Caprara et al. (2005), but briefly: samples underwent an overnight liquid–liquid extraction adapted from Pragst et al. (2001), using dimethylsulfoxide and hexane. Hexane layers were then separated, evaporated at 35°C under nitrogen, and reconstituted with hexane. Solid phase extraction was then performed using aminopropyl columns and the samples were then again evaporated and reconstituted two more times to yield final reconstitution volumes of 50 µl. Samples were analysed using a Varian Saturn 2100T GC/MS/MS with ion trap mass spectrometer in GC/MS mode, using a CPSil-8 low-bleed/MS fused silica chrompack capillary column (30 m × 0.25 mm × 0.25 µm) with helium carrier gas (1.0 ml/min). The temperature program applied was: 2 min at 100°C, ramp up 20°C/min up until 300°C. Chemical ionization mode was used with isobutene as the ionization gas. The temperatures of the injector, transfer-line, manifold, and injector trap were 260, 300, 50, and 220°C, respectively. The concentration of total FAEE (E14, E16, E18:1 and E18) was expressed as picomoles of total FAEE per milligram of hair (pmol/mg).

Maternal blood samples were collected on GD 58 at 1 h after the daily ethanol dose to determine the apparent peak blood ethanol concentration (BEC).

For our analysis, maternal hair FAEE concentrations for each pregnant guinea pig were recorded as the average of the total FAEE concentration values for the samples taken on GD 57 and 65. Total maternal systemic ethanol exposure was determined for each pregnant guinea pig by calculating the area-under-the-curve for the maternal blood ethanol concentration-time curve (AUC-BEC) (Fig. 1). The latter task was accomplished using zero-order kinetics, measured maternal BEC, and a reference value Vmax of 26.2 mg ethanol/dl blood/h specific to the pregnant guinea pig (Litvin and Switzer, 1988). Zero-order kinetics model was chosen because pregnant guinea pigs exhibit apparent zero-order kinetics of ethanol elimination at the dose level currently investigated (Litvin and Switzer, 1988). The ICR of FAEE into hair is defined as the ratio of FAEE in hair to total systemic exposure to ethanol (AUC-BEC) (Fig. 2). The ICR represents how much FAEE is incorporated per standard unit of ethanol exposure. The inverse of the ICR is the amount of systemic ethanol exposure required to produce one standard unit of FAEE. Therefore, for each pregnant animal, the value of total FAEE was divided by the AUC-BEC in order to obtain the ICR of total FAEE into hair. The median ratio was used to determine the guinea pig’s average FAEE ICR because the data were not normally distributed. Furthermore, the ICR of each ester was also investigated by calculating the ratio of each ester to the AUC-BEC separately. Once again the median ratio for each ester was used to define each ICR because the data were not normally distributed.

ICR = \frac{FAEE}{AUC-BEC}

Humans

Data from 18 alcoholic patients in a detoxification programme (14 male; 4 female) with a mean age of 44 years, and mean body-mass-index (BMI) 21.7, were obtained from Wurst et al. (2004). Alcohol intake was reported as grams of ethanol consumed during the last month. Hair was collected from these patients for analysis of total FAEE (E14, E16, E18:1, and E18) on Day 7 of hospitalization. Analytical methods have been described previously in Pragst et al. (2001) and are briefly as follows: 6 cm of hair from the root end, weighing ~50 mg, was used for analysis. Hair was externally decontaminated by n-heptane, followed by liquid–liquid extraction using dimethylsulfoxide and n-heptane. The n-heptane layer was then separated and evaporated at 40°C under nitrogen. Residues underwent solid-phase micro-extraction and were analysed using Hewlett-Packard 5973 GC, 5973 MS, with deuterated standards for each ester. A Hp5-MS capillary column (28 m × 0.25 mm × 0.25 µm) was used with helium (1 ml/min) as the carrier gas. The temperature program applied was: 2 min at 100°C, ramp up 20°C/min up to 300°C. The temperatures of the injector, the interface, the ion source, and the quadrupol were 260, 280, 230, and 106°C, respectively. The concentrations of total FAEE (E14, E16, E18:1, and E18) were expressed as nanograms of FAEE per milligram of hair but were converted for our purposes to picomoles of total FAEE per milligram of hair (pmol/mg).

Patients’ weights were estimated at 58 kg for women, and 66 kg for men, using mean BMI scores and population specific statistics for height (Grandjean, 1988). Peak BEC levels were estimated in the following manner. Daily dose (g/day) was calculated by dividing the reported monthly intake of ethanol by 30. The daily dose was then divided by reference values of volume of distribution, 0.59 l/kg for women and 0.73 l/kg
for men (Marshall et al., 1983). AUC-BEC was calculated using zero-order kinetics, with peak BEC as the y-intercept, and a reference Vmax value of 24 mg/dl/h specific to patient age group and alcoholic status was used for the slope (Adachi et al., 1989) (Fig. 1). These calculations are crude estimates, as we assumed that the daily dose is consumed all at the same time. In practice the drinking may be distributed in individual patterns, which would lead to a decrease of AUC-BEC in zero-order kinetics. In a similar way, our estimates could not address varying rates of absorption. Zero-order kinetics were used because this method has been shown to provide accurate and acceptable estimates of systemic exposure to ethanol given the high doses patients were consuming (Crow and Batt, 2001; Hardmann and Limbard, 2001). Similar to the guinea pigs, each value for total FAEE was then divided by the respective value of AUC-BEC. The median ratio was used to determine the average human FAEE ICR because like in the guinea pig the data were non-parametric. Furthermore, the ICR of each ester was also investigated by calculating the ratio of each ester to AUC-BEC separately. Once again the median ratio for each ester was used to define each ICR because the data were likewise non-parametric.

**Statistical analysis**

All statistical tests were performed using Sigma Stat, version 2.0. Total hair FAEE per total systemic ethanol exposure (AUC-BEC) ratios, as well as the individual FAEE per AUC-BEC ratios were compared between the pregnant guinea pig and the alcoholic human using the Mann–Whitney Rank Sum test because the data were not normally distributed. The relationship between AUC-BEC and total hair FAEE within species, as well as the relationship between AUC-BEC and individual FAEE within species, was also investigated using the Spearman Rank Order correlation test because the data were not normally distributed.

### RESULTS

In the pregnant guinea pig, the mean level of total hair FAEE was 0.43 ± 0.33 pmol/mg (range 0.05–1.07 pmol/mg). The most predominant esters were ethyl palmitate, ethyl oleate, and ethyl stearate, whose mean concentrations, respectively, were 0.14 ± 0.14, 0.14 ± 0.11, and 0.14 ± 0.13 pmol/mg. The mean concentration of ethyl myristate was 0.01 ± 0.01 pmol/mg. The median AUC-BEC was 2253.29 mg/dl/h (range 1632.99–3345.01 mg/dl/h). The ICRs for individual esters, as well as total FAEE, are displayed in Table 1. For convenience, the inverse ICRs and their ranges are displayed in Table 2. The ratios between guinea pig and human ICRs (column 4, Table 1) are equal to the ratios of the inverse ICRs and, therefore, are omitted in Table 2.

The mean level of total hair FAEE among alcohol detoxification patients was 4.40 ± 2.30 pmol/mg (range 1.29–10.96 pmol/mg). The most predominant esters were ethyl oleate and ethyl palmitate. Mean concentrations of ethyl oleate, palmitate, stearate, and myristate were 1.91 ± 0.92, 1.69 ± 0.15, 0.47 ± 0.17, and 0.32 ± 0.42 pmol/mg, respectively. The median AUC-BEC was 2390 mg/dl/h (range 91.90–11417.83 mg/dl/h). The incorporation rates for individual esters, as well as total FAEE, are displayed in Table 1, and for convenience their inverse is displayed in Table 2.

The FAEE ICRs of guinea pigs were significantly lower than those found in humans (P < 0.05) for all individual esters, and total FAEE, except for ethyl myristate whose median ratio was zero (Table 1). Six out of the nine guinea pigs had undetectable levels of ethyl myristate in their hair; therefore, ICR could not accurately be assessed for this ester. Guinea pigs required on average over an order of magnitude more exposure to ethanol in order to produce equivalent levels of FAEE (Table 2); the one exception was ethyl stearate in which guinea pigs only required 1.4 times the ethanol exposure required by humans to produce equivalent FAEE levels.

<table>
<thead>
<tr>
<th>FAEE</th>
<th>Guinea pig ICR*</th>
<th>Human ICR*</th>
<th>Human ICR/guinea pig ICR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethyl myristate</td>
<td>0.000000</td>
<td>0.000130</td>
<td>**</td>
</tr>
<tr>
<td>Ethyl palmitate</td>
<td>0.000071</td>
<td>0.000650</td>
<td>9.2***</td>
</tr>
<tr>
<td>Ethyl oleate</td>
<td>0.000057</td>
<td>0.000982</td>
<td>17.1***</td>
</tr>
<tr>
<td>Ethyl stearate</td>
<td>0.000119</td>
<td>0.000171</td>
<td>1.4***</td>
</tr>
<tr>
<td>Total FAEE</td>
<td>0.000151</td>
<td>0.001909</td>
<td>12.6***</td>
</tr>
</tbody>
</table>

*Units of ICR are pmol/mg of FAEE per mg/dl/h of systemic ethanol exposure.
**Inter-species ICR difference could not be assessed.
***Inter-species difference in ICR was significant.

<table>
<thead>
<tr>
<th>FAEE</th>
<th>Guinea pig ICR–1*</th>
<th>Human ICR–1*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethyl myristate</td>
<td>0 (0–208081.5)</td>
<td>7674.2 (785.5–207603.3)</td>
</tr>
<tr>
<td>Ethyl palmitate</td>
<td>14152.9 (0–47048.6)</td>
<td>1359.2 (55.6–10470.7)</td>
</tr>
<tr>
<td>Ethyl oleate</td>
<td>17417.0 (9802.4–253599.0)</td>
<td>1018.4 (64.9–5349.1)</td>
</tr>
<tr>
<td>Ethyl stearate</td>
<td>8384.4 (0–59801.1)</td>
<td>5859.5 (239.3–22300.4)</td>
</tr>
<tr>
<td>Total FAEE</td>
<td>6605.2 (3008.9–17417.0)</td>
<td>523.9 (25.7–2726.21)</td>
</tr>
</tbody>
</table>

*Units of inverse ICR are mg/dl/h of systemic ethanol exposure per pmol/mg of FAEE.
Ethyl oleate was the only ester found to correlate to systemic ethanol exposure (AUC-BEC) in either species, and it was found to correlate in both species; correlation coefficients for guinea pig and human were 0.67 ($P < 0.05$) and 0.49 ($P < 0.05$), respectively (Figs 3 and 4).

**DISCUSSION**

After standardization for systemic ethanol exposure, cumulative levels of ethyl myristate, ethyl palmitate, ethyl oleate, and ethyl stearate were ~13 times lower in guinea pigs than in humans. This result indicates that there is an order of magnitude difference in the average FAEE ICR into hair between guinea pigs and humans, with guinea pigs producing much lower FAEE concentrations for equivalent exposures. Analysis of individual FAEE ICRs revealed that different ethyl esters incorporate at different rates for each species but are still largely of an order of magnitude lower in guinea pigs, with the exception of ethyl stearate. The ICR of ethyl stearate was only 1.4 times lower than that of the humans, but this difference was still statistically significant. This result can be explained by the fact ethyl stearate is incorporated at a much higher rate in the guinea pig (almost double the rate of either of ethyl oleate or palmitate), while ethyl stearate is incorporated at a relatively low rate in humans, relative to the other esters (Table 1). However, ethyl oleate and palmitate, in addition to ethyl stearate, did, contribute largely to the total FAEE ICR in guinea pigs, while in humans ethyl stearate contributed <10% to the total FAEE ICR. The rate was instead dominated by the most prevalent and highly incorporated esters, ethyl oleate and palmitate. This difference in ethyl ester profiles of ICRs is probably the result of a natural species difference. FAEE are found throughout several matrices: meconium, hair, blood, organs most commonly affected by alcohol abuse, and in adipose tissue (Laposata and Lange, 1986; Doyle et al., 1996; Pragst et al., 2001; Chan et al., 2004). FAEE are actively produced in most of these media when exposed to ethanol, with some matrices showing slightly different ester profiles even within the same species (Laposata and Lange, 1986; Doyle et al., 1996; Bearer et al., 1999, 2003; Pragst et al., 2001; Chan et al., 2003, 2004). Lange (1982), showed that FAEE produced in rabbit myocardial tissue were made primarily from their non-esterified fatty acid precursors and that the most highly incorporated FAEE into myocardial tissue were ethyl linoleate and oleate. Hair FAEE are believed to be primarily deposited by sebum, and sebum composition between guinea pigs and humans differs drastically (Nikkari, 1974; Auwärter et al., 2001). It is likely that the difference in ethyl ester ICR profiles is the result of differences in fatty acid composition at the source of FAEE production (the sebaceous gland for example) and, perhaps, differential enzymatic specificities.

However, differences in ICR ester profiles between species do not account for the major finding that on average, guinea pigs produce an order of magnitude less FAEE for equivalent ethanol exposure than do humans. There can be several reasons for this interspecies difference; the first being FAEE production or degradation. Guinea pigs may produce or degrade FAEE at a different rate than do humans. In humans, FAEE are formed through non-oxidative ethanol metabolism primarily by acyl-coA:ethanol O-acyltransferase (AEAT) and FAEE synthase. In the guinea pig, the metabolic route by which FAEE are formed has not been confirmed; however, if FAEE synthase and AEAT are involved they may have different levels of activity. The guinea pig’s higher rate of ethanol metabolism in general could also result in faster degradation of FAEE, and consequently result in less opportunity for incorporation into hair. Another explanation for the 13-fold difference could stem from differences in FAEE deposition. Lipophilicity, membrane permeability, and melanin affinity are key factors affecting drug deposition into hair (Nakahara et al., 1995). The first two factors are unlikely to be responsible for our finding since we are discussing deposition of the same species, FAEE, into two different mammals. As for melanin affinity, certain drugs are known to bind to melanin, affecting drug concentrations in differently pigmented hair. The guinea pigs in the present study were Albino pigs, therefore it is possible that if FAEE bind to melanin, which remains unknown, that a large difference of FAEE incorporation between guinea pigs and humans could occur. However, drug-melanin interactions that occur in melanin granule formation during melanogenesis are much more important than drug-melanin interactions that occur on the surface of granules such as would occur from sebum (Pötsch et al., 1997); therefore, if FAEE deposited by sebum were binding to melanin, this interaction is not likely to affect FAEE hair concentrations. Furthermore, FAEE are non-polar so it is doubtful that they would interact with the cation exchange properties of melanin that provide most of the ionic
binding sites for drugs (Pötsch et al., 1997). The most likely explanation for species difference in total FAEE ICR is the composition of sebum between species. The composition of sebum is highly species-specific with human sebum containing twice as much saponifiable material as non-saponifiable material, and more than half of human sebum is composed of triglycerides and free fatty acids, whereas the seba of guinea pigs, other rodents, rabbits, and sheep contain <10% free fatty acids and virtually no triglycerides (Nikkari, 1974).

The present study found a significant correlation between systemic ethanol exposure and ethyl oleate for both guinea pigs and humans, 0.67 (P < 0.05) and 0.49 (P < 0.05), respectively. This indicates that ethyl oleate may be a truly important ester in hair for assessing ethanol exposure, even across species. Interestingly, ethyl oleate has been found to be one of the most, or the most, prevalent esters in meconium tested positive for ethanol exposure, the blood of acutely intoxicated individuals, the organs and adipose tissue of alcoholics, myocardial tissue of rabbit ethanol-perfused hearts, and the adipose tissue of acutely ethanol-exposed rats (Lange et al., 1981; Lange, 1982; Laposate and Lange, 1986; Doyle et al., 1996; Moore and Lewis, 2001; Salem et al., 2001; Bearer et al., 2003; Chan et al., 2004). Also, Doyle et al., (1994), reported that ethyl oleate, along with ethyl stearate, palmitate, and linoleate, correlated significantly with blood ethanol levels from a group of emergency room patients. The fact that the correlation in the present study was found despite significant limitations in assessing the systemic ethanol exposure of the humans is encouraging. We were not able to account for consumption patterns of individuals, and perhaps if systemic ethanol estimates were more accurate an even stronger correlation would have been found. However, encouraging is the fact that Soderberg et al., (1999), who found total FAEE blood concentrations to correlate with BEC, also found that the rate of alcohol consumption did not affect the FAEE concentration. The lack of correlation of the other esters with systemic ethanol exposure may be due to the sample size of the population and the large variability associated with these esters.

The present study was limited by the fact that previously published data from different studies were used. Consequently, not all variables sought in the current study were available, such as peak BECs or weight of human subjects, and therefore they had to be estimated. However, mean BMI score was available and used to estimate total body water in deriving AUC-BEC estimates. AUC-BEC is well known to correlate with ethanol dose in the human, with minimum variability from hepatic ethanol metabolism, after accounting for differences in total body water. Ethanol consumption was recorded from the subjects’ memory, a limitation often unavoidable in clinical research, while the guinea pigs’ dosage regimen was controlled and invariable. However, given the magnitude of the difference found in FAEE incorporation between the species it is very unlikely that the above limitations greatly influenced the results. Also noteworthy, the investigators in the guinea pig study used only one ethanol dose per kg body weight for all animals, minimizing the variability observed for AUC-BEC. Ideally, multiple doses of ethanol could have been used to compare mean AUC-BEC for each dose against mean FAEE. However, despite this limitation there was still sufficient variability in AUC-BEC to observe a significant correlation between AUC-BEC and hair FAEE, ethyl oleate. This fact attests to the strength of the correlation.

The current study has shed light onto the FAEE ICR of guinea pigs and humans, and the differences that exist between them. We have discovered that an order of magnitude difference exists between them, that the contributions of the esters vary slightly, and that ethyl oleate may be an especially important biological marker of ethanol exposure, particularly across species. These findings suggest that the guinea pig is still a useful model, despite lower sensitivity for FAEE in hair, because the levels are still measurable and a dose–response relationship between ethanol exposure and FAEE exists. This study furthers our laboratories’ goal of developing a neonatal hair test for fetal ethanol exposure because it amplifies our previous finding that we were able to distinguish in utero exposed guinea pig pups from controls by FAEE hair analysis, despite the decreased sensitivity of this model. The current study suggests that FAEE hair analysis is highly sensitive in humans and, coupled with our previous findings, that it holds significant potential for discriminating fetal-alcohol-exposed neonates.

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