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A comparison of infant hair, cord blood and meconium analysis to detect fetal exposure to environmental pesticides

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Abstract

OBJECTIVE—The detection of fetal exposure to environmental pesticides is important because many of the pesticides are neurotoxicants and fetal exposure to these compounds can adversely affect prenatal and subsequent neurodevelopment. The aim of this study was to determine, by the comparative analysis of infant hair, cord blood and meconium, the most sensitive matrix to detect fetal exposure to pesticides.

PATIENTS AND METHODS—Pregnant women were prospectively recruited from an agricultural site in the Philippines where a preliminary survey indicated a substantial use at home and in the farm of the following pesticides: propoxur, cyfluthrin, chlorpyrifos, cypermethrin, pretilachlor, bioallethrin, malathion, diazinon and transfluthrin. Infant hair, cord blood and meconium were obtained after birth and were analyzed by gas chromatography/mass spectrometry for the above compounds, including lindane and DDT (1,1,1-trichloro-2,2-bis, *p*-chlorophenylethane) and some of their known metabolites.

RESULTS—A total of 638 infants were included in the study. The highest exposure rate to pesticides was detected in meconium (23.8% to propoxur, 1.9% to pretilachlor, 1.9% to cypermethrin, 0.8% to cyfluthrin, 0.6% to DDT and 0.3% to malathion and bioallethrin). Cord blood was only positive for propoxur (1.9%) whereas infant hair was only positive for chlorpyrifos (0.2%). The highest exposure was to household pesticide (propoxur). The frequency and concentration of pesticides were compared in the three matrices and there was a significantly higher frequency and concentration of propoxur, pretilachlor, DDT, cyfluthrin and cypermethrin in meconium compared to cord blood and infant hair. Pesticide metabolites were not found in any of the matrices analyzed, except in one meconium sample which was positive for DDE (4,4′ dichlorodiphenyldichloro ethylene), a DDT metabolite.

CONCLUSIONS—There is significant exposure of the pregnant woman and her fetus to pesticides, particularly to the home pesticide, propoxur. Our study has demonstrated that among cord blood, meconium or infant hair, meconium is the most sensitive matrix to analyze for fetal exposure to pesticides. The accumulation of pesticides in meconium, the ease of meconium collection and the

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large amount of meconium that could be collected are factors that contribute to the increased sensitivity of this matrix.

Keywords

pesticides; pregnancy; meconium; prenatal exposure to pesticides; hair analysis; blood analysis; propoxur; bioallethrin

Introduction

There is widespread use of pesticides and vast quantities are dispersed in the environment and are subsequently found in the air, water, soil and food sources (1). Human exposure to pesticides is therefore inevitable and bioaccumulation of pesticide residues in human tissues has been reported (2). The exposure of the pregnant woman to pesticides in the environment is a major public health concern since a majority of the pesticides are neurotoxicants and the fetus is at greater risk, compared to the adult, to the toxic effects of these chemicals due to the rapid state of growth and development of its brain (3). Aberrations in neuronal proliferation, migration, differentiation, synaptogenesis, myelination and apoptosis in the fetus have been described in animals and humans antenatally exposed to these compounds (4,5). It is likely that most of the maternal exposures to environmental pesticides are subtle and result in little or no recognizable effects in the pregnant woman. Yet, serious concerns have been raised about their adverse effects on the fetus and of their potential role in subsequent developmental, learning and behavioral difficulties in children (6–9). Substantial evidence from animal and human data have demonstrated that a variety of chemicals commonly encountered in industry and the home can contribute to these disorders, even at low levels of exposure (10–14). In one study, the carbamate, propoxur was observed to impair reflex development in the offspring of rats prenatally exposed to low levels of the pesticides (14). In humans, abnormal reflexes in newborn infants, as assessed by the Brazelton Neonatal Behavioral Assessment Scale were associated with maternal exposure to environmental organophosphates during pregnancy (15). Thus, reliable biomarkers of fetal exposure to environmental pesticides are needed to identify infants who are at risk at birth and as potential predictors of adverse outcomes. A few reports have analyzed infant cord blood (16,17) or meconium (18–20) for pesticides and their metabolites, but no study has yet been conducted which compared various fetal matrices to determine the most sensitive matrix to detect exposure. The aim of this study was to determine which matrix (cord blood, infant hair or meconium) will detect the highest rate and concentration of fetal exposure to environmental pesticides.

Materials and Methods

Pregnant women were prospectively recruited from the Outpatient Clinic of the Provincial Hospital in Malolos, an agricultural town in the province of Bulacan, Philippines from June 2002 to September 2004. The subjects were not participants of other ongoing research. Our preliminary survey of pesticide use in the region showed the predominant use of the following compounds at home or in the farm: cyfluthrin/propoxur (73%), chlorpyrifos (37%), cypermethrin (31%), pretilachlor (28%), bioallethrin (26%), malathion (15%), diazinon (12%) and transfluthrin (11%). This study was approved by the Human Investigation Committees at both Wayne State University and the University of the Philippines. An informed consent was obtained from the mothers for their participation in the study, as well as that of their infants. Demographic information on the mother and infant were collected after delivery. Information about the subjects' home and environment was also obtained through a home visit using a form that is used in public health surveys in the Philippines. After birth, cord blood was collected into tubes containing EDTA as anticoagulant. While in the nursery, meconium and infant hair were obtained. For the hair samples, a small, pencil (width) size sample of hair was obtained from the infant's nape and placed in sealed plastic bags. Meconium was collected by the nurse directly from every diaper of the infant during the first 2 days of life using previously published procedures of collection (21). If an inadequate amount of meconium was collected in the nursery, meconium collection was continued at home and the mother was instructed to save the infant's diapers. Meconium was collected daily in the homes by a member of the research team. The cord blood and meconium samples were frozen at −18°C until the time of analysis. Hair samples were kept in the refrigerator. The samples were analyzed for the pesticides that were commonly used in the study site: cyfluthrin, propoxur, chlorpyrifos, cypermethrin, pretilachlor, bioallethrin, malathion, diazinon, transfluthrin. Lindane and DDT were also analyzed based on our previous study in Manila, Philippines that showed substantial exposure to these pesticides (22). Some known metabolites of these pesticides were also analyzed including: 2-isopropoxyphenol [2-IPP] for propoxur, cis-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylic acid [cis-DCCA] and trans-3-(2,2-dichlorovinyl) -2,2-dimethylcyclo propanecarboxylic acid [trans-DCCA] for cypermethrin, 3,5,6- trichloro-2-pyridinol for chlorpyrifos, 3-phenoxybenzoic acid for cyfluthrin, malathion monocarboxylic acid [MMA] for malathion and 4,4′ dichlorodiphenyldichloro ethylene [DDE] for DDT.

The pesticides and their metabolites were analyzed in the various matrices by gas chromatography/mass spectrometry (GC/MS) using published procedures (21–25) and with the following analytical characteristics:

Hair

In hair, matrix-spiked calibration curves were linear for all parent pesticides and pesticide metabolites with coefficients of linearity greater than 0.998 (23,24). Optimum recovery rates using our six-hour hexane extraction method ranged from 87–112% at a spiked concentration of 31.25 μg g^{-1}. The inter-assay and intra-assay coefficients of variability for the analysis of parent pesticides were below 11%. Limits of detection (LOD) by empirical approach ranged from 30.50 for propoxur, diazinon, and DDT to 488.00 ng g^{-1} hair for bioallethrin. Recovery rates of the metabolites by liquid-liquid extraction of the acid digest ranged from 87%–103% using a spiked concentration of 46.86 μg g^{-1}. Inter-assay and intra-assay coefficients of variability for the analysis of metabolites were <11%, and the LOD ranged from 0.18 (2-IPP and DDE) to 5.88 μg g^{-1} (for MMA)

Blood

In blood, the matrix-spiked calibration curves were linear for all parent pesticides and pesticide metabolites with coefficients of linearity greater than 0.990 (25). Optimum recovery rates ranged from 84–142% for parent compounds and 54–122% for the metabolites. The inter-assay and intra-assay coefficients of variability for the analysis of parent pesticides and metabolites were below 14.4%. The LOD by the empirical approach for parent compounds ranged from 0.003 (for propoxur, diazinon, pretilachlor and DDT) to 0.098 μg mL-1 (for bioallethrin, cyfluthrin and cypermethrin). The LOD for the metabolites ranged from 0.20 μg mL-1 (for 2-isopropoxyphenol, cis-/trans-DCCA, 3,5,6-TCP and MMA) to 0.78 μg mL-1 (for 3-PBA and DDE).

Meconium

The matrix spiked calibration curves were linear for all parent compounds and metabolites with coefficients of linearity greater than 0.981 (21). The LOD in matrix-spiked standards for the parent compounds ranged from 0.098 μg g^{-1} for propoxur to 1.56 μg g^{-1} for lindane. Inter-assay variability was <11.4% for all compounds. LODs for pesticide metabolites ranged from 0.312 μg g^{-1} for most compounds, to 4.15 μg g^{-1} for 3,5,6 trichloro-2-pyridinol. Parent pesticides recovery ranged from 82.4–109.3%; metabolites from 72.3–108.0%.

To identify the pesticides in the different matrices by GC/MS, the following criteria were strictly used: (1) a distinct peak of the pesticide in the chromatogram at the correct retention time (± 0.03 min) compared to the positive controls, (2) the target and qualifier mass ions were present in the correct ratio range, (3) there was agreement among the analytical investigators on the identity of the compound.

Statistical analysis

Mean (standard deviation) and frequency distribution were calculated to describe the demographic and socioenvironmental characteristics of the study population. When appropriate, median and interquartile ranges are presented. For statistical comparison, the unit of pesticide concentrations in hair and meconium were expressed in μg mL^{-1} to be consistent with the concentration unit in blood. The frequency of pesticide exposure was compared among the three matrices by the Cochran Q test. For very low frequency, an exact test was used. The concentrations of pesticides, presented as median and interquartile range were compared by the Friedman test. A p value of <0.05 was set as the level of statistical significance.

Results

A total of 638 infants were studied. The mean gestational age of the infants was 38.4 ± 1.9 weeks; 54.4% were male and 46.1% female. The sociodemographic characteristics of the study population are shown in Table 1. The mean ages of the fathers and mothers were 28.5 and 25.8 years, respectively and mean monthly family income was 5576 pesos (equivalent of US$100). The mean number of families and individuals in the household were 1.62 and 5.28, respectively. About 59.4% lived in their own homes, although 7.2% were squatters living in makeshift homes. The socioeconomic status (SES) was assessed using the Roberto Scale which is a widely used socioeconomic scale in the Philippines and is based on home structure and appearance (26). The standard test of SES commonly used in the United States, i.e., The Hollingshead Four Factor Index (27) was not applicable to the Philippine cohort due to differences in culture. The Roberto scale ranges from A (highest) to E (lowest). About 59% of the homes were in the class D and E category. A lead recycling plant was located near 7.1% of the homes. The cleanliness of the home and surroundings was mostly rated as fair (72.5%). The toilet was predominantly water seal (82.4%); water source was either piped in (53.3%) or from a well (38.9%), waste disposal was via sewer (26.8%) or canal (61.5%); 58.3% had organized garbage collection. Most homes had problems with flies (91.7%), roaches (89.8%) and mosquitoes (97.6%). Pesticide spray was used in 38.5% of the homes; the principal pesticide used was Baygon™ (92.8%) which contains propoxur and cyfluthrin. Spraying of home pesticides was done by 38.2% of mothers. Re-entry time after spraying of a room was <60 min in 75% of the households. The mosquito coil Katol™ (containing bioallethrin) was used in 52.7% of the households. Farm pesticides were used by 16.8% and only 4.2% used gloves to handle pesticides.

The frequency of pesticide exposure based on the analysis of meconium, cord blood and infant hair is shown in Table 2. The highest exposure rate to pesticides was detected in meconium. A total of 8 of 11 pesticides were found in this matrix (23.8% for propoxur, 1.9% for pretilachlor and cypermethrin, 0.8% for cyfluthrin, 0.6% for DDT, 0.3% for bioallethrin and malathion and 0.2% for diazinon). Cord blood was only positive for propoxur (1.9%) and one infant hair sample was positive for chlorpyrifos. Lindane and transfluthrin were not found in any of the matrices. The frequency of propoxur ($p<0.001$), pretilachlor ($p<0.001$), DDT ($p<0.037$), cyfluthrin ($p<0.012$) and cypermethrin ($p<0.001$) were significantly higher in meconium compared to cord blood or infant hair (Cochran Q test).

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The concentrations of the pesticides (µg/mL) are shown in Table 3 and median and interquartile ranges are given for cases that were positive for pesticides. However, the statistical test was based on the entire sample and showed that for toxicants, except propoxur, the p value for Friedman test was the same as Cochran Q above. This was because the ranks across the substrates are no different than dichotomous values since the toxicants are only present for one substrate and not present or tied in the other substrates. The concentrations of propoxur ($p < 0.001$), pretilachlor ($p<0.001$), cypermethrin ($p<0.001$), DDT ($p<0.037$) and cyfluthrin ($p<0.012$) were significantly higher in meconium compared to cord blood and infant hair.

Metabolites of pesticides were analyzed only in 416 meconium and cord blood samples since the analysis of remaining samples was discontinued when it became evident that the positive yield was extremely low (only 1 meconium sample was positive for DDE). Infant hair was not analyzed for pesticide metabolites due to insufficient sample.

Discussion

The aim of this study was to determine reliable measures of fetal exposure to environmental pesticides. A few studies have reported on the analysis of cord blood or meconium for pesticides. Cord blood was analyzed together with maternal blood to monitor chlorpyrifos, diazinon and propoxur exposure during pregnancy (16,17). Meconium was analyzed for organophosphates (18), DDE (19), organochlorines (20) and various pesticides (21). However, this is the first report to analyze cord blood, infant hair and meconium samples together to determine the most sensitive matrix to detect antenatal pesticide exposure. Our results show that meconium is, by far, the best matrix for this purpose. Of the eleven pesticides that were analyzed, eight were detected in meconium and for propoxur, the frequency of exposure was 23.8%. In contrast, cord blood and infant hair were each only positive for a single pesticide, propoxur and chlorpyrifos, respectively. We did not analyze infant urine due to inherent problems and difficulty associated with urine collection in infants, compared to cord blood collection. Furthermore, there are inherent problems associated with the interpretation of urine results, particularly if only spot samples were collected (28). We also felt that cord blood represented an appropriate matrix to analyze for exposure to pesticides particularly because parent pesticides can be detected in the blood in contrast to urine (28).

The high rate of detection of pesticides in meconium is consistent with the reported high sensitivity of meconium for the detection of other xenobiotics including illicit drugs, licit drugs, nicotine metabolites and alcohol metabolites (29). This is a consequence of the repository nature of meconium for xenobiotics which facilitates the measurement of a wide window of exposure. Meconium is formed early in gestation and most xenobiotics that the fetus is exposed to during gestation are deposited in meconium, through fetal swallowing and/or bile secretion up to the time of birth (30). Since meconium, unlike fetal urine, is not normally excreted in utero, xenobiotics deposited in meconium accumulate and increase in concentration which further enhances the likelihood of their detection.

In contrast, pesticides in cord blood represent acute exposure and may not be readily detected due to their low concentrations in the blood as a result of the metabolism, excretion and deposition in tissues of the pesticides. Due to the transient state of pesticides in blood, compared to meconium, blood is not an adequate matrix to measure cumulative exposure. A highly sensitive technique to detect pesticides in blood has been published with LOD’s three orders of magnitude lower than our levels. However, the specificity of such a method is compromised since in many instances, only a single mass ion, which is not the molecular ion, was used for compound identity. The authors acknowledge that lowering the LOD, in effect, was associated with an imprecision that was about double those with higher detection limits (31). On the other hand, for this study, we used more stringent criteria for compound identity including appropriate retention time based on positive controls and the presence in the mass spectra of specific mass and qualifier ions as well as appropriate mass/qualifier ion ratios. Our strict criteria may have decreased the sensitivity of the method but has retained the high specificity of the GCMS method.

We did not detect any pesticide in infant hair except in one sample that was positive for chlorpyrifos. It appears that the deposition of pesticides in infant hair does not occur as readily compared to other compounds such as illicit drugs, nicotine, and most recently, fatty acid ethyl esters (32,33). The pharmacokinetics and tissue distribution of pesticides in the fetus is largely unknown. The metabolism of pesticides is low due to the poor detoxification mechanisms (2). Furthermore, fetal hair starts to grow at approximately six to seven months of gestation (32) so that the timing of maternal exposure during pregnancy could also influence incorporation of pesticides into the growing hair shaft. It is also likely that due to the small amount of hair that could be collected from the newborn infant, the limited amount of the sample for analysis prevented the detection of minute quantities of pesticides in infant's hair. In contrast, our results with infant hair analysis differ remarkably with maternal hair which we found to be a better matrix to analyze for pesticides compared to maternal blood (24). In part, this difference may be secondary to more hair sample that could be obtained from the mother for analysis compared to newborn hair. Thus, infant hair is not ideal for the analysis of pesticides due principally to the low concentration of the pesticides and the limited amount of hair that could be collected from the subjects. Furthermore, although pesticide metabolites may deposit in hair, it has also been found that the metabolites tend to partition predominantly towards blood rather than into hair (34).

Almost no pesticide metabolites were detected in the present study in all of the matrices that were analyzed. A number of workers who have studied pesticide metabolite in meconium have found DDE (19) and organophosphate metabolites (18). Hong et al (19) randomly sampled 60 meconium samples in Germany and detected DDE in 3 of them. However, the pesticide metabolite concentration that they detected was 11.1 ng/g, which is lower than our LOD for DDE. Our method had a higher LOD since it was optimized to detect many classes of metabolites, especially the pyrethroids, whereas Hong and colleagues were selectively searching for DDE. However, we did find one meconium sample positive for DDE. Whyatt & Barr (18) found diethylthiophosphate (DETP), an organophosphate metabolite, in 100% of meconium samples studied in New York. We attempted to analyze for this compound using our current meconium liquid-liquid extraction method. However, it was discontinued due to difficulty in the chromatographic separation of DETP from TCP. The survey had reported higher use of malathion and chlorpyrifos, for which we had specific metabolites that we could accurately measure, than for diazinon, for which DETP would be a potential metabolite.

Pesticides that partition and accumulate in adipose tissues such as organochlorines may not be found in sufficient concentrations in blood, urine or meconium. Although DDT was found in meconium, the frequency of detection was low (0.6%). The use therefore of cord blood, infant hair and meconium as matrices for the detection of fetal exposure to these compounds is a recognized limitation of the study. However, access to fetal or infant adipose tissue is normally not feasible; thus its diagnostic use in clinical settings may not be practical. On the other hand, failure to detect lipophilic pesticides from the analysis of non-adipose tissue matrices should not imply non-exposure to these types of pesticides.

Overall, this study has shown that exposure to home pesticides constituted a high exposure risk among pregnant women even in an agricultural setting such as in our study. This observation parallels the reports which have shown a high exposure rate to home pesticides among pregnant women and their infants residing in urban areas (16,17,33). It is therefore evident that whether in city or rural areas, pesticides that are used at home pose a very high exposure risk among pregnant women and can be related to a number of factors such as a widespread and inappropriate use of pesticides at home. Due to a high number of pests (flies, mosquitoes and roaches) in the homes of the subjects, spray pesticides are commonly used (43%), principally Baygon™ (90%) which contains propoxur and cyfluthrin. Inappropriate use of these home pesticides was evident since 38.2% of the spraying was done by the pregnant woman and reentry time to the sprayed area was ≤ 60 minutes in 75% of the cases. Inadequate labeling on the safe use of the pesticide may be a major reason for its improper use. Labels do not warn that the product should not be used by the pregnant woman, nor explicitly instruct on the appropriate reentry time of the sprayed area. Corrective measures to prevent further pesticide exposure have been instituted as a result of our findings. Assessment of the clinical outcome in the child of prenatal and ongoing exposure to pesticides is also under way.

In conclusion, our study has demonstrated that compared to cord blood or infant hair, meconim is the most sensitive matrix to analyze for fetal exposure to pesticides. The accumulation of pesticides in meconium, the ease of meconium collection and the large amount of sample that could be obtained for analysis are all factors that contribute to the increased sensitivity of this matrix.

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Abbreviations

DDT
: 1,1,1-trichloro-2,2-bis, p-chlorophenylethane

DDE
: 4,4′ dichlorodiphenyldichloro ethylene

2-IPP
: 2-isopropoxyphenol

cis-DCCA
: cis-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylic acid

trans-DCCA
: trans-3-(2,2-dichlorovinyl) -2,2-dimethylcyclo propanecarboxylic acid

MMA
: malathion monocarboxylic acid

LOD
: limit of detection

GC/MS
: gas chromatography mass spectroscopy

SES
: socioeconomic status

DETP

diethylthiophosphate

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Table 1

Sociodemographic characteristics of the study populations (n=638)

1. Age of father (yr)	28.5 ± 7.1*
2. Age of mother (yr)	25.8 ± 5.8 *
3. Monthly income (Philippine pesos)	5576 ± 5095*
4. Number of dependents under family support	1.0 ± 1.4*
5. Mean age of children (yr)	2.8 ± 3.7*
6. Number of people in household	5.2 ± 2.6*
7. Number of families in household	1.6 ± 0.8*
8. Socioeconomic scale (Roberto classification)	
Class AB	4.9%
Class C	36.4%
Class D	48.3%
Class E	10.5%
9. Type of house	
Owned	59.4%
Rented	19.9%
Squatter	7.2%
10. Material of house	
Mixed (Cement and wood)	72.5%
Makeshift	6.2%
11. Toilet	
Water seal	82.4%
Flush	7.1%
12. Source of water	
Piped	53.3%
Well	38.9%
13. Waste disposal	
Sewage	26.8%
Canals/river	61.5%
14. Organized garbage collection	58.3%
15. Pests	
Flies	91.7%
Roaches	89.8%
Mosquitoes	97.6%
16. Pesticide spray at home	38.1%
17. Brand of pesticide (Baygon)	92.1%
18. Use of mosquito coil (Katol)	52.7%
19. Home cleanliness (poor)	17.9%
20. Lead recycling plant in environment	7.1%
21. Field pesticide use	16.8%

* mean ± sd

Table 2

Frequency of parent pesticides in meconium, cord blood and infant hair

	Matrix (n =638)			
Pesticide	**Meconium**	**Cord Blood**	**Infant Hair**	**Assymptotic p value**[**]
Propoxur	152 (23.8%)[*]	12 (1.9%)	0	<0.001
Diazinon	1 (0.2%)	0	0	N/A
Lindane	0	0	0	N/A
Transfluthrin	0	0	0	N/A
Malathion	2 (0.3%)	0	0	0.333[a]
Chlorpyrifos	0	0	1 (0.2%)	N/A
Bioallethrin	2 (0.3%)	0	0	0.333[a]
Pretilachlor	12 (1.9%)	0	0	<0.001
DDT	4 (0.6%)	0	0	0.037[a]
Cyfluthrin	5 (0.8%)	0	0	0.012[a]
Cypermethrin	12 (1.9%)	0	0	<0.001

[*] number of positive samples (% of total)

[**] based on Cochran Q test

[a] based on exact test

Table 3

Concentration of parent pesticides in meconium, cord blood and infant hair (μg/mL).

	Substrate (n=638)			
Toxin	**Meconium**	**Cord Blood**	**Infant Hair**	**Assymptotic p value** **
Propoxur	0.33 (0.24–1.51) *	0.77 (0.77–0.77)	0	<0.001
Diazinon	0.34	0	0	N/A
Malathion	4.15 (2.92–5.38)	0	0	0.333[a]
Chlorpyrifos	0	0	2.16	N/A
Bioallethrin	1.20 (0.61–1.79)	0	0	0.333[a]
Pretilachlor	0.52 (0.37–1.38)	0	0	<0.001
DDT	1.75 (1.08–3.13)	0	0	0.037[a]
Cyfluthrin	2.22 (1.21–5.14)	0	0	0.012[a]
Cypermethrin	2.33 (1.91–2.54)	0	0	<0.001

* median and interquartile range given for cases with positive concentration.

** based on Friedman test.

[a] based on exact test