(ADRs) due to the very low frequency of occurrence and thus the ability to acquire a significant patient cohort. In this study, access to an archive of 1900 clinical liver biopsies has enabled the identification of a cohort of 53 individuals displaying histological and biochemical evidence of ADRs. The Pregnane X Receptor (PXR) is a ligand-activated transcription factor known to regulate the transcription of a number of genes involved in hepatic xenobiotic metabolism and bile acid homeostasis. The PXR gene is a candidate for altered functionality in patients with ADRs, in particular drug-induced cholestasis. Sequence analysis of the PXR protein-coding region revealed the presence of a novel non-synonymous single nucleotide polymorphism within the ligand-binding domain. This resulted in a cysteine to arginine change at residue 301 (C301R), identified in 2 of the 53 ADR patients as a heterozygote. The variant has not been found in a cohort of over 300 non-ADR individuals of various ethnic origins. Electrophoretic Mobility Shift Assays using the CYP3A-DR3 response element show that the C301R variant binds to DNA with approximately the same affinity as the wild-type PXR. However, transfection studies using a CYP3A-DR3 reporter plasmid show that C301R has reduced basal transcriptional activity, and impaired responses to the PXR ligands rifampicin and hyperforin, compared to wild-type receptor. Since hepatic ADRs occur at such low frequency, and given that they appear to be multifactorial in their aetiology, it is possible that having enriched for a population of ADRs, one single genetic factor among a large number may have been identified. In the general population this may have such a low occurrence as to have remained undetected without such "enrichment".

1277 MEASURING CHOLINESTERASE ACTIVITY IN HUMAN SALIVA.

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Biomonitoring of organophosphorous and carbamate pesticides has focused primarily on the inhibition of blood cholinesterase. Blood biomonitoring, however, can be invasive, time-consuming, and costly, especially in young children and infants. Therefore, saliva biomonitoring has recently been explored as a practical and feasible alternative to blood. To determine whether an individual's salivary cholinesterase was consistent over time and which of two methods was more accurate and preferable, saliva samples were collected once per week for five consecutive weeks from 20 adults using a Salivette (cotton swab) and pipette. To measure cholinesterase activity, the radiometric method developed by Johnson and Russell (1975) was modified for human saliva by increasing tissue volume, substrate volume, incubation time, and incubation temperature. Using this method, cholinesterase was found to be present and measurable, with good repeatability (2.2% average difference between duplicate samples). Activity in pipette-collected samples ranged from 0 to 153.7 nmol hydrolyzed/min/ml saliva, while activity in Salivette-collected samples was slightly higher: 3.4 to 264.7 nmol hydrolyzed/min/ml saliva. The activity for some individuals was very consistent during the five weeks, whereas for others it was variable, and, in general, variability in activity for the two collection methods was comparable (mean coefficient of variation [CV] for pipette=34.8%; Salivette=35.6%). Cholinesterase levels from the two collection methods were significantly correlated ($r=0.41$, $n=100$, $p<0.05$, two tails). In terms of participant preference, the Salivette was preferred to the pipette method at the majority (86%) of visits. Results from this study demonstrate that (1) cholinesterase is measurable in saliva, (2) in some people (about 50% of our population) the activity is consistent from week to week, and (3) the collection methods yield comparable results, though participants prefer the Salivette. This is an abstract of a proposed presentation and does not reflect Agency policy.

1278 A CONVERSION FACTOR BETWEEN TWO CHOLINESTERASE ASSAYS AND ITS APPLICATION IN ESTABLISHING A NORMAL RANGE FOR HUMAN RBC ACHE.

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The Cholinesterase (ChE) Reference Laboratory (CRL) at the US Army Center for Health Promotion and Preventive Medicine (USACHPPM) uses a modification of the delta pH method of Michel to annually analyze over 15, 000 blood specimens from personnel that predominantly work at chemical agent storage sites and chemical demilitarization facilities. UC Davis and CRL are collaborating to derive a conversion factor between the delta pH and the colorimetric Ellman ChE assays. The factor is used to estimate a normal range of Ellman determined human blood acetylcholinesterase (AChE) levels based on CHPPM's data. Human red blood cells (RBCs) from three volunteers were assayed at UCD by the delta pH and Ellman methods according to standard procedures. Both assays were carried out at 25 °C, and with optimal final substrate concentrations: 10 mM acetylcholine bromide for the delta pH assay and 1 mM acetylthiocholine iodide for the Ellman assay. RBCs were treated with diisopropyl fluorophosphate to generate a dose/response curve of inhibition. This yielded an approximate conversion factor: delta pH = 0.091 Ellman + 0.052 with an r^2 of 0.96. This approach permits converting the extensive CRL database of baseline (presumably unexposed) delta pH AChE values into a normal range of Ellman AChE activities, assays used to evaluate occupational exposure to pesticides. The estimated normal 95% range of human AChE for the Ellman assay was 7.12 to 9.10 umol/min/mL with a mean value of 8.23 ± 0.62 SD umol/min/mL. This work was supported by the US Army Medical Research and Materiel Command under Grant Project Order DAMD17-01-1-0772, NIOSH (#CDC U07/CCU906162-06) and NIEHS (#ESO5707).

1279 PESTICIDE EXPOSURE ASSESSMENT: CONCURRENT PASSIVE DOSIMETRY AND BIOLOGICAL MONITORING OF TRICLOPYR AND 2, 4-D EXPOSURES OF A BACKPACK APPLICATOR CREW.

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Strategies for pesticide exposure assessment represent different levels of quantitative certainty. This study concerned the consistency of exposure monitoring of workers using backpack sprayers. A crew of 8 applicators, a mixer/loader, and a supervisor applied two herbicides, triclopyr and 2, 4-D, as a tank mix for weed control in forestry. When coveralls were used as a passive dosimeter, the average residues recovered were 2.50 ± 1.55 mg equiv/d for triclopyr and 0.75 ± 0.52 mg equiv/d for 2, 4-D. When the herbicides were collected on cotton whole body dosimeters worn beneath the coveralls, measurements were reduced to 0.22 ± 0.23 mg equiv/d and 0.14 ± 0.17 mg equiv/d (n=5) respectively. Cotton gloves (under nitrile gloves) and socks, and face/neck skin wipes were included in each case but they contributed less than 1% to the exposure estimate. Urine specimens (24 h) were analyzed for triclopyr and 2, 4-D, the biomarkers. The excreted doses of triclopyr and 2, 4-D were 5.2 ± 4.3 µg equiv/d and 3.8 ± 3.4 µg equiv/d respectively. Their corresponding excreted daily dosage was 0.072 ± 0.057 and 0.052 ± 0.044 µg equiv/kg-d respectively. Based upon these results, the estimated clothing penetration was 11% for triclopyr and 20% for 2, 4-D. Their respective dermal absorption rates were 3.6%/d and 4.2%/d. For backpack application of triclopyr and 2, 4-D, worker dose based upon external pesticide deposition on coveralls was nearly 340-times and 180-times more than the dose determined by biomonitoring. Although external measures predicted excessive applicator exposures, use of backpack sprayers in a rugged forest terrain minimized releases to the forest environment and resulted in worker exposures far below toxic levels.

1280 ENVIRONMENTAL INDUCTION OF CYP1A-, CYP2M1- AND CYP2K1-LIKE PROTEINS IN TROPICAL FISH SPECIES BY PRODUCED FORMATION WATER ON THE NORTHWEST SHELF OF AUSTRALIA.

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Normal operation of oil well platforms results in the discharge of produced formation water (PFW). The expression of CYP1A, CYP2M1- and 2K1-like proteins was examined in Gold-Spotted Trevally (Carangoides fulvoguttatus) and Bar-Cheeked Coral Trout (Plectropomus maculatus) as possible biomarkers of PFW impact. The results of this pilot study indicated PFW contamination near the Harriet A platform may contribute to induction of CYP1A- and 2M1-like proteins in Trevally, while other contaminants associated with PFW may induce a CYP2K1-like protein. In a 2003 caged fish study, Stripey seaperch (Lutjanus carponotatus) were caught at a clean site, then distributed to three caging sites: A (near field), B (far field) and C (a non-impacted reference site). Fish were sampled at time (T) zero, T=3 and T=10 days. Significant increases of CYP1A, one CYP2K1- and two CYP2M1-like proteins were noted at Site A at T=10. For the other CYP2K1-like protein, a significant increase was observed at site A only at T=3, but not at T=10. Prevailing winds switched between day 6 and day 10 of sampling, moving the surface water due west, therefore exposing the fish to different components of PFW that may possibly induce this CYP2K1-like protein. These results indicate that CYP1A protein is sensitive to PFW exposure and may act as a good biomarker. Importantly, statistically significant environmental induction of both CYP2M1- and CYP2K1-like proteins in tropical fish due to PFW exposure has not previously been described and represents possible new biomarkers (other than CYP1A) of PFW fraction-specific contamination. (Supported by Apache Energy Party Ltd., Australian Institute of Marine Science and the Environmental Toxicology Research Program of University of Mississippi)

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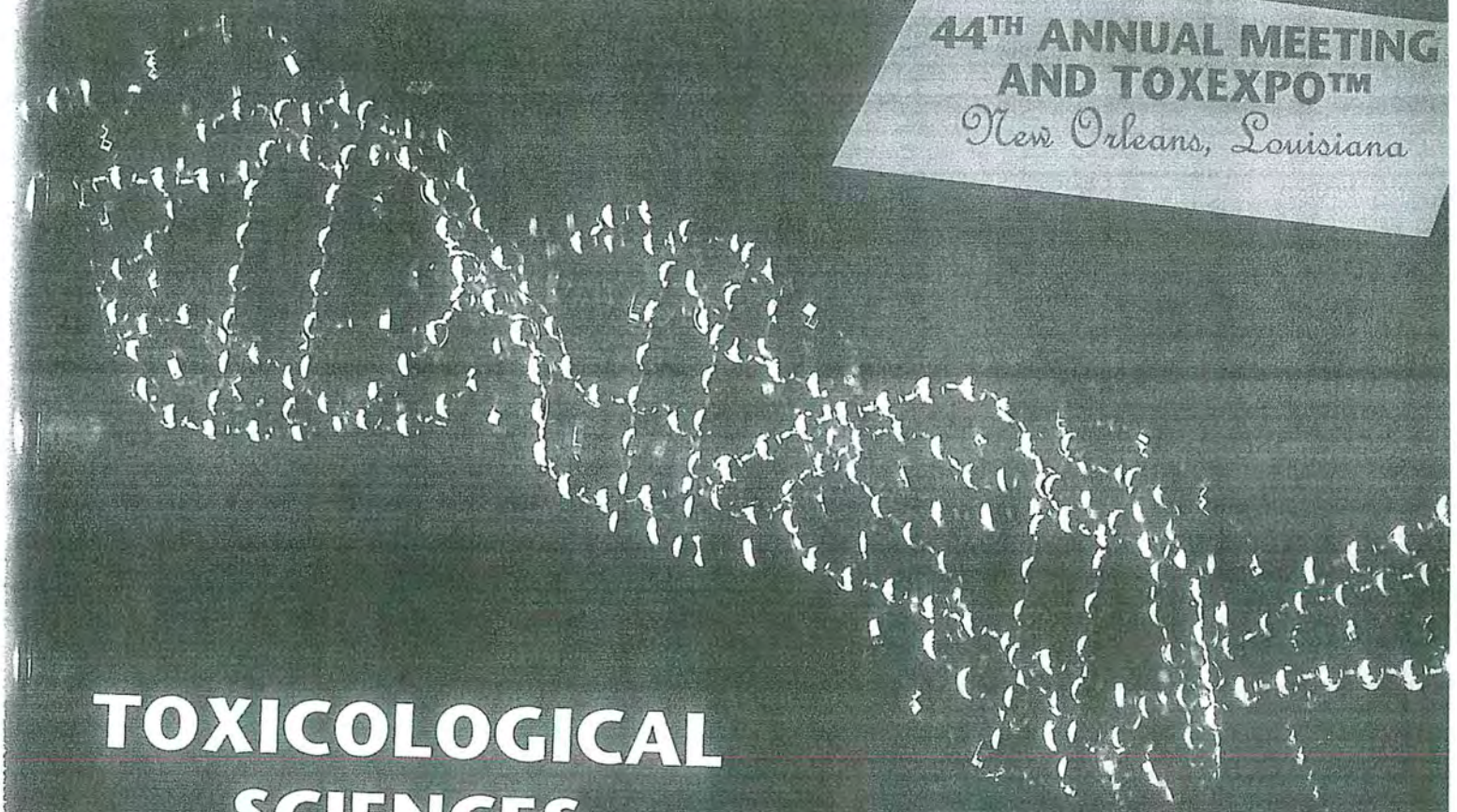

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