TRIMETHYLBENZENE PRELIMINARY SEARCH RESULTS: CHRONIC AND LESS-THAN-LIFETIME TOXICITY STUDIES
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POTENTIAL KEY REFERENCES (38)

1. Brasington RD, Jr., Thorpe-Swenson AJ. (1991) Systemic sclerosis associated with cutaneous exposure to solvent: case report and review of the literature. Arthritis Rheum 34(5):631-633.
   Sclerodermatous skin changes and systemic sclerosis have been reported to occur as a result of contact with several different organic solvents. We describe a 41-year-old man who developed systemic sclerosis after working for 15 years in a foundry, where he had extensive cutaneous contact with multiple organic solvents (trichloroethane, xylene, trimethylbenzene, and naphthalene). Cutaneous exposure to organic solvents may be a factor in the etiology of some cases of systemic sclerosis.

2. Dahl AR, Damon EG, Mauderly JL, Rothenberg SJ, Seiler FA, McClellan RO. (1988) Uptake of 19 hydrocarbon vapors inhaled by F344 rats. Fundam Appl Toxicol 10(2):262-269.
   The comparative rates of uptake of 19 hydrocarbon vapors by rats were determined by a dual-column gas chromatograph method. The hydrocarbons ranged in volatility from propylene (BP -47.7 degrees C) to 1,2,4-trimethylbenzene (BP 169 degrees C). Representative compounds from the chemical classes of alkenes, alkynes, straight-chain and branched alkanes, alicyclics, and aromatics were examined. Trends observed included: (1) highly volatile hydrocarbons were less well-absorbed than less volatile hydrocarbons; (2) unsaturated compounds were better absorbed than saturated ones; and (3) branched hydrocarbons were less well-absorbed than unbranched ones. The data indicate that uptake rates among inhaled hydrocarbon vapors may be predicted from the molecular structures and physical properties of the hydrocarbons.

3. Eide I, Zahlsen K. (1996) Inhalation experiments with mixtures of hydrocarbons. Experimental design, statistics and interpretation of kinetics and possible interactions. Arch Toxicol 70(7):397-404.
   The paper describes experimental and statistical methods for toxicokinetic evaluation of mixtures in inhalation experiments. Synthetic mixtures of three C9 n-paraffinic, naphthenic and aromatic hydrocarbons (n-nonane, trimethylcyclohexane and trimethylbenzene, respectively) were studied in the rat after inhalation for 12h. The hydrocarbons were mixed according to principles for statistical experimental design using mixture design at four vapour levels (75, 150, 300 and 450 ppm) to support an empirical model with linear, interaction and quadratic terms (Taylor polynome). Immediately after exposure, concentrations of hydrocarbons were measured by head space gas chromatography in blood, brain, liver, kidneys and perirenal fat. Multivariate data analysis and modelling were performed with PLS (projections to latent structures). The best models were obtained after removing all interaction terms, suggesting that there were no interactions between the hydrocarbons with respect to absorption and distribution. Uptake of paraffins and particularly aromatics is best described by quadratic models, whereas the uptake of the naphthenic hydrocarbons is nearly linear. All models are good, with high correlation (r2) and prediction properties (Q2), the latter after cross validation. The concentrations of aromates in blood were high compared to the other hydrocarbons. At concentrations below 250 ppm, the naphthene reached higher concentrations in the brain compared to the paraffin and the aromate. Statistical experimental design, multivariate data analysis and modelling have proved useful for the evaluation of synthetic mixtures. The principles may also be used in the design of liquid mixtures, which may be evaporated partially or completely.

4. Fukaya Y, Saito I, Matsumoto T, Takeuchi Y, Tokudome S. (1994) Determination of 3,4-dimethylhippuric acid as a biological monitoring index for trimethylbenzene exposure in transfer printing workers. Int Arch Occup Environ Health 65(5):295-297.
   The relationship between exposure to 1,2,4-trimethylbenzene (1,2,4-TMB) and urinary concentration of 3,4-dimethylhippuric acid (3,4-DMHA), one of its metabolites, was studied in workers involved in transfer printing. Airborne TMBs were sampled by an organic vapor monitoring badge and analyzed by capillary gas chromatography. Urinary 3,4-DMHA and creatinine were analyzed under the same conditions of high-performance liquid chromatography. The exposure concentration of 1,2,4-TMB among workers was around

25 ppm, the threshold limit value (TLV). The urinary concentration of 3,4-DMHA was low at the start of each shift and high at the end. Exposure to the TLV (25 ppm) of 1,2,4-TMB results in a urinary 3,4-DMHA concentration of 410 mg/g creatinine ($r = 0.897$, $P < 0.001$). Urinary 3,4-DMHA concentration could be used as a biological monitoring index for 1,2,4-TMB exposure.

5. Gralewicz S, Wiaderna D. (2001) Behavioral effects following subacute inhalation exposure to m-xylene or trimethylbenzene in the rat: a comparative study. Neurotoxicology 22(1):79-89.
   Trimethylbenzene (TMB), like xylene (dimethylbenzene), is a significant constituent of some industrial solvent mixtures. In earlier studies, we found that in the rat a subacute low-level inhalation exposure to some of the TMB isomers may result in behavioral alterations detectable weeks after the exposure [Neurotoxicol Teratol 19;1997:327; Int J Occup Med Environ Health 11;1998:319]. The purpose of the present study was to compare m-xylene (XYL) and each of the TMB isomers: 1,2,3-TMB (hemimellitene - HM), 1,2,4-TMB (pseudocumene - PS), and 1,3,5-TMB (mesitylene - MES) with respect to the ability for inducing behavioral effects in the rat. The rats (10-11 animals per group) were exposed repeatedly for 4 weeks (6 h per day, 5 days per week) to XYL (XYL group), HM (HM group), PS (PS group) or MES (MES group) at 100 ppm, or sham exposed (C group) in 1.3 cu/m dynamic inhalation chambers. Starting 2 weeks after exposure the following forms of rat's behavior were assessed: radial maze performance, spontaneous activity in an open field, learning and retention of passive and active (two-way) avoidance response, and heat-induced paw licking before and after a 2 min footshock (a test for assessment of the stress response). None of the solvent-exposed groups differed considerably from the control one with respect to the radial maze performance. Compared to control rats, the rats of the XYL, PS and MES groups, but not those of HM group, showed a significantly higher spontaneous locomotor activity in the open field, an impaired passive avoidance learning and significantly longer paw-lick latencies 24 h after footshock. Acquisition, but not retention, of the two-way active avoidance response was significantly impaired in all solvent-exposed groups. The XYL group did not differ significantly from PS, MES or HM group in any of the behavioral parameters. The above results show that a short-term exposure to any of the TMB isomers or m-xylene at concentration as low as 100 ppm may induce persistent behavioral alterations in the rat.

6. Gralewicz S, Wiaderna D, Tomas T. (1997) Retardation of the age-related increase in spontaneous cortical spike-wave discharges (SWD) in rats after a 28-day inhalation (SWD) in rats after a 28-day inhalation exposure to an industrial solvent, pseudocumene (1,2,4-trimethylbenzene). Int J Occup Med Environ Health 10(2):213-222.
   It has been hypothesized that exposure to neurotoxins may hasten the process of brain ageing. Volatile hydrocarbons are in common use as solvents and their neurotoxic properties are acknowledged. In the rat, the age-related neurodegenerative changes in the brain develop together with an increased occurrence of bursts of spontaneous spike-wave discharges (SWD) in the neocortex. Therefore, the number and/or duration of SWD bursts may serve as an index allowing to distinguish between young and old brains (7). Measuring the SWD activity after exposure may thus reveal the effect of the studied neurotoxicant on brain ageing. Pseudocumene (1,2,4-trimethylbenzene, TMB), is a component of industrial solvent mixtures. The present study investigated the effect of a 4-week (6h/day, 5 days/week) inhalation exposure to TMB at concentrations of 0, 25, 100 or 250 ppm on the occurrence of SWD bursts. EEG recordings were performed before and one day, 30 days and 4 months after exposure. In rats exposed to TMB at 0 and 25 ppm, the level of the SWD activity increased progressively after exposure. In rats exposed to TMB at 100 or 250 ppm, the SWD activity did not increase during the post-exposure period or even dropped below the pre-exposure level. This result indicates that the persistent changes in the rat central nervous system (CNS), following the exposure to TMB, differ in some respects from those which develop in the course of normal ageing.

7. Gralewicz S, Wiaderna D, Tomas T, Rydzynski K. (1997) Behavioral Changes Following 4-Week Inhalation Exposure to Pseudocumene (1,2,4-Trimethylbenzene) in the Rat. Neurotoxicology and Teratology 19(4):327-333.
   Pseudocumene (1,2,4-trimethylbenzene, TMB) is a component of several solvent mixtures. During recent studies on rats we investigated the effect of a 4-week (6 h/day, 5 days/week) inhalation exposure to TMB at concentrations of 0, 25, 100, or 250 ppm on radial maze performance, open field activity, passive avoidance, active two-way avoidance, and shock-induced changes in the pain sensitivity reflecting the magnitude of the shock-induced fear response (hot plate test). The tests were performed between days 14

and 54 after the last exposure. The radial maze performance was not disturbed in any dose group. During testing in the open field grooming was significantly increased in rats exposed to 100 ppm TMB. In rats exposed to 100 and 250 ppm TNB, a foot shock applied after stepping off an elevated platform (a safe area) resulted in a significantly smaller increase in the step-down latency (i.e., passive avoidance, on days 3 and 7 after the foot shock) than in sham-exposed animals. Learning of a two-way active avoidance was slightly retarded in rats exposed to 250 ppm of TMB. Results of the hot plate test revealed no differences between groups in the paw sensitivity to heat (54.5°C) before a 2-min intermittent foot shock, but in rats exposed to 100 and 250 ppm of TMB the foot shock-induced fear response persisted apparently longer. These results suggest that inhalation exposure to TMB may lead to long-lasting disturbances in CNS functions.

8. Hissink AM, Kruse J, Kulig BM, Verwei M, Muijser H, Salmon F, Leenheers LH, Owen DE, Lammers JH, Freidig AP and others. (2007) Model studies for evaluating the neurobehavioral effects of complex hydrocarbon solvents III. PBPK modeling of white spirit constituents as a tool for integrating animal and human test data. Neurotoxicology 28(4):751-760.
   As part of a project designed to develop a framework for extrapolating acute central nervous system (CNS) effects of hydrocarbon solvents in animals to humans, experimental studies were conducted in rats and human volunteers in which acute CNS effects were measured and toxicokinetic data were collected. A complex hydrocarbon solvent, white spirit (WS) was used as a model solvent and two marker compounds for WS, 1,2,4-trimethyl benzene (TMB) and n-decane (NDEC), were analyzed to characterize internal exposure after WS inhalation. Toxicokinetic data on blood and brain concentrations of the two marker compounds in the rat, together with in vitro partition coefficients were used to develop physiologically based pharmacokinetic (PBPK) models for TMB and NDEC. The rat models were then allometrically scaled to obtain models for inhalatory exposure for man. The human models were validated with blood and alveolar air kinetics of TMB and NDEC, measured in human volunteers. Using these models, it was predicted that external exposures to WS in the range of 344-771mg/m(3) would produce brain concentrations similar to those in rats exposed to 600mg/m(3) WS, the no effect level (NOEL) for acute CNS effects. Assuming similar brain concentration-effect relations for humans and rats, the NOEL for acute CNS effects in humans should be in this range. The prediction was consistent with data from a human volunteer study in which the only statistically significant finding was a small change in the simple reaction time test following 4h exposure to approximately 570mg/m(3) WS. Thus, the data indicated that the results of animal studies could be used to predict a no effect level for acute CNS depression in humans, consistent with the framework described above.

9. Huo JZ, Aldous S, Campbell K, Davies N. (1989) Distribution and metabolism of 1,2,4-trimethylbenzene (pseudocumene) in the rat. Xenobiotica 19(2):161-170.
   1. Single doses of 1,2,4-trimethylbenzene (124TMB) or 14C-124TMB were administered orally to rats for metabolism and distribution studies. 2. 14C-124TMB was rapidly and widely distributed throughout the body with the highest levels in adipose tissue. No other preferential uptake of 14C-124TMB by any of the organs or tissues examined was evident. 3. Tissue levels declined rapidly within 24 h after dosage, with more than 99% of the administered radioactivity recovered in the urine during this period. 4. A complex mixture of isomeric trimethylphenols, dimethylbenzyl alcohols, dimethylbenzoic acids and dimethylhippuric acids excreted in the urine accounted for more than 81% of the administered dose. The major metabolites were 3,4-dimethylhippuric acid (30.2% dose), 2,4-dimethylbenzyl alcohol (12.7% dose, primarily as sulphate and glucuronide conjugates) and 2,5-dimethylbenzyl alcohol (11.7% dose, primarily as sulphate and glucuronide conjugates).

10. Ichiba M, Hama H, Yukitake S, Kubota M, Kawasaki S, Tomokuni K. (1992) Urinary excretion of 3,4-dimethylhippuric acid in workers exposed to 1,2,4-trimethylbenzene. Int Arch Occup Environ Health 64(5):325-327.
    The urinary excretion of 3,4-dimethylhippuric acid (34DMHA), a 1,2,4-trimethylbenzene (124TMB) metabolite, was investigated in workers exposed to 124TMB vapor. The time-weighted average of exposure to 124TMB was determined with a diffusive sampler. For biological monitoring of exposure, urine samples were collected from individual workers and analyzed for metabolites by high-pressure liquid chromatography. The concentration of urinary 34DMHA had a positive correlation with the level of exposure to 124TMB ($r = 0.72$). The data suggest that 34DMHA is one of the useful indicators for biological monitoring of 124TMB exposure.

11. Jajte J, Korsak Z, Rydzynski K, Stetkiewicz J, Swiercz R. (1995) Toxic Effects of 1,2,4-Trimethylbenzene (Pseudocumene) After Acute and Subchronic Inhalation Exposure. Toxicology Letters 78:49-49.
POSTER ABSTRACT -- Single inhalation exposure to pseudocumene was found to produce concentration-dependent neurotoxic effects in rats and sensory respiratory tract irritation in mice. The disturbances in rotarod performance (EC50 = 954 ppm) and a decrease in pain sensitivity (EC50 = 1155 ppm) were noted. The concentration of pseudocumene which reduced the respiratory rate by 50% in Balb/C mice (RD50) was 578 ppm. 90-day repeated inhalation exposure of rats to pseudocumene at concentrations of 25, 100 and 250 ppm brought about concentration-dependent pathological changes in the respiratory system, as well as erythropenia, leucocytosis and decreased coagulation time. Ultrastructure of pneumocytes (type II) was affected at concentration of 250 ppm. Increased total protein content, LDH, beta-glucuronidase, and phosphatase activities in bronchoalveolar lavage supernatant were observed. Rotarod performance test revealed also neurotoxic effects of the compound during and 14 days after 90-day repeated exposure. Based on the respiratory tract irritation, hematopoietic and neurotoxic effects a NOAEL of 25 ppm and LOAEL of 100 ppm is proposed.

12. Janasik B, Jakubowski M, Jalowiecki P. (2007) Excretion of unchanged volatile organic compounds (toluene, ethylbenzene, xylene and mesitylene) in urine as result of experimental human volunteer exposure. Int Arch Occup Environ Health.
OBJECTIVES: To investigate elimination of unchanged volatile organic compounds (VOC's) through urine and the use of respective data for occupational exposure assessment, six volunteers were exposed under controlled conditions to toluene (TOL), ethylbenzene (EB), xylene (XYL) and mesitylene (MES) at concentrations ranging from 20 to 200 mg/m(3). The study was to elicit the toxicokinetic data and compare the precision of VOC's exposure assessment based on determining unchanged compounds in blood, urine and their metabolites in urine. METHODS: During and after exposure blood and urine samples were analysed by gas chromatography using the headspace and SPME headspace technique RESULTS: The kinetics of VOC's elimination in urine complied with an open two-compartment model. The (half-time) T (1/2)values varied from 0.45 to 0.88 h for phase I and from 6.7 to 19.2 h for phase II. The precision of the method for unchanged VOC's was similar to that based on unchanged compounds in blood and better than their main metabolites in urine. CONCLUSION: The obtained result indicate that determining unchanged VOC's in urine can be used as an exposure test even in the ranges of VOC's in the air that are much lower than the current TWA for occupational exposure.

13. Janik-Spiechowicz E, Wyszynska K, Dziubaltowska E. (1998) Genotoxicity evaluation of trimethylbenzenes. Mutat Res 412(3):299-305.
The three trimethyl isomers of benzene (hemimellitene, 1,2,3-TMB; pseudocumene, 1,2,4-TMB and mesitylene, 1,3,5-TMB) were investigated for different genotoxicity endpoints: in vitro, in the Ames test with Salmonella typhimurium TA97a, TA98, TA100 and TA102 strains in the presence and absence of rat liver S9 metabolic activation; in vivo, in the micronucleus and sister chromatid exchange (SCE) tests with bone marrow cells of Imp:Balb/c mice. Only the isomer of benzene with the methyl-group at position 1, 2, 3 was found to have mutagenic effect on S. typhimurium cells. Increase in bacterial reversions was observed in four conventional strains used in this study, but most clearly in TA97a. The mutagenic responses of 1,2,3-TMB with the SalmonellaL tester strains were observed in the experiments performed in the absence of enzymatic activation. None of the compounds had an influence on the frequency of micronucleated polychromatic erythrocytes in bone marrow cells of mice. However, all the three compounds were observed to have a cytogenetic potential of increasing the SCE level in these cells. Significant responses in SCE induction, compared with the level of those changes in corresponding solvent-administered controls, were obtained at three test doses of 1,2,3-TMB (730, 1470, 2200 mg/kg) and 1,2,4-TMB (900, 1800, 2700 mg/kg) and at two doses of 1,3,5-TMB (1800, 2700 mg/kg). These data provided a limited evidence for the genotoxic activity of 1,2,3-TMB and inadequate evidence for genotoxic activity of 1,2,4-TMB and 1,3,5-TMB.

14. Jarnberg J, Johanson G. (1999) Physiologically based modeling of 1,2,4-trimethylbenzene inhalation toxicokinetics. Toxicol Appl Pharmacol 155(3):203-214.
A physiologically based toxicokinetic model was developed for inhalation exposure of 1,2,4-trimethylbenzene (TMB) in man. The model consists of six compartments for TMB and one compartment

for the metabolite 3,4-dimethylhippuric acid (DMHA). Based on previous experimental findings from human exposures to TMB, liver metabolism was divided in two pathways, one of the first order and one of the Michaelis-Menten type. Muscle tissue was split in two compartments to account for working and resting muscle tissues during bicycle exercise. The model was used to investigate how various factors influence potential biomarkers of exposure, i.e., TMB in blood and exhaled air and DMHA in urine. Increasing the work load from rest to moderate exercise (100 W) more than doubled all biomarker levels end of shift. The effect on next morning levels was even more pronounced, illustrated by a fivefold increase in the DMHA excretion rate. Simulations of five daily 8-h exposures suggest that biomarker levels end of shift remain fairly constant whereas the levels prior to shift increase gradually during the week. This suggests that end of shift levels reflect the exposure of the same day whereas levels Friday morning reflect exposure during the entire working week. Simulations with randomly generated exposures show that the variability due to fluctuating exposure is lower next morning than end of shift. End of shift exhalation rate of TMB is more sensitive to fluctuation than TMB in venous blood and DMHA in urine. Biomarker levels for 25 ppm exposure at different sampling times are given.

15. Jarnberg J, Johanson G, Lof A. (1996) Toxicokinetics of inhaled trimethylbenzenes in man. Toxicol Appl Pharmacol 140(2):281-288.
    The objective of this study was to determine the uptake and disposition of inhaled trimethylbenzenes (TMBs) in man. The toxicokinetics were studied in 10 male, healthy volunteers exposed to TMB vapor in an exposure chamber for 2 hr during a work load of 50 W. The subjects were exposed on four occasions to 25 ppm of 1,2,4-TMB, 1,2,3-TMB, and 1,3,5-TMB, and to 2 ppm of 1,2,4-TMB. The TMB isomers were analyzed in blood, urine, and exhaled air by gas chromatography. The relative respiratory uptake was in the range 56-64%. The elimination of TMBs was moderate compared to other aromatic solvents, with a total blood clearance of 0.6-1.0 liter hr(-1) kg(-1). Large volumes of distribution (30-39 liters/kg) and long terminal half-lives of the TMBs in blood (78-120 hr) imply extensive accumulation in adipose tissue. Exhalation during and postexposure accounted for 20-37% of the absorbed amount, whereas the urinary excretion of unchanged TMBs was low (< or = 0.002%). The kinetics of 1,2,4-TMB seemed linear up to 25 ppm. In addition, the occurrence of symptoms of acute effects was studied by means of a questionnaire. The subjects rated the degree of irritation and central nervous system symptoms on a 100-mm visual analog scale. No discomfort was reported at these exposure conditions.

16. Jarnberg J, Johanson G, Lof A, Stahlbom B. (1998) Toxicokinetics of 1,2,4-trimethylbenzene in humans exposed to vapours of white spirit: comparison with exposure to 1,2,4-trimethylbenzene alone. Arch Toxicol 72(8):483-491.
    This study compares the toxicokinetics of inhaled 1,2,4-trimethylbenzene (124TMB) in men exposed to white spirit with that previously observed in the same individuals exposed to 124TMB alone. The appropriateness of using dimethylhippuric acid (DMHA) metabolites of 124-, 123- and 135TMB in urine as biomarkers of exposure is also addressed and the kinetics of n-decane, n-undecane and 123TMB is investigated. The toxicokinetics of 124TMB was studied in nine male, healthy volunteers exposed to solvent vapours in an exposure chamber for 2 h during a work load of 50 W. The subjects were exposed to 2 ppm (11 mg/m3) of 124TM B during exposure to 300 mg/m3 of white spirit. The 124TMB isomer was analysed in blood, urine and exhaled air by gas chromatography. The DMHA metabolites of all three TMB isomers were analysed in urine by high-performance liquid chromatography. The results were compared with previously published exposures to 2 and 25 ppm (120 mg/m3) of 124TMB vapour alone. In addition, the occurrence of acute effects was studied by means of a questionnaire. Irritation and central nervous system (CNS) symptoms were recorded by ratings on a 100 mm visual analogue scale. Blood levels of 124TMB and excretion rates of 3,4-DMHA in urine were markedly elevated both during and after exposure to white spirit compared to the same exposure level of 124TMB alone. No irritation or CNS effects were reported in the questionnaire at any exposure condition. It appears that components in white spirit interfere with the metabolic elimination of 124TMB. This should be considered in biological exposure monitoring as well as in risk assessment.

17. Jarnberg J, Stahlbon B, Johanson G, Lof A. (1997) Urinary excretion of dimethylhippuric acids in humans after exposure to trimethylbenzenes. Int Arch Occup Environ Health 69(6):491-497.
    The aim of this study was to determine the urinary excretion of dimethylhippuric acids (DMHAs) in humans after experimental chamber exposure to trimethylbenzene (TMB) vapor. The DMHAs have been

put forward as suitable biomarkers of exposure to products containing TMBs such as white spirit and petrol. Ten healthy male volunteers were exposed to TMB vapor in an exposure chamber for 2 h at a work load of 50 W. The subjects were exposed on four occasions, to 25 ppm of 1,2,4-TMB, 1,2,3-TMB, and 1,3,5-TMB, respectively, and 2 ppm of 1,2,4-TMB. Urine was collected from the onset of exposure until the following morning. All six possible DMHA isomers were analyzed by high-performance liquid chromatography. About 22% of the inhaled amount of 1,2,4-TMB was excreted as DMHAs within 24 h, mainly as 3,4-DMHA. The 24-h recovery of 1,2,3-TMB as DMHAs was 11%. Only 3% of the absorbed amount of 1,3,5-TMB was excreted as 3,5,-DMHA. The half-times of the different DMHA isomers ranged from 4 to 16 h. In addition to analysis of DMHAs, the excretion of unconjugated dimethylbenzoic acids in urine was estimated to account for approximately 3% of the dose of all TMBs. In conclusion, the urinary excretion of DMHA isomers may serve as a good indicator of TMB exposure. In this controlled short-term-exposure study the sum of excretion rate of several DMHA isomers reflected exposure more closely than did the excretion rate of any single DMHA.

18. Jones K, Meldrum M, Baird E, Cottrell S, Kaur P, Plant N, Dyne D, Cocker J. (2006) Biological monitoring for trimethylbenzene exposure: a human volunteer study and a practical example in the workplace. Ann Occup Hyg 50(6):593-598.
    This paper presents data from both a human volunteer study looking at exposure to 1,3,5-trimethylbenzene (TMB) and an occupational hygiene study of a printing firm using screen wash containing technical grade TMB. The biomarkers measured were TMB in blood and breath, and urinary dimethylbenzoic acids (DMBAs). The volunteer (N = 4) study showed that TMB was rapidly absorbed into the bloodstream reaching a mean level of 0.85 micromol l(-1) during a 4 h exposure to 25 p.p.m. TMB. There was little decline 1 h post-exposure possibly indicating storage of TMB in adipose tissue. Breath TMB levels peaked within an hour of exposure commencing and averaged 137 nmol l(-1) during exposure. Elimination of TMB in breath was biphasic with an initial half-life of 60 min. Peak excretion of urinary DMBA occurred 4-8 h after the end of exposure and averaged 40 mmol mol(-1) creatinine. Elimination of DMBA in urine was biphasic with half-lives of 13 and 60 h indicating that accumulation of body burden throughout the working week is likely if exposure is repeated. The occupational hygiene study demonstrated an excellent correlation between personal air TMB levels and post-shift urinary DMBA levels (r = 0.997) collected on the third working day. The regression equation from this study indicates that 8 h exposure to 25 p.p.m. TMB would result in a urinary DMBA level of 206 mmol mol(-1) creatinine. All workers showed pre-shift levels of DMBA from exposure to TMB on previous days. Both urinary DMBA and breath TMB levels can be used as biomarkers of TMB exposure. Urine samples should be taken post-shift towards the end of the working week as significant body burden accumulation throughout the working week can be expected. Breath sampling is more suited to task or single-shift monitoring.

19. Kenndler E, Schwer C, Huber JF. (1989) Determination of 1,2,4-trimethylbenzene (pseudocumene) in serum of a person exposed to liquid scintillation counting solutions by GC/MS. J Anal Toxicol 13(4):211-213.
    1,2,4-Trimethylbenzene (pseudocumene) is often used as the solvent for liquid scintillation counting solutions. In the present work, the determination of 1,2,4-trimethylbenzene in the serum of a person exposed to the solvent vapor during the handling of liquid scintillation counting cocktails is described. The identification of 1,2,4-trimethylbenzene was carried out by GC/MS. The analyte was quantified by GC with flame ionization detection. The detection limit of the method is 0.01 ppm. Two hours after exposure of a person to the solvent vapor, the concentration of 1,2,4-trimethylbenzene in her serum was found to be 0.20 ppm.

20. Korsak Z, Rydzynski K. (1996) Neurotoxic effects of acute and subchronic inhalation exposure to trimethylbenzene isomers (pseudocumene, mesitylene, hemimellitene) in rats. Int J Occup Med Environ Health 9(4):341-349.
    Neurotoxic effects of trimethylbenzene isomers (pseudocumene, mesitylene and hemimellitene) in male rats were investigated in conditions of acute and subchronic inhalation exposure. Rotarod performance and pain sensitivity behaviour were tested in rats exposed to trimethylbenzenes at concentrations of 250-2,000 ppm immediately after termination of a 4-hour exposure. Exposure to each of trimethylbenzene isomers resulted in concentration-dependent disturbances in rotarod performance, and decrease in pain sensitivity in rats. Pseudocumene, mesitylene and hemimellitene EC50 values for rotarod performance behaviour disturbances were 954, 963, 768 ppm and for decreases in pain sensitivity EC50 were 1,115, 1,212, 848,

ppm, respectively. In conditions of subchronic inhalation exposure, pseudocumene and hemimellitene at concentrations of 25, 100 and 250 ppm caused concentration-dependent disturbances in rotarod performance behaviour and decrease in pain sensitivity. Neurotoxic effect of hemimellitene was more pronounced than that of pseudocumene and mesitylene. Two weeks after cessation of inhalation exposure to pseudocumene or hemimellitene no recovery in rotarod performance behaviour was observed.

21. Korsak Z, Rydzynski K, Jajte J. (1997) Respiratory irritative effects of trimethylbenzenes: an experimental animal study. Int J Occup Med Environ Health 10(3):303-311.
Sensory respiratory irritation effects of trimethylbenzene isomers (TMBs) (hemimellitene, mesitylene and pseudocumene) in male Balb/C mice were investigated in conditions of acute exposure and in male Wistar rats in conditions of repeated 90-day inhalation exposure to pseudocumene. The pseudocumene, mesitylene and hemimellitene concentrations depressing the respiratory rate to 50% (RD50) were 578, 519, 541 ppm, respectively. Inhalation exposure to pseudocumene for 90 days increased the total number of cell macrophages, polymorphonuclear leukocytes and lymphocytes number at all three test concentrations compared with the controls. Total protein lactate dehydrogenase (LDH) and acid phosphatase activity in bronchoalveolar lavage (BAL) were significantly increased in all exposed groups. Based on the effects observed in the respiratory tract, the threshold limit value of at least 10 ppm should be considered for the occupational exposure to trimethylbenzene isomers.

22. Korsak Z, Stetkiewicz J, Majcherek W, Stetkiewicz I, Jajte J, Rydzynski K. (2000) Sub-chronic inhalation toxicity of 1,2,4-trimethylbenzene (pseudocumene) in rats. Int J Occup Med Environ Health 13(2):155-164.
Toxic effects of exposure of 1,2,4-trimethylbenzene (pseudocumene) in the condition of sub-chronic inhalation experiment were examined. Rats were exposed to vapours of pseudocumene at concentrations of 123 mg/m3, 492 mg/m3 and 1230 mg/m3, 6 h/day, 5 days/week for 3 months. After 3 months of inhalation exposure animals were necropsied. Blood samples were obtained and selected organs were weighted and prepared for histological examinations. Sub-chronic inhalation exposure to pseudocumene resulted in an overall low degree of systemic toxicity. There were no changes in body weight gain, food consumption and absolute and relative organ weights. Slightly higher activity of sorbitol dehydrogenase was observed in male rats exposed to all concentrations applied. Some disturbances in hematological parameters characterised by decrease in red and increase in white blood cells were observed in male rats exposed to high concentration of 1230 mg/m3. The pulmonary lesions observed in male and female rats were statistically significant at mid and high concentrations of pseudocumene.

23. Korsak Z, Swiercz R, Rydzynski K. (1995) Toxic effects of acute inhalation exposure to 1,2,4-trimethylbenzene (pseudocumene) in experimental animals. Int J Occup Med Environ Health 8(4):331-337.
Neurotoxic and sensory respiratory irritation effects of 1,2,4-trimethylbenzene (pseudocumene) in male rats and male Balb/C mice were investigated in condition of acute inhalation exposure. Rotarod performance and pain sensitivity behaviour were tested in rats exposed to pseudocumene at concentrations of 1230-9840 mg/m3 (250-2000 ppm) immediately after termination of a four-hour exposure. The respiratory rate was measured in mice by the whole body plethysmographic method in 6 min duration exposure to various concentrations of pseudocumene. Exposure to pseudocumene resulted in concentration-dependent disturbances in rotarod performance, decrease in pain sensitivity in rats and depression of respiratory rate in mice. The EC50 value for rotarod performance behaviour disturbances was 4693 mg/m3 (954 ppm) and for decrease pain sensitivity EC50 was 5682 mg/m3 (1155 ppm). The concentration depressing the respiratory rate to 50% (RD50) was 2843 mg/m3 (578 ppm). As based on RD50 value the MAC values for pseudocumene 85 mg/m3 (17.0 ppm) is suggested.

24. Kostrewski P, Wiaderna-Brycht A. (1995) Kinetics of elimination of mesitylene and 3,5-dimethylbenzoic acid after experimental human exposure. Toxicology Letters 77(1):259-264.
The possibility of evaluating occupational exposure to mesitylene based on the determination of unchanged solvent in capillary blood or 3,5-dimethylbenzoic acid in urine was investigated. The volunteers were exposed to mesitylene in a toxicological chamber (range 10–150 mg/m3). Concentrations of solvent or its metabolite in biological material were determined by gas chromatography. The toxicokinetic data concerning retention in the lung, absorption and elimination of mesitylene and its metabolite in biological fluids were obtained. The highest correlation coefficient value was obtained for the relationship between the absorbed dose of mesitylene and the excretion rate of 3,5-dimethylbenzoic acid in urine (r = 0.95). The

biological indices of exposure for mesitylene have been proposed, taking the maximum allowable concentration (MAC) value in Poland (100 mg/m3) as the basis

25. Kostrzewski P, Wiaderna-Brycht A, Czerski B. (1997) Biological monitoring of experimental human exposure to trimethylbenzene. Sci Total Environ 199(1-2):73-81.
Trimethylbenzene (TMB) is a component of numerous commercial preparations of organic solvents (Farbasol, Solvesso, Shellsol) used in the chemical, plastics, printing and other industries. TMB is a mixture of three isomers (pseudocumene-1,2,4-TMB; mesitylene-1,3,5-TMB; hemimellitene-1,2,3-TMB). The proportion of individual isomers in the mixture differs. The aim of this study was to obtain toxicokinetic data on the absorption and elimination of trimethylbenzene and its metabolites in biological fluids and to investigate the relationship between the biological indices of exposure and the absorbed dose. Eight-hour inhalation tests were performed in a toxicological chamber, The subjects were eight volunteers aged 20-39 with no history of exposure to TMB. They were exposed to pseudocumene, mesitylene or hemimellitene at concentrations ranging from 5 to 150 mg/m3 air. Exhaled air, capillary blood and urine samples were collected before, during and after the exposure. The determinations of TMB or its metabolites were performed using gas chromatography (HP 5890 II Plus, MSD, FID). Pulmonary ventilation in the volunteers ranged from 0.56 to 1.0 m3/h. The retention of 1,2,4-TMB; 1,3,5-TMB; 1,2,3-TMB in the lungs was 68%, 67% and 71%, respectively. The elimination of TMB from capillary blood occurred in accordance with the open three-compartment model. Urinary excretion of dimethylbenzoic acids (DMBA) proceeded according to the open two-compartment model. Based on the toxicokinetic data, a simulation model of accretion and excretion of DMBA in urine during a 14-day period was developed. The highest rates of metabolite excretion and the highest quantities of DMBA in urine during 24-h intervals were observed on day 5 of exposure. The relationship between the levels of TMB or DMBA in biological material and TMB air concentration or absorbed dose were determined. To select the urine fraction suitable for determining occupational TMB exposure, linear regression analysis was performed. The biological exposure limit (BEL) for TMB has been proposed, with the current maximum allowable concentration (MAC) value of 100 mg/m3 (Polish standard) baseline value.

26. Lammers JH, Emmen HH, Muijser H, Hoogendijk EM, McKee RH, Owen DE, Kulig BM. (2007) Model studies for evaluating the neurobehavioral effects of complex hydrocarbon solvents II. Neurobehavioral effects of white spirit in rat and human. Neurotoxicology 28(4):736-750.
To evaluate the neurobehavioral effects of hydrocarbon solvents and to establish a working model for extrapolating animal test data to humans, studies were conducted which involved inhalation exposure of rats and humans to white spirit (WS). The specific objectives of these studies were to evaluate the behavioral effects of exposure to WS in rats and humans and to determine relationships between internal levels of exposure and behavioral effects. In both animals and volunteers, methods for assessment of similar functional effects were used to enable interspecies comparisons. A battery of tests including standardized observational measures, spontaneous motor activity assessments and learned visual discrimination performance was utilized in rat studies to evaluate acute central nervous system (CNS) depression. Groups of rats were exposed to WS at target concentrations of 0, 600, 2400 or 4800mg/m(3), 8h/day for 3 consecutive days. Blood and brain concentrations of two WS constituents; 1,2,4-trimethylbenzene (TMB) and n-decane (NDEC), were used as biomarkers of internal exposure. In a volunteer study, 12 healthy male subjects were exposed for 4h to either 57 or 570mg/m(3) WS in two test sessions spaced 7 days apart, and neurobehavioral effects were measured using a computerized neurobehavioral test battery. Blood samples were taken at the end of the exposure period to measure internal concentrations of TMB and NDEC. Results of the behavioral tests in rats indicated WS-induced changes particularly in performance and learned behavior. In humans, some subtle performance deficits were observed, particularly in attention. The behavioral effects were related to concentrations of the WS components in the central nervous system. These studies demonstrated a qualitative similarity in response between rats and humans, adding support to the view that the rodent tests can be used to predict levels of response in humans and to assist in setting occupational exposure levels for hydrocarbon solvents.

27. Maltoni C, Ciliberti A, Pinto C, Soffritti M, Belpoggi F, Menarini L. (1997) Results of long-term experimental carcinogenicity studies of the effects of gasoline, correlated fuels, and major gasoline aromatics on rats. Ann N Y Acad Sci 837:15-52.
Unleaded gasoline, with high aromatic content, leaded gasoline, gasoil (diesel), kerosene, toluene, xylenes,

ethylbenzene, and 1,2,4-trimethyl-benzene were submitted to long-term experimental carcinogenicity bioassays. The mixtures and the compounds were administered by stomach tube, in olive oil, once daily, 4 days weekly, for 104 weeks, to male and female Sprague-Dawley rats. The animals were kept under control until the end of the experiments. With varying degrees of evidence, all the tested materials were found to increase the total number of malignant tumors and of some site-specific tumors. They must therefore be considered carcinogenic. On the basis of our results the rank of carcinogenic potency of the tested aromatic hydrocarbons increases in the following order: 1,2,4-trimethylbenzene, ethylbenzene, xylenes, toluene (benzene).

28. Ritchie G, Still K, Rossi J, 3rd, Bekkedal M, Bobb A, Arfsten D. (2003) Biological and health effects of exposure to kerosene-based jet fuels and performance additives. J Toxicol Environ Health B Crit Rev 6(4):357-451.
    Over 2 million military and civilian personnel per year (over 1 million in the United States) are occupationally exposed, respectively, to jet propulsion fuel-8 (JP-8), JP-8 +100 or JP-5, or to the civil aviation equivalents Jet A or Jet A-1. Approximately 60 billion gallon of these kerosene-based jet fuels are annually consumed worldwide (26 billion gallon in the United States), including over 5 billion gallon of JP-8 by the militaries of the United States and other NATO countries. JP-8, for example, represents the largest single chemical exposure in the U.S. military (2.53 billion gallon in 2000), while Jet A and A-1 are among the most common sources of nonmilitary occupational chemical exposure. Although more recent figures were not available, approximately 4.06 billion gallon of kerosene per se were consumed in the United States in 1990 (IARC, 1992). These exposures may occur repeatedly to raw fuel, vapor phase, aerosol phase, or fuel combustion exhaust by dermal absorption, pulmonary inhalation, or oral ingestion routes. Additionally, the public may be repeatedly exposed to lower levels of jet fuel vapor/aerosol or to fuel combustion products through atmospheric contamination, or to raw fuel constituents by contact with contaminated groundwater or soil. Kerosene-based hydrocarbon fuels are complex mixtures of up to 260+ aliphatic and aromatic hydrocarbon compounds (C(6) -C(17+); possibly 2000+ isomeric forms), including varying concentrations of potential toxicants such as benzene, n-hexane, toluene, xylenes, trimethylpentane, methoxyethanol, naphthalenes (including polycyclic aromatic hydrocarbons [PAHs], and certain other C(9)-C(12) fractions (i.e., n-propylbenzene, trimethylbenzene isomers). While hydrocarbon fuel exposures occur typically at concentrations below current permissible exposure limits (PELs) for the parent fuel or its constituent chemicals, it is unknown whether additive or synergistic interactions among hydrocarbon constituents, up to six performance additives, and other environmental exposure factors may result in unpredicted toxicity. While there is little epidemiological evidence for fuel-induced death, cancer, or other serious organic disease in fuel-exposed workers, large numbers of self-reported health complaints in this cohort appear to justify study of more subtle health consequences. A number of recently published studies reported acute or persisting biological or health effects from acute, subchronic, or chronic exposure of humans or animals to kerosene-based hydrocarbon fuels, to constituent chemicals of these fuels, or to fuel combustion products. This review provides an in-depth summary of human, animal, and in vitro studies of biological or health effects from exposure to JP-8, JP-8 +100, JP-5, Jet A, Jet A-1, or kerosene.

29. Saillenfait AM, Gallissot F, Sabate JP, Morel G. (2005) Developmental toxicity of two trimethylbenzene isomers, mesitylene and pseudocumene, in rats following inhalation. Food and Chemical Toxicology 43(7):1055-1063.
    The developmental toxicity of two trimethylbenzene isomers, mesitylene (1,3,5-trimethylbenzene) and pseudocumene (1,2,4-trimethylbenzene) was studied in Sprague–Dawley rats following inhalation exposure. Pregnant rats were exposed whole body to vapours of mesitylene (0, 100, 300, 600, and 1200 ppm) or pseudocumene (0, 100, 300, 600, and 900 ppm), 6 h/day, on gestational days (GD) 6 through 20. Significant decrease in maternal body weight gain and food consumption was observed at concentrations of 300 ppm mesitylene, 600 ppm pseudocumene, or greater. Fetal toxicity, expressed as significant reduction in fetal body weight, occurred at 600 and 1200 ppm mesitylene, and at 600 and 900 ppm pseudocumene. There was no evidence of embryolethal or teratogenic effects following inhalation exposure to either of these chemicals. In summary, the no-observed-adverse-effect-level (NOAEL) for maternal toxicity was 100 ppm for mesitylene and 300 ppm for pseudocumene, and the NOAEL for developmental toxicity was 300 ppm for mesitylene and pseudocumene

30. Swiercz R, Rydzynski K, Wasowicz W, Majcherek W, Wesolowski W. (2002) Toxicokinetics and metabolism of pseudocumene (1,2,4-trimethylbenzene) after inhalation exposure in rats. Int J Occup Med Environ Health 15(1):37-42.
The objective of this study was to evaluate the toxicokinetics and metabolism of pseudocumene after inhalation exposure. Male Wistar rats were exposed to pseudocumene vapors at nominal concentrations of 25,100 or 250 ppm in the dynamic inhalation chambers for 6 h. Blood samples were collected during (between 1st and 6th h) and after exposure (betwen 6th min and 6th h). Blood concentrations of pseudocumene were estimated by gas chromatography using the headspace technique. During a six-hour exposure, the concentration of pseudocumene in blood increased rapidly within the first 2 h reaching then a plateau. The elimination of pseudocumene from blood followed an open two-compartment model. Urine samples were collected from the exposed animals, and metabolites were analyzed by gas chromatography with a flame ionization detector. Three metabolites were measured in the rat urine after hydrolysis: 3,4-dimethylbenzoic acid (3,4-DMBA), 2,4-dimethylbenzoic acid (2,4-DMBA) and 2,5-dimethylbenzoic acid (2,5-DMBA). A significant linear correlation was found between the level of exposure and the concentration of dimethylbenzoic acids. The enzyme kinetics of pseudocumene biotransformation was calculated by Lineweaver-Burk equation. Metabolic constants, Km (mg/l) and Vmax (mg/h/kg), the parameters for pseudocumene biotransformation by rats were estimated (3,4-DMBA - Km = 28, Vmax = 96; 2,4-DMBA - Km = 7, Vmax = 25; 2,5-DMBA - Km = 7, Vmax = 23).

31. Swiercz R, Wiaderna D, Wasowicz W, Rydzynski K. (2003) Pseudocumene in brain, liver, lung and blood of rats after single and repeated inhalation exposure. Int J Occup Med Environ Health 16(1):61-66.
Male Wistar rats were exposed to pseudocumene vapors at nominal concentration of 25, 100 or 250 ppm in the dynamic inhalation chambers for 6 h or 4 weeks (6 h/day; 5 days/week). Following the inhalation exposure, pseudocumene concentrations were estimated in the brain, liver and lung homogenates, as well as in the brain (brainstem, hippocampus, temporal cortex, cerebellum) and blood (arterial, venous) structures. To estimate pseudocumene concentrations in biological material gas chromatography using the headspace technique was applied. The elimination of pseudocumene from venous blood after repeated inhalation exposures followed an open two-compartment model. Venous blood concentration was about twice as high as that in arterial blood. In tissues, the highest values were found in the liver after single exposure to pseudocumene vapor at concentrations of 100 and 250 ppm. There were no statistically significant differences in pseudocumene concentrations between the brain, lungs or arterial blood. In the brain structures of the animals exposed to pseudocumene vapors, significantly higher concentration of psedocumene was found in the brainstem.

32. Tomas T, Swiercz R, Wiaderna D, Gralewicz S. (1999) Effects of acute exposure to aromatic hydrocarbons C 9 on locomotor activity in rats. Trimethylbenzene isomers. Int J Occup Med Environ Health 12(4):331-343.
This study was performed to find out whether in acute exposure to trimethylbenzene (TMB) isomers the dose effect relationship is linear or biphasic. In experiments performed on rats, the effect of four solvents was studied: three TMB isomers: 1,3,5-TMB (mesitylene), 1,2,3-TMB (hemimellitene), and 1,2,4-TMB (pseudocumene), and toluene, known for its biphasic activity, was used as a reference compound. The solvents were dissolved in olive oil and administered to rats orally at the doses of 0.008, 0.016, and 0.032 mol/kg. Spontaneous locomotor activity was assessed with the open-field test. Solvent concentrations in peripheral blood were determined parallelly by gas chromatography on separate groups of animals. Statistics employed a two-way analysis of variance (ANOVA) and Tukey's test. The results showed that oral administration of toluene at a dose of 0.008 mol/kg induced biphasic changes in the animal locomotor activity. It was found that TMB at applied doses increased slightly the animal locomotor activity, but the magnitude of changes did not indicate their stimulating effect. Contrary to toluene, no time-effect relationship was observed after administration of trimethylbenzene isomers. The mean blood concentrations of solvents were dose-related. The highest concentrations were observed after toluene administration.

33. Tomas T, Wiaderna D, Swiercz R. (1999) Neurotoxicity assessment of selected organic solvents based on spontaneous and evoked cortical and hippocampal activity in rats. Int J Occup Med Environ Health 12(1):73-84.
In a series of acute experiments on rats the potential of toluene, mesitylene, hemimellitene and pseudocumene to affect the CNS function was assessed following an analysis of spontaneous and evoked

hippocampal and cortical activity. The electrophysiological examinations were performed on rats with recording electrodes chronically implanted into selected brain structures. Solvent concentration in peripheral blood was determined by gas chromatography combined with the head space technique in rats with no surgical treatment. The experiments revealed significant quantitative differences between hippocampal and cortical EEG after i.p. injections of equimolar doses of the solvents. A relationship was found between the changes in spontaneous EEG and blood concentration of the solvents. Hemimellitene, with the lowest recorded blood level was found to have the highest potential for inducing the CNS effects.

34. Tsujimoto Y, Warashina, M., Nam, Vu Duc, Noda, T., Shimizu, M., Yamaguchi, Y., Moriwaki, H., Morimoto, T., Kakiuchi, K., Maeda, Y. and M. Tanaka. (2005) Determination of Urinary Phenolic Metabolites from Rats Treated with 1,2,3- and 1,3,5- Trimethylbenzenes. J Occup Health 47:337-339.
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35. Tsujimoto Y, Noda T, Shimizu M, Moriwaki H, Tanaka M. (2000) Identification of the dimethylbenzyl mercapturic acid in urine of rats administered with 1,2,4-trimethylbenzene. Chemosphere 40(8):893-896.
A study was undertaken of the mercapturic acid metabolism of 1,2,4-trimethylbenzene in the rat. Of three regioisomeric dimethylbenzyl mercapturic acids, i.e. 2,4-, 2,5- and 3,4-dimethylbenzyl isomers, the third isomer was not found in the urinary mercapturic acid isolated by preparative HPLC, from the comparison of NMR spectrum of the isolate with those of authentic specimens. The urinary mercapturate was then assigned to 2,4- and/or 2,5-dimethylbenzyl isomers. The excretion rate of the mercapturic acid was 14-20% of dose as 2,4-dimethylbenzyl isomer.

36. Wiaderna D, Gralewicz S, Tomas T. (2002) Assessment of long-term neurotoxic effects of exposure to mesitylene (1,3,5-trimethylbenzene) based on the analysis of selected behavioral responses. Int J Occup Med Environ Health 15(4):385-392.
Trimetylbenzene isomers: pseudocumene, hemimellitene and mesitylene, are major components of numerous commercial solvents and high-grade fuels. In our earlier research on rats we have proved that inhalation exposure to pseudocumene or hemimellitene at concentrations close to the MAC value results in behavioral changes detectable many weeks after cessation of the exposure. The aim of our present study is to determine whether exposure to mesitylene causes effects similar to those observed for pseudocumene and hemimellitene. Male rats were used in the experiment. The animals were exposed in the inhalation chambers to mesitylene vapors at the following concentrations: 0 ppm--group MES0; 25 ppm (125 mg/m3)--group MES25; 100 ppm (500 mg/m3)--group MES100 and 250 ppm (1,250 mg/m3)--group MES250 for 4 weeks (6 h/day, 5 days/week). The following behaviors were tested: 1) ability to find water in a radial maze (14-19 days after the exposure); 2) open field locomotor activity (25 days after the exposure); 3) acquiring the conditioned reaction of active avoidance (35-45 days after the exposure); 4) sensitivity to pain and stress-induced changes of pain sensitivity (50-51 days after the exposure); and 5) acquiring the conditioned reaction of two-way active avoidance (54-60 days after the exposure). Significant between-group differences were noted in passive and active avoidance tests and sensitivity to pain. In the MES25, MES100 and MES250 rats, the persistence of the passive avoidance reaction was shorter, and more trials were required to produce the active avoidance reaction than in controls (group MES0), the MES100 group appeared to be more fearful on the second day of testing on the hot plate. The exposed groups did not differ in the magnitudes of the detected changes (no concentration-effect relationship). These results indicate that inhalation exposure to mesitylene, like that to pseudocumene and hemimellitene, at concentrations close to the current hygiene standard value for trimethylbenzene, may produce long-term functional changes in the rat central nervous system.

37. Zahlsen K, Nilsen AM, Eide I, Nilsen OG. (1990) Accumulation and distribution of aliphatic (n-nonane), aromatic (1,2,4-trimethylbenzene) and naphthenic (1,2,4-trimethylcyclohexane) hydrocarbons in the rat after repeated inhalation. Pharmacol Toxicol 67(5):436-440.
The concentrations of the C9 hydrocarbons n-nonane, 1,2,4-trimethylbenzene and 1,2,4-trimethylcyclohexane were measured in rat blood, brain and perirenal fat after exposures to 1000 p.p.m. of the individual compounds. Measurements were made by head space gas chromatography at the end of 12 hr exposures on days 1, 3, 7, 10 and 14 of the exposure periods. The relative concentrations of hydrocarbons in each organ were, brain: n-nonane "trimethylcyclohexane approximately trimethylbenzene, blood: trimethylbenzene "n-C9 greater than trimethylcyclohexane and perirenal fat: trimethylbenzene greater than

n-nonane greater than trimethylcyclohexane, showing the widely different distribution properties of the different hydrocarbons. Brain/blood ratios of 11.4, 2.0 and 11.4, and fat/blood ratios of 113, 63 and 135 were found for n-nonane, trimethylbenzene and trimethylcyclohexane, respectively. A marked decrease in biological concentrations of trimethylbenzene and trimethylcyclohexane during the initial phase of exposure indicate that these hydrocarbons are capable of inducing their own metabolic conversion resulting in lower steady state levels. A special attention was made to n-nonane showing the highest concentration in brain concomitantly with a low blood concentration. This observation demonstrate that biological monitoring of occupational exposure by blood measurements not should be performed without knowledge of the distribution properties of the compounds investigated.

38. Zajworoniuk H, Rzeczycki W. (1992) Effect of mesitylene on ethanol metabolism in rat liver microsomes. Acta Biochim Pol 39(4):335-343.
Increased catalase activity was observed in the liver microsomal fraction of ethanol-treated rats (10% v/v aqueous ethanol solution per os for 5 weeks). In contrast, cytochrome P-450 concentration and specific activity of NADPH-cytochrome c reductase remained at the same level as in the liver of control rats (drinking water). The ratio of microsomal H2O2-generation to catalase activity was lower in the "ethanol" group than in the control one. This phenomenon seems to be related to the increased contribution of the "peroxidatic" reaction (increased rate of ethanol oxidation). Administration of mesitylene (1,3,5-trimethylbenzene) by gastric tube for 3 days (5 mmoles per kg daily) increased cytochrome P-450 concentration, specific activity of NADPH-cytochrome c reductase and ethanol metabolism.

OTHER LOW PRIORITY OR SUPPORTING REFERENCES (43)

1. Abe H, Aoyagi Y, Inouye M. (2005) A rigid C3v-symmetrical host for saccharide recognition: 1,3,5-tris(2-hydroxyaryl)-2,4,6-trimethylbenzenes. Org Lett 7(1):59-61.
A rigid C(3v)-symmetrical host molecule, syn-1,3,5-tris(2-hydroxy-5-pentylphenyl)-2,4,6-trimethylbenzene, was readily obtained via Suzuki coupling and thermal atropisomerization. The host molecule effectively associated with various saccharides by multipoint hydrogen bonds, whereas its anti-atropisomer and analogue lacking in methyl groups showed much weaker association with saccharides. Thermodynamic analyses suggested that the difference of the association strength was caused by entropic factors.

2. Anderson RC, Anderson JH. (2000) Respiratory toxicity of fabric softener emissions. J Toxicol Environ Health A 60(2):121-136.
To determine whether there is any biological basis for complaints that fabric softener emissions can cause acute adverse effects in certain individuals, screening tests were performed in which groups of mice were exposed to the emissions of 5 commercial fabric softener products (antistatic pads used in laundry dryers) for 90 min. Pneumotachographs and a computerized version of ASTM test method E-981 were used to measure acute changes in several respiratory cycle parameters, especially the pause after inspiration, the pause after expiration, and the midexpiratory airflow velocity. From these changes, sensory irritation (SI), pulmonary irritation (PI), and airflow limitation (AFL) of differing intensities were measured with each of the five brands tested. At the peak effect, SI ranged from 21 to 58% of the breaths, PI ranged from 4 to 23% of the breaths, and AFL ranged from 6 to 32% of the breaths. After three exposures, histopathology revealed mild inflammation of interalveolar septae of the lungs. Gas chromatography/ mass spectroscopy (GC/MS) analysis of the emissions of one pad identified several known irritants (isopropylbenzene, styrene, trimethylbenzene, phenol, and thymol). Laundry that had been dried with one the fabric softener pads emitted sufficient chemicals to elicit SI in 49% of breaths at the peak effect Placing one fabric softener pad in a small room overnight resulted in an atmosphere that caused marked SI (61% of breaths). These results demonstrate that some commercial fabric softeners emit mixtures of chemicals that can cause SI, PI, and reduce midexpiratory airflow velocity in normal mice. The results provide a toxicological basis to explain some of the human complaints of adverse reactions to fabric softener emissions.

3. Anundi H, Langworth S, Johanson G, Lind ML, Akesson B, Friis L, Itkes N, Soderman E, Jonsson BA, Edling C. (2000) Air and biological monitoring of solvent exposure during graffiti removal. Int Arch Occup Environ Health 73(8):561-569.

OBJECTIVE: The principal aim of the study was to estimate the level of exposure to organic solvents of graffiti removers, and to identify the chemicals used in different cleaning agents. A secondary objective was to inform about the toxicity of various products and to optimise working procedures. METHODS: Exposure to organic solvents was determined by active air sampling and biological monitoring among 38 graffiti removers during an 8-h work shift in the Stockholm underground system. The air samples and biological samples were analysed by gas chromatography. Exposure to organic solvents was also assessed by a questionnaire and interviews. RESULTS: Solvents identified were N-methylpyrrolidone (NMP), dipropylene glycol monomethyl ether (DPGME), propylene glycol monomethyl ether (PGME), diethylene glycol monoethyl ether (DEGEE), toluene, xylene, pseudocumene, hemimellitine, mesitylene, ethylbenzene, limonene, nonane, decane, undecane, hexandecane and gamma-butyrolactone. The 8-h average exposures [time-weighted average (TWA)] were below 20% of the Swedish permissible exposure limit value (PEL) for all solvents identified. In poorly ventilated spaces, e.g. in elevators etc., the short-term exposures exceeded occasionally the Swedish short-term exposure limit values (STEL). The blood and urine concentrations of NMP and its metabolites were low. Glycol ethers and their metabolites (2-methoxypropionic acid (MPA), ethoxy acetic acid (EAA), butoxy acetic acid (BAA), and 2-(2-methoxyethoxy) acetic acid (MEAA)) were found in low concentrations in urine. There were significant correlation between the concentrations of NMP in air and levels of NMP and its metabolites in blood and urine. The use of personal protective equipment, i.e. gloves and respirators, was generally high. CONCLUSIONS: Many different cleaning agents were used. The average exposure to solvents was low, but some working tasks included relatively high short-term exposure. To prevent adverse health effects, it is important to inform workers about the health risks and to restrict the use of the most toxic chemicals. Furthermore, it is important to develop good working procedures and to encourage the use of personal protection equipment.

4. Baines CJ, McKeown-Eyssen GE, Riley N, Cole DE, Marshall L, Loescher B, Jazmaji V. (2004) Case-control study of multiple chemical sensitivity, comparing haematology, biochemistry, vitamins and serum volatile organic compound measures. Occup Med (Lond) 54(6):408-418.
   BACKGROUND: Multiple chemical sensitivity (MCS), although poorly understood, is associated with considerable morbidity. AIM: To investigate potential biological mechanisms underlying MCS in a case-control study. METHODS: Two hundred and twenty-three MCS cases and 194 controls (urban females, aged 30-64 years) fulfilled reproducible eligibility criteria with discriminant validity. Routine laboratory results and serum levels of volatile organic compounds (VOCs) were compared. Dose-response relationships, a criterion for causality, were examined linking exposures to likelihood of case status. RESULTS: Routine laboratory investigations revealed clinically unimportant case-control differences in means. Confounder-adjusted odds ratios (OR) showed MCS was negatively associated with lymphocyte count and total plasma homocysteine, positively associated with mean cell haemoglobin concentration, alanine aminotransferase and serum vitamin B6, and not associated with thyroid stimulating hormone, folate or serum vitamin B12. More cases than controls had detectable serum chloroform ($P = 0.001$) with the OR for detectability 2.78 (95% confidence interval = 1.73-4.48, $P < 0.001$). Chloroform levels were higher in cases. However, cases had significantly lower means of detectable serum levels of ethylbenzene, m&p-xylene, 3-methylpentane and hexane, and means of all serum levels of 1,3,5- and 1,2,3-trimethylbenzene, 2- and 3-methylpentane, and m&p-xylene. CONCLUSIONS: Our findings are inconsistent with proposals that MCS is associated with vitamin deficiency or thyroid dysfunction, but the association of lower lymphocyte counts with an increased likelihood of MCS is consistent with theories of immune dysfunction in MCS. Whether avoidance of exposures or different metabolic pathways in cases explain the observed lower VOC levels or the higher chloroform levels should be investigated.

5. Beliveau M, Lipscomb J, Tardif R, Krishnan K. (2005) Quantitative structure-property relationships for interspecies extrapolation of the inhalation pharmacokinetics of organic chemicals. Chem Res Toxicol 18(3):475-485.
   The objectives of this study were to (i) develop quantitative structure-property relationships (QSPRs) for blood:air partition coefficients (Pb:a), tissue:air partition coefficients (Pt:a), and hepatic clearance (CLh) and (ii) conduct interspecies extrapolations of the pharmacokinetics of low molecular weight volatile organic chemicals (VOCs) by incorporating the above QSPRs within a physiologically based pharmacokinetic (PBPK) modeling framework. Pb:a and Pt:a were predicted using the following algorithm: FnlxPo:a+FwxPw:a+f(b)xFpxPp:a, where Fnl=content of neutral lipid equivalents in biological matrix,

Fw=content of water equivalents in biological matrix, Fp=protein content of blood and tissues, Po:a=vegetable oil:air partition coefficient, Pw:a=water:air partition coefficient, f(b)=fraction of total protein involved in the partitioning process, and Pp:a=protein:air partition coefficient. CLh was estimated as follows: Qlx[(CLintxC(P4502E1)xVl)/(Ql+CLintxC(P4502E1)xVl)], where CLint=intrinsic clearance normalized for P450 2E1 content, Ql=blood flow to the liver, C(P4502E1)=hepatic concentration of P450 2E1 in the species of interest, and Vl=volume of liver. QSPRs relating molecular fragments of 46 VOCs and parameters required for estimating Pb:a, Pt:a, and CLh (namely, Po:a, Pw:a, Pp:a, and CLint) were established using a group contribution method (f(i)xCi, where f=frequency of occurrence of the group i in a given molecule and Ci=contribution of the group i to Po:a, Pw:a, Pp:a, or CLint). Values of group contributions were determined by multilinear regression of experimental data. The species specific parameters required for solving the above algorithms were obtained from the literature. These algorithms, once incorporated into a multispecies PBPK modeling framework, enabled extrapolation of the kinetics of chemicals across species. The inhalation pharmacokinetics of dichloromethane and toluene as well as two de novo compounds (1,2,4-trimethyl benzene and ethyl benzene) were extrapolated from rat to human, using the present modeling methodology. This study has demonstrated that it is possible to extrapolate the pharmacokinetic behavior of chemicals from rats to humans on the basis of QSPRs and species specific physiological information.

6. Beliveau M, Tardif R, Krishnan K. (2003) Quantitative structure-property relationships for physiologically based pharmacokinetic modeling of volatile organic chemicals in rats. Toxicol Appl Pharmacol 189(3):221-232.
The objective of present study was to develop quantitative structure-property relationships (QSPRs) for the chemical-specific input parameters of rat physiologically based pharmacokinetic (PBPK) models (i.e., blood:air partition coefficient (P(b)), liver:air partition coefficient (P(l)), muscle:air partition coefficient (P(m)), fat:air partition coefficient (P(f)), and hepatic clearance (CL(h))), for simulating the inhalation pharmacokinetics of volatile organic chemicals (VOCs). The literature data on P(b), P(l), P(f), and P(m) for 46 low-molecular-weight VOCs as well as CL(h) for 25 such VOCs primarily metabolized by CYP2E1 (alkanes, haloalkanes, haloethylenes, and aromatic hydrocarbons) were analysed to develop QSPRs. The QSPRs developed in this study were essentially multilinear additive models, which imply that each fragment in the molecular structure has an additive and constant contribution to partition coefficients and hepatic clearance. Most of the values in the calibration set could be reproduced adequately with the QSPR approach, which involved the calculation of the sum of the frequency of occurrence of fragments (CH(3), CH(2), CH, C, C=C, H, Cl, Br, F, benzene ring, and H in benzene ring structure) times the fragment-specific contributions determined in this study. The QSPRs for P(b), P(l), P(m), P(f), and CL(h) were then included within a PBPK model, which only required the specification of the frequency of occurrence of fragments in a molecule along with exposure concentration and duration as input for conducting pharmacokinetic simulations. This QSPR-PBPK model framework facilitated the prediction of the inhalation pharmacokinetics of four VOCs present in the calibration dataset (toluene, dichloromethane, trichloroethylene, and 1,1,1-trichloroethane) and four VOCs that were not part of the calibration set (1,2,4-trimethyl benzene, ethyl benzene, 1,3-dichloropropene, and 2,2-dichloro-1,1,1-trifluoroethane) but that could be described using the molecular fragments investigated in the present study. The QSPRs developed in this study should be potentially useful for providing a first-cut evaluation of the inhalation pharmacokinetics of VOCs prior to experimentation, as long as the number and nature of the fragments do not exceed the ones in the calibration dataset used in this study.

7. Borden RC, Black DC, McBlief KV. (2002) MTBE and aromatic hydrocarbons in North Carolina stormwater runoff. Environ Pollut 118(1):141-152.
A total of 249 stormwater samples were collected from 46 different sampling locations in North Carolina over an approximate 1-year period and analyzed to identify land use types where fuel oxygenates and aromatic hydrocarbons may be present in higher concentrations and at greater frequency. Samples were analyzed by gas chromatography-mass spectrometry in ion selective mode to achieve a quantitation limit of 0.05 microg/l. m-,p-Xylene and toluene were detected in over half of all samples analyzed, followed by MTBE: o-xylene: 1,3,5-trimethylbenzene: ethylbenzene; and 1,2,4-trimethylbenzene. Benzene, DIPE, TAME and 1,2,3-trimethylbenzene were detected in < 10% of the samples analyzed. Median contaminant concentrations (when detected) varied from 0.07 microg/l for ethylbenzene to 0.11 microg/l for toluene. All of the locations with significantly higher contaminant concentrations were associated with direct runoff from a gas station or discharge of contaminated groundwater from a former leaking underground storage

tank. For all of the aromatic hydrocarbons, the maximum observed contaminant concentrations were over an order of magnitude lower than current drinking water standards.

8. Chang FH, Lin TC, Huang CI, Chao HR, Chang TY, Lu CS. (1999) Emission characteristics of VOCs from athletic tracks. J Hazard Mater 70(1-2):1-20.
Dynamic and flow-through flux chambers are convenient tools for field measurements of gas or VOC emission flux from solid surfaces in the field. This study was undertaken to collect on site and quantify the emissions of volatile organic compounds (VOCs) released from athletic running tracks. Three typical types of tracks, one synthetic rubber and two tracks (types I and II) consisting mainly of polyurethane, were studied. They were all installed with adhesives and backings, both of which contributed significant amount of VOCs. VOCs released from the track surface were collected with a flux chamber and subsequently analyzed by a gas chromatograph/mass spectrometer (GC/MS). Also, for each track and at each selected time the emission flux and mass emission were measured on site under outdoor conditions over a period of 40 min. GC/MS analyses show that the VOCs emitted include 2-methyl furan, butanal, methyl ethyl ketone, benzene, heptane, methyl isobutyl ketone, toluene+octane, hexanal, nonane+ethylbenzene, xylenes+styrene, propyl benzene, decane, 1,3,5-trimethyl benzene, 1,2,4-trimethyl benzene, 1,2, 3-trimethyl benzene and undecane. Of these, hexanal was the common and principal compound for all three types of tracks. 2-Methyl furan and methyl isobutyl ketone were the characteristic compounds for the synthetic rubber and the type II of polyurethane tracks, respectively. In the field studies, no unique compounds were found in the type I of polyurethane tracks. For each of these three types of tracks the total-VOCs emission flux was correlated to the track age and track surface temperature. The results of multiple regression analysis showed good correlation. The type II polyurethane track had the highest decay rate, while the synthetic rubber track had the lowest decay rate. Two years after the track installation, the VOC concentrations measured at 1.5 m above the track, the breathing height of school children, were not significantly higher than the background levels.

9. Chou CC, Riviere JE, Monteiro-Riviere NA. (2003) The cytotoxicity of jet fuel aromatic hydrocarbons and dose-related interleukin-8 release from human epidermal keratinocytes. Arch Toxicol 77(7):384-391.
Many jet fuel aromatic hydrocarbons are known carcinogens with the ability to both readily penetrate the skin with high absorptive flux and cause skin irritation. In order to evaluate the in vitro cutaneous toxicity of individual aromatic hydrocarbons in jet fuels and their potential for inducing skin irritation, we evaluated the LD(50), the highest non-cytotoxic (5% mortality) dose (HNTD), and interleukin-8 (IL-8) release activity of nine major jet fuel aromatic hydrocarbons in human epidermal keratinocytes (HEK). LD(50) ranged from 1.8 mM (0.03%) for cyclohexylbenzene to 82.9 mM (0.74%) for benzene, with a rank order potency of cyclohexylbenzene >trimethylbenzene >/=xylene >dimethylnaphthalene >ethylbenzene >toluene >benzene. The HNTD values ranged from 0.1 mM (0.001%) for cyclohexylbenzene to 48.2 mM (0.43%) for benzene. Naphthalene and methylnaphthalene could not be ranked in this comparison since their concentrations, presented as percentage saturation, were not comparable to the others presented as solutes in solution. There was a dose-related differential response in IL-8 release at 24 h. Toluene, xylene, trimethylbenzene, cyclohexylbenzene and dimethylnaphthalene significantly decreased IL-8 release at the respective HNTDs, while IL-8 release did not continue to decrease, or significantly increased (cyclohexylbenzene and dimethylnaphthalene), at the LD(50). IL-8 significantly increased with both doses of methylnaphthalene and naphthalene. The presence of hexadecane and mineral oil greatly attenuated the cytotoxicity elicited by individual aromatic hydrocarbons in HEK cells.

10. Cooper SP, Burau K, Sweeney A, Robison T, Smith MA, Symanski E, Colt JS, Laseter J, Zahm SH. (2001) Prenatal exposure to pesticides: a feasibility study among migrant and seasonal farmworkers. Am J Ind Med 40(5):578-585.
BACKGROUND: Migrant and seasonal farmworkers have a high potential for pesticide exposures, yet are rarely included in epidemiologic studies. This study examined the feasibility of assessing prenatal exposures to pesticides and other compounds in pregnant Hispanic farmworkers. METHODS: Nine women completed a survey about work experiences during pregnancy. Maternal urine, cord blood, and placenta samples were obtained at delivery for analysis of 51 analytes, including 6 phenoxy acid or triazine herbicides, 21 organochlorine insecticides, 10 PCBs, and 14 volatile organic compounds. RESULTS: Seven of 51 analytes were found in the biological samples. DDE, DDT, dichlorbenzene, toluene, trimethylbenzene, and endosulfan sulfate were detected in cord blood samples, and 2,4-D in urine from one

or more women. CONCLUSIONS: We documented the feasibility of following farmworkers to assess in utero exposure to pesticides and other contaminants, and demonstrated exposure to these compounds. Difficulties in measuring pesticides with short half lives were noted.

11. Cruden DL, Wolfram JH, Rogers RD, Gibson DT. (1992) Physiological properties of a Pseudomonas strain which grows with p-xylene in a two-phase (organic-aqueous) medium. Appl Environ Microbiol 58(9):2723-2729.
    Pseudomonas putida Idaho utilizes toluene, m-xylene, p-xylene, 1,2,4-trimethylbenzene, and 3-ethyltoluene as growth substrates when these hydrocarbons are provided in a two-phase system at 5 to 50% (vol/vol). Growth also occurs on Luria-Bertani medium in the presence of a wide range of organic solvents. The ability of the organism to grow in the presence of organic solvents is correlated with the logarithm of the octanol-water partition coefficient, with dimethyl-phthalate (log P(OCT) = 2.3) being the most polar solvent tolerated. During growth with p-xylene (20% [vol/vol]), there was an initial lag period accompanied by cell death, which was followed by a period of exponential growth. The stationary phase of growth was characterized by a dramatic decrease in cell viability, although cell dry weight and turbidity measurements slowly increased. Electron micrographs revealed that during growth in the presence of p-xylene, the outer cell membrane becomes convoluted and membrane fragments are shed into the culture medium. At the same time, the cytoplasmic membrane invaginates, forming vesicles, and becomes disorganized. Electron-dense intracellular inclusions were observed in cells grown with p-xylene (20% [vol/vol]) and p-xylene vapors, which are not present in cells grown with succinate. Attempts to demonstrate the presence of plasmid DNA in P. putida Idaho were negative. However, polarographic studies indicated that the organism utilizes the same pathway for the degradation of toluene, m-xylene, and p-xylene as that used by P. putida mt-2 which contains the TOL plasmid pWWO.(ABSTRACT TRUNCATED AT 250 WORDS)

12. Douglas JF, McKee RH, Cagen SZ, Schmitt SL, Beatty PW, Swanson MS, Schreiner CA, Ulrich CE, Cockrell BY. (1993) A neurotoxicity assessment of high flash aromatic naphtha. Toxicol Ind Health 9(6):1047-1058.
    Catalytic reforming is a refining process that converts naphthenes to aromatics by dehydrogenation to make higher octane gasoline blending components. A portion of this wide-boiling range hydrocarbon stream can be separated by distillation and used for other purposes. One such application is a mixture of predominantly 9-carbon aromatic molecules (C9 Aromatics, primarily isomers of ethyltoluene and trimethylbenzene), which is removed and used as a solvent also known as High Flash Aromatic Naphtha (HFAN). A program was initiated to assess the toxicological properties of HFAN since there may be human exposure, especially in the workplace. The current study was conducted to assess the potential for neurotoxicity in the rat. Adult male Sprague-Dawley rats of approximately 300 grams body weight, in groups of twenty, were exposed by inhalation to HFAN for 90 days at concentrations of 0, 100, 500, and 1500 ppm. During this period the animals were tested monthly for motor activity and in a functional observation battery. After three months of exposure, for 6 hours/day, 5 days/week, 10 animals/group/sex were sacrificed and selected nervous system tissue was examined histopathologically. No signs of neurotoxicity were seen in any of the evaluated parameters, nor was there evidence of pathologic changes in any of the examined tissues.

13. Dyne D, Cocker J, Wilson HK. (1997) A novel device for capturing breath samples for solvent analysis. Sci Total Environ 199(1-2):83-89.
    We have developed a novel breath sampling device suitable for capturing a portion of end-tidal air. This breath sample is then transferred onto a Perkin Elmer automated thermal desorption (ATD) sampling tube which is subsequently analysed by ATD-gas chromatography-mass spectrometry (GCMS). The breath sampler has been evaluated in the laboratory, in brief field trials and in human volunteer studies. The method is sensitive with a typical detection limit of 1 nmol/l and reproducible with an overall coefficient of variation between 5% and 15% for collection and analysis of breath samples from volunteers. The field trials used the sampler to assess exposure to solvents in several industries including the shoe manufacturing industry, the inks and coatings industry and at dry cleaning establishments. The sampler was found easy to use and reliable. Solvents detected include ethyl acetate (6.4-25.5 nmol/l), propan-2-ol (3.4-39.3 nmol/l), 2-butanone (0-6.6 nmol/l) and tetrachloroethene (0-557 nmol/l). The breath sampler was also used to monitor the elimination of solvents in breath from human volunteers after exposure chamber studies. More than 500 breath samples have been analysed from 24 volunteers in exposures to 10 different solvents (toluene, trimethyl benzene, tetrachloroethene, tetrahydrofuran, acetone, propan-2-ol, xylene, 2-butanone, 1-

methoxy-2-propanol and n-hexane). The breath sampler allowed the rapid and non-invasive collection of data on elimination of solvents.

14. Freundt KJ, Romer KG, Federsel RJ. (1989) Decrease of inhaled toluene, ethyl benzene, m-xylene, or mesitylene in rat blood after combined exposure to ethyl acetate. Bull Environ Contam Toxicol 42(4):495-498.

15. Janasik BM, Jakubowski M. (2006) Excretion of unchanged toluene, ethylbenzene, xylene and mesitylene in urine after experimental exposure of human. Toxicology Letters 164:S123-S123.

16. Jang YC, Townsend TG. (2001) Occurrence of organic pollutants in recovered soil fines from construction and demolition waste. Waste Manag 21(8):703-715.
The objective of this study was to characterize recovered soil fines from construction and demolition (C&D) waste recycling facilities for trace organic pollutants. Over a period of 18 months, five sampling trips were made to 14 C&D waste recycling facilities in Florida. Screened soil fines were collected from older stockpiles and newly generated piles at the sites. The samples were analyzed for the total concentration (mg/kg) of a series of volatile organic compound (VOCs) and semi-volatile organic compounds (semi-VOCs). The synthetic precipitation leaching procedure (SPLP) test was also performed to evaluate the leachability of the trace organic chemicals. During the total analysis only a few volatile organic compounds were commonly found in the samples (trichlorofluoromethane, toluene, 4-isopropyltoluene, trimethylbenzene, xylenes, and methylene chloride). A total of nine VOCs were detected in the leaching test. Toluene showed the highest leachability among the compounds (61.3-92.0%), while trichlorofluoromethane, the most commonly detected compound from both the total and leaching tests, resulted in the lowest leachability (1.4-39.9%). For the semi-VOC analysis, three base-neutral semi-VOC compounds (bis(2-ethylhexyl)phthalate, butyl benzyl phthalate, and di-n-butyl phthalate) and several PAHs (acenaphthene, pyrene, fluoranthene, and phenanthrene) were commonly detected in C&D fines samples. These compounds also leached during the SPLP leaching test (0.1-25%). No acid extractable compounds, pesticides, or PCBs were detected. The results of this study were further investigated to assess risk from land applied recovered soil fines by comparing total and leaching concentrations of recovered soil fines samples to risk-based standards. The results of this indicate that the organic chemicals in recovered soil fines from C&D debris recycling facilities were not of a major concern in terms of human risk and leaching risk to groundwater under reuse and contact scenarios.

17. Jarnberg J, Johanson G, Lof A, Stahlbom B. (1997) Inhalation toxicokinetics of 1,2,4-trimethylbenzene in volunteers: comparison between exposure to white spirit and 1,2,4-trimethylbenzene alone. Sci Total Environ 199(1-2):65-71.
The objective of this study was to compare the toxicokinetics of inhaled 1,2,4-trimethylbenzene (1,2,4-TMB) in man after exposure to white spirit with that observed after exposure to 1,2,4-TMB alone. TMBs occur mainly in petroleum products and the TMBs or their metabolites have been suggested as suitable biomarkers of exposure to white spirit and other distillation products. The toxicokinetics were studied in 9 male, healthy volunteers exposed to solvent vapours in an exposure chamber for 2 h during a work load of 50 W. The subjects were exposed to 11 mg/m3 of 1,2,4-TMB on two occasions; during exposure to 1,2,4-TMB vapour alone and during exposure to 300 mg/m3 of white spirit. The 1,2,4-TMB isomer was analyzed in blood and exhaled air by gas chromatography. In addition, a major urinary metabolite of 1,2,4-TMB, 3,4-dimethylhippuric acid (3,4-DMHA), was analyzed by high performance liquid chromatography. Further the occurrence of acute effects was studied by means of a questionnaire. Irritation and central nervous system symptoms were recorded by ratings on a 100-mm visual analogue scale. Blood levels of 1,2,4-TMB and excretion rates of 3,4-DMHA in urine were markedly elevated both during and after exposure to white spirit as compared to exposure to TMB alone. Thus, it appears that components in white spirit inhibit the metabolic elimination of 1,2,4-TMB. This should be considered in biological exposure monitoring as well as in risk assessment. No irritation or central nervous system effects were reported at these conditions.

18. Kim JK, Shin HS, Lee JH, Lee JJ, Lee JH. (2003) Genotoxic effects of volatile organic compounds in a chemical factory as evaluated by the Tradescantia micronucleus assay and by chemical analysis. Mutat Res 541(1-2):55-61.

The clastogenic effects of volatile organic compounds in the workplace air of a chemical factory were studied by means of the Tradescantia micronucleus (Trad-MCN) assay and chemical analysis. Sampling was performed at a chemical factory producing PVC film in Cheong-ju, South Korea. Inflorescences of Tradescantia BNL 4430 were placed for 2, 6, and 9 h at the height of 1.40 m at two locations in the workplace and one outdoor of the chemical industry. Air samplings were conducted in the same places and the collected tube samples were analyzed by automatic thermal desorption/gas chromatography/mass spectrometry (ATD/GC/MS). The frequencies of micronuclei in specimens exposed for 2 h in sites 1-3 were 6.13 +/- 0.47, 5.40 +/- 1.60, and 2.93 +/- 0.43 MCN per 100 tetrads, respectively. GC/MS analysis proved the presence of various volatile organic compounds such as trichloroethylene, toluene, ethyl benzene, (m, p, o)-xylene, styrene, 1,3,5-trimethyl benzene, and 1,2,4-trimethyl benzene. Mean values of toluene measured by 2 h sampling in sites 1-3 were 1946.6, 1368.3, and 340.1 microg/m3, respectively. The toluene concentrations in sites 1 and 2 were at least four to six times higher than that in site 3. The micronucleus frequencies increased with exposure time. In addition, there was a correlation between the micronucleus frequencies and toluene concentration in the air (R2 = 0.96). The results of this in situ monitoring proved the applicability of the Trad-MCN assay combined with chemical analysis for monitoring genotoxic chemicals in the work environment.

19. Kimura K, Nagata T, Hara K, Kageura M. (1988) Gasoline and kerosene components in blood--a forensic analysis. Hum Toxicol 7(4):299-305.
    A reliable method to analyse small amounts of fuel components in biological materials, using two simultaneous procedures, head space and solvent extraction methods has been developed. Gas chromatography/mass spectrometry (GC/MS) was used for qualitative and quantitative determinations. The aliphatic hydrocarbons with carbon numbers of 5 to 8 and aromatics such as benzene, toluene and xylenes were detected in laboratory animals, following exposure to gasoline vapour, using the head space method. Aliphatic hydrocarbons with carbon numbers over 9 as well as the aromatics with carbon number 9 group including cumene, mesitylene, pseudocumene and 1,2,3-trimethylbenzene were determined by the solvent extraction method following exposure to kerosene vapour. The lower limits of detection were 0.01 micrograms and 50 pg in gasoline and kerosene components, respectively. The methods were found to be applicable in confirming the cause of human deaths.

20. Korsak Z, Rydzynski K. (1997) Neurotoxic effects of acute and subchronic inhalation exposure to trimethylbenzene isomers (Pseudocumene, mesitylene. Occupational Health and Industrial Medicine 36(5):216-216.
    Neurotoxic effects of trimethylbenzene isomers (pseudocumene, mesitylene and hemimellitene) in male rats were investigated in conditions of acute and subchronic inhalation exposure. Rotarod performance and pain sensitivity behaviour...

21. McDougal JN, Garrett CM. (2007) Gene expression and target tissue dose in the rat epidermis after brief JP-8 and JP-8 aromatic and aliphatic component exposures. Toxicol Sci 97(2):569-581.
    Exposures of jet propulsion fuel 8 (JP-8) to human and laboratory animal skin have resulted in skin irritation. JP-8 is a mixture of aromatic and aliphatic hydrocarbons, which in some cases have also been shown to be irritating to the skin. In an attempt to determine if aromatic or aliphatic components could mimic the JP-8-induced gene expression response, we exposed rats to JP-8, undecane (UND), tetradecane (TET), trimethylbenzene (TMB), and dimethylnaphthalene (DMN) for 1 h and examined the epidermis to characterize the gene expression response. We also measured the concentrations of the JP-8 components in the epidermis with gas chromatography/mass spectrometry after 1-h exposures to JP-8 and pure components to determine if differences in potency could be identified. Changes in gene expression, compared to sham treatment, were studied with microarray techniques and analyzed for changes in gene ontology categories. UND and TMB exposures caused the greatest number of changes in transcript levels compared to DMN and TET. When only the specific functional and signaling pathways that were changed by JP-8 were considered, these pathways were nearly all activated by the components, but to different extents. After pure component exposures, the epidermal concentrations of the components showed no significant differences, although the differences in magnitude of either total or pathway-specific gene expression differed by a factor of 10-fold. We conclude that no single component that we studied mimicked the gene expression resulting from the JP-8 exposure but that UND had the most similar responses. These data suggest that there are differences in potency between the four components studied.

22. McGregor DB, Brown A, Cattanach P, Edwards I, McBride D, Riach C, Caspary WJ. (1988) Responses of the L5178Y tk+/tk- mouse lymphoma cell forward mutation assay: III. 72 coded chemicals. Environ Mol Mutagen 12(1):85-154.
Seventy-two chemicals were tested for their mutagenic potential in the L5178Y tk+/- mouse lymphoma cell forward mutation assay, using procedures based upon those described by Clive and Spector (Mutat Res 44:269-278, 1975) and Clive et al. (Mutat Res 59:61-108, 1979). Cultures were exposed to the chemicals for 4 hr, then cultured for 2 days before plating in soft agar with or without trifluorothymidine (TFT), 3 micrograms/ml. The chemicals were tested at least twice. Significant responses were obtained with allyl isothiocyanate, p-benzoquinone dioxime, benzyl acetate, 2-biphenylamine HCl, bis(2-chloro-1-methylethyl)ether, cadmium chloride, chlordane, chlorobenzene, chlorobenzilate, 2-chloroethanol, chlorothalonil, cytarabine.HCl, p,p'-DDE, diazinon, 2,6-dichloro-p-phenylenediamine, N,N-diethylthiourea, diglycidylresorcinol ether, 2,4-dimethoxy aniline.HCl, disperse yellow 3, endosulfan, 1,2-epoxyhexadecane, ethyl acrylate, ethyl benzene, ethylene thiourea, F D and C yellow Number 6, furan, heptachlor, isophorone, mercuric chloride, 4,4'-methylenedianiline.2 HCl, methyl viologen, nickel sulfate.6H2O, 4,4'-oxydianiline, pentachloroethane, piperonyl butoxide, propyl gallate, quinoline, rotenone, 2,4,5,6-tetrachloro-4-nitro-anisole, 1,1,1,2-tetrachloroethane, trichlorfon, 2,4,6-trichlorophenol, 2,4,5-trimethoxybenzaldehyde, 1,1,3-trimethyl-2-thiourea, 1-vinyl-3-cyclopetene dioxide, vinyl toluene, and ziram. Apart from 2-biphenylamine.HCl, 2-chloroethanol, disperse yellow 3, ethylene thiourea, FD and C yellow number 6, phenol, and 1,1,2-tetrachloroethane, rat liver S9 mix was not a requirement for these compounds. Chemicals not identified as mutagens were acid red, 11-aminoudecanoic acid, boric acid, 5-chloro-o-toluidine, coumaphos, cyclohexanone, decabromodiphenyl oxide, di(2-ethylhexyl)adipate, ferric chloride, fluometuron, melamine, monuron, phenesterin, phthalimide, reserpine, sodium dodecyl sulfate, 4,4-sulfonyldianiline, tetrachloroethylene, and zearalenone. The assay was incapable of providing a clear indication of whether some chemicals were mutagens; these were benzyl alcohol, 1,4-dichlorobenzene, phenol, succinic acid-2,2-dimethyl hydrazide, and toluene.

23. McKee RH, Wong ZA, Schmitt S, Beatty P, Swanson M, Schreiner CA, Schardein JL. (1990) The reproductive and developmental toxicity of High Flash Aromatic Naphtha. Toxicol Ind Health 6(3-4):441-460.
Catalytic reforming is a refining process that converts naphthenes to aromatics by dehydrogenation to make higher octane gasoline blending components. A portion of this wide boiling range hydrocarbon stream can be separated by distillation and used for other purposes. One such application is a mixture of predominantly 9-carbon aromatic molecules (C9 aromatics, primarily isomers of ethyltoluene and trimethylbenzene), which is removed and used as a solvent--High Flash Aromatic Naphtha. A program was initiated to assess the toxicological properties of High Flash Aromatic Naphtha since there may be human exposure through inhalation or external body contact. The current study was conducted to assess the potential for developmental toxicity in the mouse and for reproductive toxicity in the rat. In the developmental toxicity study in CD-1 mice, exposure of dams by inhalation to near lethal levels (1500 ppm) resulted in fetal mortality, reduced weight, delayed ossification, and an increased incidence of cleft palate. At 500 ppm, a level at which maternal weight gain was slightly reduced, fetal weight gain was also reduced, but there was no other evidence of developmental effects. The lowest exposure level (100 ppm) did not cause any maternal or developmental toxicity. There was no consistent evidence of reproductive toxicity in rats, even at exposure levels which resulted in significantly reduced parental weight gain. In addition, when parental exposure was stopped on GD (gestation day) 20, birth weights as well as postnatal survival were generally similar to control values, even in the 1500 ppm exposure group. Postnatal weight gain was also similar to controls early in weaning, but, if maternal exposure was reinitiated, weight gain was reduced in the high exposure group. However, when exposure was continued until delivery, pups in the high exposure group exhibited reduced litter size, birth weight and poor survival. Thus it was likely that the reduction in fetal weight, seen in the developmental toxicity study in mice, was transient and had no postnatal consequences if maternal exposure was terminated at any time prior to delivery.

24. Muhammad F, Monteiro-Riviere NA, Riviere JE. (2005) Comparative in vivo toxicity of topical JP-8 jet fuel and its individual hydrocarbon components: identification of tridecane and tetradecane as key constituents responsible for dermal irritation. Toxicol Pathol 33(2):258-266.
Despite widespread exposure to military jet fuels, there remains a knowledge gap concerning the actual toxic entities responsible for irritation observed after topical fuel exposure. The present studies with

individual hydrocarbon (HC) constituents of JP-8 jet fuel shed light on this issue. To mimic occupational scenarios, JP-8, 8 aliphatic HC (nonane, decane, undecane, dodecane, tridecane, tetradecane, pentadecane, hexadecane) and 6 aromatic HC (ethyl benzene, o-xylene, trimethyl benzene, cyclohexyl benzene, naphthalene, dimethyl naphthalene) soaked cotton fabrics were topically exposed to pigs for 1 day and with repeated daily exposures for 4 days. Erythema, epidermal thickness, and epidermal cell layers were quantitated. No erythema was noted in 1-day in vivo HC exposures but significant erythema was observed in 4-day tridecane, tetradecane, pentadecane, and JP-8 exposed sites. The aromatic HCs did not produce any macroscopic lesions in 1 or 4 days of in vivo exposures. Morphological observations revealed slight intercellular and intracellular epidermal edema in 4-day exposures with the aliphatic HCs. Epidermal thickness and number of cell layers significantly increased ($p < 0.05$) in tridecane, tetradecane, pentadecane, and JP-8-treated sites. No significant differences were observed in the aromatic HC-exposed sites. Subcorneal microabscesses containing inflammatory cells were observed with most of the long-chain aliphatic HCs and JP-8 in 4-day exposures. Ultrastructural studies depicted that jet fuel HC-induced cleft formation within intercellular lipid lamellar bilayers of the stratum corneum. The degree of damage to the skin was proportional to the length of in vivo HC exposures. These data coupled with absorption and toxicity studies of jet fuel HC revealed that specific HCs (tridecane and tetradecane) might be the key constituents responsible for jet fuel-induced skin irritation.

25. Murray P, Willans C, Bredenkamp MW, Gertenbach JA. (2007) 2,4,6-Tris(bromomethyl)-1,3,5-trimethylbenzene. Acta Crystallographica Section E: Structure Reports Online.
The title compound, C12H15Br3, has been synthesized and its structure is reported here. The bulky Br atoms are accommodated above and below the plane of the benzene ring.

26. Myhre O, Fonnum F. (2001) The effect of aliphatic, naphthenic, and aromatic hydrocarbons on production of reactive oxygen species and reactive nitrogen species in rat brain synaptosome fraction: the involvement of calcium, nitric oxide synthase, mitochondria, and phospholipase A. Biochem Pharmacol 62(1):119-128.
This study investigated the effects of C7 and C9 aliphatic (n-heptane, n-nonane), naphthenic (methylcyclohexane, 1,2,4-trimethylcyclohexane (TMCH)) and aromatic (toluene, 1,2,4-trimethylbenzene (TMB)) hydrocarbons on the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) in rat brain synaptosome fraction. Methyl mercury (MeHg) was included as a positive control. Exposure of the synaptosomes to the hydrocarbons produced a concentration-dependent linear increase in the formation of the fluorescence of 2',7'-dichlorofluorescein (DCF) as a measure of the production of ROS and RNS. Formation of RNS was demonstrated by preincubation of the synaptosome fraction with the neuronal nitric oxide synthase (nNOS) inhibitor Nomega-nitro-L-arginine methyl ester (L-NAME), which reduced the MeHg and TMCH-stimulated fluorescence by 51% and 65%, respectively. The naphthenic hydrocarbon TMCH showed the strongest potential for ROS and RNS formation in rat brain synaptosomes, followed by TMB, toluene, n-nonane, n-heptane, and methylcyclohexane, respectively. TMCH was selected for mechanistic studies of the formation of ROS. Both MeHg and TMCH induced an increase in intracellular calcium concentration [Ca(2+)]i as measured with Fura-2. Blockade of voltage-dependent Ca(2+) channels with lanthanum prior to stimulation with MeHg and TMCH led to a reduction in the ROS/RNS formation of 72% and 70%, respectively. Furthermore, addition of cyclosporin A (CSA), a blocker of the mitochondrial permeability transition pore (MTP), lowered both the MeHg and TMCH-elevated DCF fluorescence by 72% and 59%. Preincubation of the synaptosome fraction with the protein tyrosine kinase inhibitor genistein lowered the MeHg and TMCH-stimulated fluorescence by 85% and 91%, respectively. Addition of the extracellular signal-regulated protein kinase (MEK)-1 and -2 inhibitor U0126 reduced the fluorescence stimulated by MeHg and TMCH by 62% and 63%. Furthermore, the protein kinase C inhibitor bisindolylmaleimide reduced the fluorescence stimulated by MeHg and TMCH by 52% and 56%. The compound 1-(6-[17beta-3-methoxyestra- 1,3,5(10)-trien- 17-yl]-aminohexyl)-1H-pyrrole-2,5-dione (U73122), which inhibits phospholipase C, was shown to decrease the ROS and RNS formation induced by MeHg and TMCH by 49% and 64%, respectively. The phospholipase A2 (PLA2) inhibitor 7,7-dimethyl eicosadienoic acid (DEDA) reduced fluorescence in response to MeHg and TMCH by 49% and 54%. Simultaneous addition of L-NAME, CSA, and DEDA to the synaptosome fraction totally abolished the DCF fluorescence. In conclusion, C7 and C9 aliphatic, naphthenic, and aromatic hydrocarbons stimulated formation of ROS and RNS in rat brain synaptosomes. The naphthenic hydrocarbon TMCH stimulated formation of ROS and RNS in the synaptosomes through Ca(2+)-dependent activation of PLA2 and nNOS, and through increased transition permeability of the MTP.

Exposure of humans to the naphthenic hydrocarbon TMCH may stimulate formation of free radicals in the brain, which may be a key factor leading to neurotoxicity.

27. Myhre O, Vestad TA, Sagstuen E, Aarnes H, Fonnum F. (2000) The effects of aliphatic (n-nonane), naphtenic (1,2, 4-trimethylcyclohexane), and aromatic (1,2,4-trimethylbenzene) hydrocarbons on respiratory burst in human neutrophil granulocytes. Toxicol Appl Pharmacol 167(3):222-230.
This study investigates the effects of aliphatic (n-heptane, n-nonane), naphtenic (methylcyclohexane, 1,2,4-trimethylcyclohexane (TMCH)), and aromatic (methylbenzene, 1,2,4-trimethylbenzene (TMB)) hydrocarbons on respiratory burst in human granulocytes. The free radical formation was measured as 2,7-dichlorofluorescein diacetate-amplified (DCF) fluorescence, by electron paramagnetic resonance (EPR) spectroscopy and by hydroxylation of 4-hydroxybenzoate. The chemotactic peptide N-formyl-met-leu-phe (fMLP) and phorbol 12-myristate 13-acetate (PMA), a diacylglycerol analogue, were included as positive controls. DCF fluorescence was elevated in a concentration-dependent manner by C9 hydrocarbons. The C7 hydrocarbons did not stimulate respiratory burst in the concentration range examined. The naphtenic hydrocarbon TMCH showed the strongest effect on respiratory burst and was therefore selected for mechanistic studies of this free radical formation. In the absence of extracellular Ca(2+), fluorescence in response to TMCH and fMLP was reduced by 77 and 90%, respectively. Preincubation of the granulocytes with the protein kinase C inhibitor bisindolylmaleimide reduced the DCF fluorescence stimulated with TMCH, fMLP, and PMA by 82, 56, and 90%, respectively. The phospholipase C inhibitor U73122 lowered the TMCH- and fMLP-activated DCF fluorescence by 87 and 76%. In addition, the TMCH- and fMLP-induced DCF fluorescence, after the preincubation with the phospholipase D modulator n-butanol, was lowered by 83 and 52%, respectively. The importance of protein kinase C, phospholipase C, and phospholipase D for elevation of respiratory burst was also demonstrated by the EPR experiments using the spin trap 5-diethoxyphosphoryl-5-methyl-1-pyrroline-N-oxide (DEPMPO). Preincubation with the NADPH oxidase inhibitor diphenyleneiodonium and diethyldithiocarbamate, which inhibits superoxide dismutase, led to an almost complete reduction of DCF fluorescence in response to TMCH, fMLP, and PMA. Preincubation with diethyldithiocarbamate led to the elevation of superoxide adducts of DEPMPO. The hydrocarbons stimulated formation of mainly the superoxide (O(*-)(2)) adduct of DEPMPO (DEPMPO-OOH) but also small amounts of the hydroxyl adduct ((*)OH) (DEPMPO-OH). Using 4-hydroxybenzoate as a hydroxyl radical trap confirmed formation of (*)OH after stimulation with the hydrocarbons. In conclusion, our findings indicate that TMCH-activated respiratory burst is dependent on the Ca(2+)-dependent phospholipase C, phospholipase D, and protein kinase C prior to activation of the NADPH oxidase.

28. NIOSH. 2005. NIOSH Pocket Guide to Chemical Hazards (2005-149) : trimethylbenzene. National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control and Prevention, Department Of Health And Human Services.
Colorless solid or liquid (above 77°F) with a camphor-like odor. [Note: Often used in aqueous solutions.

29. NIOSH. 2006. The Registry of Toxic Effects of Chemical Substances (RTECS): Mesitylene. National Institute of Occupational Safety and Health (NIOSH), DHHS (Updated August 2006).
RTECS is a compendium of data extracted from the open scientific literature. The data are recorded in the format developed by the RTECS staff and arranged in alphabetical order by prime chemical name. Six types of toxicity data are included in the file: (1) primary irritation; (2) mutagenic effects; (3) reproductive effects; (4) tumorigenic effects; (5) acute toxicity; and (6) other multiple dose toxicity. Specific numeric toxicity values such as LD50, LC50, TDLo, and TCLo are noted as well as species studied and route of administration used. For each citation, the bibliographic source is listed thereby enabling the user to access the actual studies cited. No attempt has been made to evaluate the studies cited in RTECS. The user has the responsibility of making such assessments.

30. Norseth T, Waage J, Dale I. (1991) Acute effects and exposure to organic compounds in road maintenance workers exposed to asphalt. Am J Ind Med 20(6):737-744.
Subjective symptoms and exposure to organic compounds were recorded in road repair and construction workers. Abnormal fatigue, reduced appetite, laryngeal/pharyngeal irritation, and eye irritation were recorded more often in such workers handling asphalt than in a corresponding reference group without asphalt exposure. Mean daily exposure to volatile compounds was only occasionally above 1 ppm. Mean

exposure to asphalt fume was 0.358 mg/m3. There was no correlation between symptoms and total amount of volatile compounds, but a significant positive correlation was demonstrated between symptoms and some substances. The highest correlation was found for 1, 2, 4 trimethyl benzene. Symptoms increased with increasing asphalt temperature and with increasing concentrations of asphalt fumes. Amine addition did not increase the sum of symptoms, but soft asphalt seems to result in fewer symptoms than the harder types. Symptoms were not related to external factors like weather, traffic density, or specific working operations. As preventive measures, asphalt temperature should be kept below 150 degrees C, fume concentrations below 0.40 mg/m3, and if possible, the use of harder asphalt types which also require high temperatures should be avoided.

31. Ritchie GD, Still KR, Alexander WK, Nordholm AF, Wilson CL, Rossi J, 3rd, Mattie DR. (2001) A review of the neurotoxicity risk of selected hydrocarbon fuels. J Toxicol Environ Health B Crit Rev 4(3):223-312.
Over 1.3 million civilian and military personnel are occupationally exposed to hydrocarbon fuels, emphasizing gasoline, jet fuel, diesel fuel, or kerosene. These exposures may occur acutely or chronically to raw fuel, vapor, aerosol, or fuel combustion exhaust by dermal, respiratory inhalation, or oral ingestion routes, and commonly occur concurrently with exposure to other chemicals and stressors. Hydrocarbon fuels are complex mixtures of 150-260+ aliphatic and aromatic hydrocarbon compounds containing varying concentrations of potential neurotoxicants including benzene, n-hexane, toluene, xylenes, naphthalene, and certain n-C9-C12 fractions (n-propylbenzene, trimethylbenzene isomers). Due to their natural petroleum base, the chemical composition of different hydrocarbon fuels is not defined, and the fuels are classified according to broad performance criteria such as flash and boiling points, complicating toxicological comparisons. While hydrocarbon fuel exposures occur typically at concentrations below permissible exposure limits for their constituent chemicals, it is unknown whether additive or synergistic interactions may result in unpredicted neurotoxicity. The inclusion of up to six performance additives in existing fuel formulations presents additional neurotoxicity challenge. Additionally, exposures to hydrocarbon fuels, typically with minimal respiratory or dermal protection, range from weekly fueling of personal automobiles to waist-deep immersion of personnel in raw fuel during maintenance of aircraft fuel tanks. Occupational exposures may occur on a near daily basis for from several months to over 20 yr. A number of published studies have reported acute or persisting neurotoxic effects from acute, subchronic, or chronic exposure of humans or animals to hydrocarbon fuels, or to certain constituent chemicals of these fuels. This review summarizes human and animal studies of hydrocarbon fuel-induced neurotoxicity and neurobehavioral consequences. It is hoped that this review will support ongoing attempts to review and possibly revise exposure standards for hydrocarbon fuels.

32. Ryan TJ, Hart EM, Kappler LL. (2002) VOC exposures in a mixed-use university art building. AIHA J (Fairfax, Va) 63(6):703-708.
Despite a sizable educational art enterprise in the United States there is a dearth of rigorously performed studies of exposures to persons engaged in such activities. Exposures to 45 EPA-designated volatile organic compounds were examined in printmakers in a mixed-use university art school served by a 100% exhausted mechanical ventilation system. Personal exposures (n = 90) were compared with area concentrations (n = 36) in the studio area and at a second location at the same facility. For personal exposure assessments a cohort of 12 students wore passive dosimeters twice weekly over a 6-week period. Numerous compounds were found, the most prevalent being toluene at an average concentration of 64.6 microg/m3 (17.1 ppb; range < 1-319 ppb); 1,1,1, trichloroethane at 40.5 microg/m3 (7.5 ppb; range < 1-211 ppb); xylenes at 8.0 microg/m3 (1.8 ppb; range < 1-43 ppb); 1,3,5-trimethyl benzene at 6.2 microg/m3 (1.3 ppb; range < .3-32 ppb); propyl benzene at 5.0 microg/m3 (1.0 ppb; range < .5-27 ppb); methylene chloride at 4.9 microg/m3 (1.4 ppb; range < 1-10 ppb); and ethyl benzene at 4.5 microg/m3 (1.1 ppb; range < .4-23 ppb). Personal exposures were considerably higher than average area air concentrations, with the exception of methylene chloride concentrations, which were five times higher at the print cleaning operation. Floors where solvents were not used had no detectable exposures (typical lower limit of detection approximately 1 ppb) and were free of solvent odors. Despite frequent solvent contact with skin, personal protective equipment was seldom used. Results indicate that in mixed-use facilities such as this, nonrecirculating general ventilation systems can effectively eliminate indoor air quality issues between floors, despite perceptible odors on solvent use floors. For total exposure assessments in such processes, contact exposures from printmaking solvents during cleaning procedures are a potentially important consideration.

33. Schreiner CA, Edwards DA, McKee RH, Swanson M, Wong ZA, Schmitt S, Beatty P. (1989) The mutagenic potential of high flash aromatic naphtha. Cell Biol Toxicol 5(2):169-188.
Catalytic reforming is a refining process that converts naphthenes to aromatics by dehydrogenation to make higher octane gasoline blending components. A portion of this wide boiling range hydrocarbon stream can be separated by distillation and used for other purposes. One such application is a mixture of predominantly 9-carbon aromatic molecules (C9 aromatics, primarily isomers of ethyltoluene and trimethylbenzene), which is removed and used as a solvent--high-flash aromatic naphtha. A program was initiated to assess the toxicological properties of high-flash aromatic naphtha since there may be human exposure through inhalation or external body contact. The current study was conducted partly to assess the potential for mutagenic activity and also to assist in an assessment of carcinogenic potential. The specific tests utilized included the Salmonella/mammalian microsome mutagenicity assay, the hypoxanthine-guanine phosphoribosyl transferase (HGPRT) forward mutation assay in CHO cells, in vitro chromosome aberration and sister chromatid exchange (SCE) assays in CHO cells, and an in vivo chromosome aberration assay in rat bone marrow.

34. Schupp T, Bolt HM, Jaeckh R, Hengstler JG. (2006) Benzene and its methyl-derivatives: derivation of maximum exposure levels in automobiles. Toxicol Lett 160(2):93-104.
Automobile drivers are exposed to several organic hydrocarbons. Concentrations measured in passenger compartments have been reported to range between 13 and 560 microg/m(3) for benzene, 33-258 microg/m(3) for toluene, 20-250 microg/m(3) for xylene (mixed isomers) and 3-23 microg/m(3) for trimethylbenzene (mixed isomers). These aromatic hydrocarbons are emitted from gasoline and from materials inside a car. In the present study we evaluated, whether these exposures pose a potential risk to the health of drivers. Therefore, we derived maximum exposure levels inside cars for chronic (ELIA(chronic)) and short-term (STELIA) exposure. The lowest ELIA's(chronic) for benzene, toluene, xylene and trimethylbenzene were 0.083, 1.2, 8.8 and 0.31 mg/m(3), respectively. The respective STELIA's were 16, 30, 29 and 25 mg/m(3). Obviously concentrations of toluene, xylene and trimethylbenzene inside cars do not exceed their individual STELIA's. In contrast, benzene seems to be problematic, since concentrations inside cars amount up to 0.56 mg/m(3), which exceeds the ELIA(chronic) derived for benzene. This should not be underestimated, since benzene is a genotoxic carcinogen that probably acts by non-threshold mechanisms. In conclusion, concentrations of toluene, xylene and trimethylbenzene usually observed inside cars are unlikely to pose a risk to the health of drivers. A systematic toxicological evaluation of the risk associated with benzene exposure in cars seems to be necessary.

35. Sulkowski WJ, Kowalska S, Matyja W, Guzek W, Wesolowski W, Szymczak W, Kostrzewski P. (2002) Effects of occupational exposure to a mixture of solvents on the inner ear: a field study. Int J Occup Med Environ Health 15(3):247-256.
Some clinical and laboratory studies indicate that industrial solvents such as toluene, styrene, xylene, trichloroethylene and carbon disulfide or their mixtures may affect the inner ear, although the mechanism of this process is still not well understood. The aim of this investigation was to assess the incidence of hearing and vestibular disorders (using modem audiological and vestibular tests) in 61 workers exposed to a mixture of organic solvents at the production of paints and varnishes; the control group included 40 age-matched non-exposed subjects. Environmental and biological monitoring revealed that the most significant exposure can be attributed to the following mixture constituents: ethylbenzene, xylene and trimethylbenzene isomers such as pseudocumene, mesitylene and hemimellitene. Electronystagmographic examinations showed the symptoms of vestibular dysfunction, as well as the decreased duration, amplitude and slow phase angular velocity of induced nystagmus in 47.5% of the subjects exposed versus 5% of controls. This was accompanied by sensorineural high frequency hearing loss, identified by means of pure tone audiometry in 42% of those exposed versus 5% controls, and reduced amplitudes of transiently evoked and distortion-product otoacoustic emissions. The findings closely correspond with the rate of the total exposure to the solvent mixture. A possible mechanism responsible for ototoxicity of solvents is discussed.

36. Takamiya M, Niitsu H, Saigusa K, Kanetake J, Aoki Y. (2003) A case of acute gasoline intoxication at the scene of washing a petrol tank. Leg Med (Tokyo) 5(3):165-169.
We encountered a case of acute gasoline intoxication at the scene of washing the inner wall of a petrol tank. The decedent was a 50-year-old male, who was the supervisor. Two young workers wearing mask respirators began to wash the inner wall of the gasoline tank under poor ventilation. About 1 h later,

because one of the workers lost consciousness, the supervisor entered the tank, without a mask respirator, to rescue the worker. However, the supervisor immediately fainted, and died 26 h after the accident. In the autopsy, blisters were observed on the skin of the face, neck, anterior chest, upper extremities, and back. The heart contained hemolyzed blood. Histologically, hemorrhagic pulmonary edema, pneumonia, and proximal tubular necrosis were found. In the toxicological analyzes, toluene, xylene, and trimethylbenzene were detected in the blood, brain, and gastric contents. Toluene concentrations in the blood and brain were 0.3 mug/ml and 3.7 mug/g, respectively. Since pathological findings were consistent with the reported findings concerning gasoline intoxication, and constituents of gasoline were in the body, death was attributed to acute gasoline intoxication. It was considered that sufficient ventilation and proper use of a mask respirator were essential for this kind of work.

37. Tang Y, Tang KZ, Zhang J. (2005) 2,4-Bis[2-(benzylaminocarbonyl)phenoxymethyl]-1,3,5-trimethylbenzene. Acta Crystallographica Section E: Structure Reports Online.
The title compound, C39H38N2O4, possesses crystallographically imposed C2 symmetry, with the twofold axis bisecting the central benzene ring. There is an intramolecular hydrogen bond between the phenoxy O atom and the amide N atom.

38. Tomas T, Lutz P, Wiaderna D. (2000) Changes in electrocortical arousal following acute trimethylbenzene administration in rats. Int J Occup Med Environ Health 13(1):67-78.
The purpose of this investigation was to compare the neurotoxic potential of trimethylbenzene (TMB) isomers (the solvents) with that of benzene derivatives with a smaller number of methyl groups (toluene). The experiments were performed on WAG/Rij rats with EEG recording electrodes implanted in the fronto-parietal cortex. The solvents, toluene or TMB isomers: 1,3,5-TMB (mesitylene), 1,2,3-TMB (hemimellitene) or 1,2,4-TMB (pseudocumene), were diluted with olive oil and administered intragastrically via gavage at an acute dose of 0.002, 0.008, or 0.032 mol/kg. The electrocortical activity was recorded for 20 min before, and for 60 min after the solvent administration. The electrocorticograms were analysed with respect to the number and duration of the high-voltage spindles (HVS), a form of activity sensitive to the arousal level. In case of each solvent the observed effect--inhibition of the HVS activity--was dose-related. However, the effect produced by TMB isomers was in each case less pronounced than that of toluene. Among TMBs, pseudocumene displayed the least significant effect, and the efficacy of two other TMB isomers was similar.

39. Triebig G, Schaller KH, Weltle D. (1992) Neurotoxicity of solvent mixtures in spray painters. I. Study design, workplace exposure, and questionnaire. Int Arch Occup Environ Health 64(5):353-359.
A multidisciplinary cross-sectional study was carried out in 105 spray painters with long-term solvent exposure (10-44 years) and in 58 control subjects not exposed to solvents. By means of air monitoring the solvent concentrations in the ambient air during spray painting were determined using charcoal and silicagel tubes with pumps and passive samplers. In general, the air concentrations of the individual compounds did not exceed the current limit values (MAK values). Aromatic hydrocarbons like toluene, xylene, ethylbenzene, trimethylbenzene, aliphatic hydrocarbons (e.g., heptane) and acetates (ethylacetate, butylacetate) were determined to be important components of paint solvents. However, in unfavorable work conditions the "exposure index" could exceed the permissible limits two or three times. To assess the body solvent load at the time of examination, biological monitoring (BM) was performed. The main finding was that there was no evidence of neurotoxicologically relevant solvent exposure. Only in the case of methyl hippuric acid in urine spot samples did the spray painters show a higher mean value (80 mg/l) than control subjects (below 20 mg/l), indicating recent xylene exposure. Elevated urinary chromium concentrations (maximum value 29 micrograms/l) were found in 28 spray painters as a result of using zinc chromate-containing wash primers without taking protective measures. To assess the degree of past solvent exposure a special questionnaire was used. This included variables like duration and amount of solvent exposure, the presence of a technical ventilation system, health complaints during painting, etc. Additionally, three "solvent exposure indices" (SEI) were calculated and used for evaluation of "dose-effect relationships."(ABSTRACT TRUNCATED AT 250 WORDS)

40. Tsujimoto Y, Noda T, Shimizu M, Moriwaki H, Tanaka M. (1999) Identification of the dimethylbenzyl mercapturic acid in urine of rats treated with 1,2,3-trimethylbenzene. Chemosphere 39(5):725-730.
The structure was investigated of the mercapturic acid excreted in urine of rats after the i.p. administration

of 1,2,3-trimethylbenzene. Of the two regioisomeric mercapturic acids, i.e. N-acetyl-S-(2,3-dimethylbenzyl)-L-cysteine and N-acetyl-S-(2,6-dimethyl-benzyl)-L-cysteine, only the former was isolated by preparative HPLC and identified, by comparison with an authentic specimen. The excretion rate of the mercapturate was estimated to be approximately 5% of dose, not a substantial metabolic route.

41. Wilson PF, Freeman CG, McEwan MJ, Milligan DB, Allardyce RA, Shaw GM. (2002) In situ analysis of solvents on breath and blood: a selected ion flow tube mass spectrometric study. Rapid Commun Mass Spectrom 16(5):427-432.
We report measurements of residual vapour levels of xylenes and trimethylbenzenes, present following a floor re-surfacing procedure, using the technique of selected ion flow tube mass spectrometry (SIFT-MS). A subject exposed to controlled amounts of xylene and mesitylene was monitored by direct breath exhalation over a 4-hour period after exposure to the volatile organic compounds (VOCs) had stopped. The headspace gases above 5 mL blood samples taken over this period were also monitored. The decays of the solvent levels with time were fitted to a two-compartment model with residence times for xylene and mesitylene of 0.37 h and 0.38 h, respectively (compartment one) and 2.5 h and 2.8 h, respectively (compartment two).

42. Yamaguchi T, Nakajima D, Ezoe Y, Fujimaki H, Shimada Y, Kozawa K, Arashidani K, Goto S. (2006) Measurement of volatile organic compounds (VOCs) in new residential buildings and VOCs behavior over time. J Uoeh 28(1):13-27.
For the purpose of the investigation of characteristics of VOCs found indoors in recently constructed residential buildings, we measured the behavior of VOCs which were sampled at one-month intervals over a period of one year from the, initial occupancy date in both a detached house and an apartment in a multiple' dwelling. At the first passive sampling from the wooden detached residential building, n-hexane, n-undecane, toluene, ethylacetate, methylethylketone, alpha-pinene and (+)-limonene were present in relatively high concentrations of 10 ppb or higher in the living room. Then these VOCs showed a declining trend with time. p-Dichlorobenzene showed an extremely high concentration (approx. 320 ppb) in June, which subsequently declined with each passing month. There is a high possibility that the cause was the use of a pesticide containing p-dichlorobenzene during the period of changeover from winter to summer clothes in June. On the other hand, from the multiple dwelling, four VOCs showed values of 10 ppb or more (toluene, 1,2,4-trimethylbenzene, methylethylketone and alpha-pinene). Of these VOCs, methylethylketone concentration was in excess of 100 ppb, and then also showed a declining trend with time. Even for new residential buildings completed during the same time frame, it was shown that the types of VOC contaminants and their concentrations varied significantly.

43. Zibrowski EM, Hoh TE, Vanderwolf CH. (1998) Fast wave activity in the rat rhinencephalon: elicitation by the odors of phytochemicals, organic solvents, and a rodent predator. Brain Res 800(2):207-215.
Recent research has shown that bursts of approximately 20 Hz fast waves are elicited in rhinencephalic cortex in rats by the odors of a number of different organic solvents and of components of the secretions of predators such as the weasel and the fox. We now show that a number of phytochemicals (benzyl alcohol, carvacrol, eucalyptol, and salicylaldehyde) will elicit fast wave bursts of about 20 Hz in the rat pyriform cortex. Additional organic solvents (carbon tetrachloride, chloroform, diethyl ether, 1, 2-dimethoxyethane, n-heptane, mesitylene, methylcyclohexane, and commercial gasoline and kerosene, but not N,N-dimethylformamide or dimethyl sulfoxide) and another component of fox secretions (isopentenylmethyl sulfide) were also effective. Many of these compounds will also elicit fast wave bursts of about 20 Hz in the dentate gyrus. The effectiveness of benzyl alcohol, camphor, carvacrol, eucalyptol, isopentenylmethyl sulfide, 2-propylthietane, salicylaldehyde, toluene, and trimethylthiazoline (all of which elicit rhinencephalic fast waves in rats) in suppressing feeding in various small herbivores suggests that the recording of odor-induced rhinencephalic fast waves may provide an easy means of identifying new antifeedants. We found no evidence that the bursts of 20-Hz activity seen in the rat rhinencephalon were kindling-induced seizure-like reactions of the olfactory brain to the vapors of toxic chemicals.