N-BUTANOL PRELIMINARY SEARCH RESULTS: CHRONIC AND LESS-THAN-LIFETIME TOXICITY STUDIES EndNote Library: Full Reference List with Abstracts As of 10/12/2007

POTENTIAL KEY REFERENCES (12)

1. Albano E, Tomasi A, Persson JO, Terelius Y, Goria-Gatti L, Ingelman-Sundberg M, Dianzani MU. (1991) Role of ethanol-inducible cytochrome P450 (P450IIE1) in catalyzing the free radical activation of aliphatic alcohols. Biochem Pharmacol 41(12):1895-1902.
   BIOSIS COPYRIGHT: BIOL ABS. Incubation of rat liver microsomes with 1-propanol and 1-butanol in the presence of NADPH and of the spin trapping agent 4-pyridyl-1-oxide-t-butyl nitrone (4-POBN) allowed the detection of free radical intermediates tentatively identified as 1-hydroxypropyl and 1-hydroxybutyl radical, respectively. Microsomes isolated from rats treated chronically with ethanol (EtOH) or with the combination of starvation and acetone treatment (SA), exhibited a two-fold increase in the ESR signal intensity as compared to untreated controls, whereas no increase was observed in phenobarbital-induced (PB) microsomes. Consistently, in reconstituted membrane vesicles, ethanol-inducible cytochrome P450IIE1 was twice as active as phenobarbital-inducible P450IIB1 in producing 1-butanol free radicals. In the microsomal preparations from EtOH and SA pretreated rats the addition of antibodies against cytochrome P450IIE1, but nto of preimmune IgGs, lowered the ESR signal of 1-butanol radicals by more

2. Arsov Z, Zorko M, Schara M. (2005) Inhibition of erythrocyte acetylcholinesterase by n-butanol at high concentrations. Arch Biochem Biophys 437(1):78-84.
   Erythrocyte acetylcholinesterase (AChE) is bound to the membrane by a complex glycosylphosphatidylinositol anchor, so the effect of alcohol on AChE activity may reflect direct and/or membrane-mediated effects. The indication of a direct interaction between n-butanol and AChE molecules is the activation/inhibition of AChE by occupation of the enzyme's active and/or regulatory sites by alcohol. The activation of AChE can occur only at low concentrations of alcohols, while at high concentrations AChE is inhibited. In this work the mechanism of inhibition of erythrocyte AChE by n-butanol at high concentrations was studied. The values of activity, calculated assuming parabolic competitive inhibition, which implies that one or two molecules of inhibitor bind to the enzyme, fit well to the experimental values. From the values of the inhibition constants it was concluded that at high n-butanol concentrations two alcohol molecules usually interact with AChE.

3. Ashley DL, Prah JD. (1997) Time dependence of blood concentrations during and after exposure to a mixture of volatile organic compounds. Archives of Environmental Health 52(1):26-33.
   BIOSIS COPYRIGHT: BIOL ABS. Volatile organic compounds constitute a group of important environmental pollutants that have been associated with the constellation of symptoms known as sick building syndrome. An understanding of the kinetics of uptake and elimination of volatile organic compounds is important for the proper interpretation of the internal dose concentrations of people exposed to these compounds. Blood concentrations measured before, during and after exposure of five individuals to a mixture of volatile organic compounds in a controlled chamber are described. Blood concentrations were related directly to air exposure concentrations and appeared to be a function of the blood/air partition coefficient. The half-lives of the internal dose of the volatile organic compounds measured were less than 1/2 h, but the elimination time courses were multiexponential. The complexity of the elimination curve suggested the existence of multiple storage sites within the body. The presence of a long-ter

4. Boman A, Hagelthorn G, Magnusson K. (1995) Percutaneous absorption of organic solvents during intermittent exposure in guinea pigs. Acta Derm Venereol 75(2):114-119.

Skin absorption under intermittent exposure of guinea pigs to n-butanol, toluene, 1,1,1-trichloroethane was studied. Groups of guinea pigs were exposed to test organic solvents for 1 min at 30-min intervals during 4 h, in all 8 exposures. Skin absorption of solvent was assessed by following the concentration of solvent in the blood. This intermittent exposure was compared to continuous exposure over 4 h. Absorption of toluene and 1,1,1-trichloroethane was low, but a considerable amount of butanol was absorbed through the skin on intermittent exposure. A typical serrated absorption profile was seen for butanol that was less pronounced for toluene and 1,1,1-trichloroethane. The absorption of butanol was highest at the end of the exposure period. The differences in absorption profiles may be due to the differences in vapour pressure in the solvents in association with the animal method used. The amount absorbed varied inversely with vapour pressure. Hair stubble may act as a trap for solvents with low vapour pressure. Adequate ventilation reduces unoccluded skin absorption of volatile organic solvents.

5. Carlson GP, Olson RM. (1995) Comparison of the metabolism of alcohols by rat hepatic and pulmonary alcohol dehydrogenase. Biochem Mol Biol Int 37(1):65-71.
The metabolism of 1-butanol, 1-pentanol and 1-propanol by rat hepatic and pulmonary cytosolic preparations was measured with regard to ADH activity as influenced by pH and substrate concentration. Compared to lung, hepatic ADH activity showed little pH dependence with apparent Vmax values similar for the 3 alcohols. Apparent Km values were also similar and were lower than previously reported for ethanol. In contrast to the liver, little ADH activity was observed in pulmonary preparations at pH 7.2 or 9.0 with any alcohol. Pulmonary apparent Km values were considerably higher than those in the liver. Thus the optimum conditions for pulmonary ADH activity require an alkaline pH and high substrate concentrations.

6. Ema M, Hara H, Matsumoto M, Hirose A, Kamata E. (2005) Evaluation of developmental toxicity of 1-butanol given to rats in drinking water throughout pregnancy. Food Chem Toxicol 43(2):325-331.
The objective of this study was to evaluate the developmental toxicity of 1-butanol in rats. Pregnant rats were given drinking water containing 1-butanol at 0.2%, 1.0% or 5.0% (316, 1454 or 5654 mg/kg/day) on days 0-20 of pregnancy. A significant decrease in maternal body weight gain accompanied by reduced food and water consumption was found at 5.0%. No significant increase in the incidence of pre- and postimplantation embryonic loss was observed in any groups treated with 1-butanol. Fetal weight was significantly lowered at 5.0%. Although a significant increase in the incidence of fetuses with skeletal variations and decreased degree of ossification was found at 5.0%, no increase in the incidence of fetuses with external, skeletal and internal abnormalities was detected in any groups treated with 1-butanol. The data demonstrate that 1-butanol is developmental toxic only at maternal toxic doses. No evidence for teratogenicity of 1-butanol was noted in rats. Based on the significant decreases in maternal body weight gain and fetal weight, it is concluded that the no observed adverse effect levels (NOAELs) of 1-butanol for both dams and fetuses are 1.0% (1454 mg/kg/day) in rats.

7. Nelson BK, Brightwell WS, Krieg EF, Jr. (1990) Developmental toxicology of industrial alcohols: a summary of 13 alcohols administered by inhalation to rats. Toxicol Ind Health 6(3-4):373-387.
The developmental toxicology of 13 industrial alcohols (methanol, ethanol, 1-propanol, isopropanol, 1-butanol, 2-butanol, tertiary-butanol, 1-pentanol, 1-hexanol, 2-ethyl-1-hexanol, 1-octanol, 1-nonanol, and 1-decanol), and the behavioral teratogenicity of 4 of these alcohols, were assessed in a series of experiments. The results of individual alcohols have been published previously, but the present paper summarizes the results in view of structure-activity relationships among these alcohols. The alcohols were administered by inhalation for 7 hours per day (6 hours/day for 1-decanol) on gestation days 1-19 to groups of approximately 15 pregnant Sprague-Dawley rats. For developmental toxicology evaluations, dams were sacrificed on gestation day 20. Fetuses were serially removed, weighed, sexed, and examined for external malformations. The frequency of visceral malformations and variations was determined in one-half of the fetuses, and the frequency of skeletal deviations was determined in the other half. Behavioral teratology endpoints were investigated in groups of 15 pregnant rats exposed to one of four alcohols (ethanol, 1-propanol, 1-butanol, and tertiary-butanol) and also involved groups of 18 male rats which were exposed to the same concentrations of each alcohol for 6 weeks, and

then mated to untreated females. In the behavioral teratology evaluations, all litters were culled to eight pups and fostered to unexposed mothers. Offspring were tested from days 10-90 on a series of behavioral tests designed to evaluate neuromotor integrity, activity levels, learning, and memory. Additionally, brains were removed from 10 offspring per group at 21 days of age, and were dissected into cerebrum, cerebellum, brainstem, and midbrain; these samples were assayed for steady-state levels of protein and the neurotransmitters acetylcholine, dopamine, norepinephrine, 5-hydroxytryptamine (serotonin), substance P, B-endorphin, and met-enkephalin. Congenital malformations were noted for methanol, 1-propanol, isopropanol, and 1-butanol, but only at concentrations in excess of 5000 ppm. These concentrations also produced toxicity in the maternal animals; thus, there was little evidence of selective developmental toxicity among the alcohols. Although sporadic behavioral and neurochemical deviations were detected, no consistent pattern of effects was seen for any of the alcohols we tested. It should be noted that alcohols with chain lengths longer than the butyl series could not be generated as vapors at sufficiently high concentrations to produce observable toxicity in the maternal animals. This limits the generality of these findings to the possible developmental effects of these alcohols when taken through other routes of exposure.(ABSTRACT TRUNCATED AT 400 WORDS)

8. NTP. (1995) NTP Toxicology and Carcinogenesis Studies of t -Butyl Alcohol (CAS No. 75-65-0) in F344/N Rats and B6C3F1 Mice (Drinking Water Studies). Natl Toxicol Program Tech Rep Ser 436:1-305.
t -Butyl alcohol is widely used in the manufacture of perfumes and a variety of cosmetics. It is also used as a raw material in the production of isobutylene, which may be used to produce methyl tertiary butyl ether, a common gasoline additive, or to produce butyl elastomers used in the production of automobile tires. Male and female F344/N rats and B6C3F1 mice were given t -butyl alcohol (greater than 99% pure) in drinking water for 13 weeks or 2 years. The genetic toxicity of t -butyl alcohol was assessed by testing the ability of the chemical to induce mutations in various strains of Salmonella typhimurium and in L5178Y mouse lymphoma cells, sister chromatid exchanges and chromosomal aberrations in cultured Chinese hamster ovary cells, and by measuring the frequency of micronucleated erythrocytes in mouse peripheral blood. 13-WEEK STUDY IN RATS: Groups of 10 male and 10 female F344/N rats were given 0, 2.5, 5, 10, 20, or 40 mg/mL t -butyl alcohol in drinking water for 13 weeks. All males and six females given 40 mg/mL died during the study. Final mean body weights of 10 and 20 mg/mL males and of 40 mg/mL females were 12%, 17%, or 21% less than those of the corresponding controls, respectively. Serum sorbitol dehydrogenase activities in 10 and 20 mg/mL males were greater than that in the controls after 13 weeks. Serum alanine aminotransferase activity in 40 mg/mL females was greater than that in the controls after 2 weeks and greater in all exposed females after 13 weeks. Urine volumes of 10, 20, and 40 mg/mL males and females decreased, and urine specific gravity values increased. Transitional epithelial hyperplasia and inflammation of the urinary bladder were observed in 20 and 40 mg/mL males and 40 mg/mL females. Absolute and relative liver weights of all exposed groups of females and relative liver weights of 5, 10, and 20 mg/mL males were significantly greater than those of the controls. Absolute and relative kidney weights of all exposed groups of males and females were significantly greater than those of the controls. Incidences of mineralization of the kidney were significantly increased in 10, 20, and 40 mg/mL males. The severity of nephropathy in 2.5, 5, 10, and 20 mg/mL males was significantly greater than that of the controls as was the accumulation of hyaline droplets in the kidney of 5, 10, and 20 mg/mL males. The incidences of nephropathy in 10, 20, and 40 mg/mL females were significantly greater than that of the controls. 13-WEEK STUDY IN MICE: Groups of 10 male and 10 female B6C3F1 mice were given 0, 2.5, 5, 10, 20, or 40 mg/mL t -butyl alcohol in drinking water for 13 weeks. The deaths of two males and one female in the 40 mg/mL group were attributed to exposure to t -butyl alcohol. The final mean body weights of 20 and 40 mg/mL males and 40 mg/mL females were significantly lower than those of the controls. There were no biologically significant differences in hematology parameters of exposed and control groups of mice. Transitional epithelial hyperplasia and inflammation were observed in the urinary bladder of 20 and 40 mg/mL males and 40 mg/mL females. 2-YEAR STUDY IN RATS: Groups of 60 F344/N rats were given 0, 1.25, 2.5, or 5 mg/mL t -butyl alcohol (males) or 0, 2.5, 5, or 10 mg/mL t -butyl alcohol (females) in drinking water for 2 years. These correspond to average daily doses of

approximately 90, 200, or 420 mg t -butyl alcohol/kg body weight for males and approximately 180, 330, or 650 mg t -butyl alcohol/kg body weight for females. Ten rats per group were evaluated after 15 months of chemical administration. Survival, Body Weights, and Water Consumption: Survival rates of 5 mg/mL males and 10 mg/mL females were significantly lower than those of the controls. The final mean body weights of exposed groups of males were 15% to 24% lower than that of the controls, and the final mean body weight of 10 mg/mL females was 21% lower than that of the controls. Water consumption by males increased with dose; water consumption by females decreased with dose. Hematology and Urinalysis: At the 15-month inte. Hematology and Urinalysis: At the 15-month interim evaluation, there were no significant differences in hematology parameters in males and females, and there were no significant differences in urinalysis parameters in males. Females given 5 or 10 mg/mL had increased urine specific gravities and decreased urine volumes. Pathology Findings: At the 15-month interim evaluation, relative kidney weights of 2.5 and 5 mg/mL males and absolute and relative kidney weights of 2.5, 5, and 10 mg/mL females were significantly greater than those of the controls. At 2 years, the incidence of mineralization in the kidney increased with dose and that of 5 mg/mL males was significantly greater than that of the controls. In the standard evaluation at the end of the study, the incidences of focal renal tubule hyperplasia and of adenoma were increased in exposed males and a carcinoma was observed in one 5 mg/mL male. Renal tubule hyperplasia occurred in one 10 mg/mL female. An extended evaluation of the kidney identified additional male rats with hyperplasia (control, 11/50; 1.25 mg/mL, 13/50; 2.5 mg/mL, 11/50; 5 mg/mL, 19/50) and renal tubule adenoma (7/50, 8/50, 15/50, 10/50); renal tubule carcinomas were identified in two 1.25 mg/mL males and in one 2.5 mg/mL male. Renal tubule adenoma was identified in one 5 mg/mL male from the 15-month extended evaluation. In the standard and extended evaluations combined, there were dose-related increased incidences of hyperplasia and adenoma. The severity of nephropathy and the incidence and severity of transitional cell hyperplasia of the kidney were increased in exposed male and female rats. Linear foci of mineralization were present in the renal papilla of exposed males. 2-YEAR STUDY IN MICE: Groups of 60 male and 60 female B6C3F1 mice were given 0, 5, 10, or 20 mg/mL t -butyl alcohol in drinking water for 2 years. Exposure levels of 5, 10, or 20 mg/mL delivered average daily doses of approximately 540, 1,040, or 2,070 mg t -butyl alcohol/kg body weight to males and approximately 510, 1,020, or 2,110 mg/kg to females. Survival, Body Weights, and Water Consumption: Survival of 20 mg/mL males was significantly lower than that of the controls. The final mean body weights of exposed groups of males were similar to those of the controls. The mean body weights of females given 20 mg/mL were 10% to 15% lower than those of the controls from week 13 to the end of the study. Water consumption by exposed groups of males and females was similar to that by the controls. Pathology Findings: Incidences of thyroid gland follicular cell hyperplasia were significantly increased in all exposed groups of males and in 10 and 20 mg/mL females. The incidence of follicular cell adenoma or carcinoma (combined) was marginally increased in 10 mg/mL males (0 mg/mL, 1/60; 5 mg/mL, 0/59; 10 mg/mL, 4/59; 20 mg/mL, 2/57). The incidence of follicular cell adenoma was significantly increased in 20 mg/mL females (2/58, 3/60, 2/59, 9/59). The incidences of chronic inflammation and transitional epithelial hyperplasia of the urinary bladder were increased in 20 mg/mL males and to a lesser extent in 20 mg/mL females. GENETIC TOXICOLOGY: t -Butyl alcohol was tested for induction of genetic damage in vitro and in vivo, and all results were negative. In vitro, t -butyl alcohol was negative in Salmonella typhimurium and mouse lymphoma cell mutation tests, and it did not induce sister chromatid exchanges or chromosomal aberrations in cultured Chinese hamster ovary cells. These in vitro studies were conducted with and without metabolic activation (S9). In vivo, no increase in micronucleated erythrocytes was observed in peripheral blood samples from mice administered t -butyl alcohol in drinking water for 13 weeks. CONCLUSIONS: Under the conditions of these 2-year drinking water studies, there was some evidence of carcinogenic activity of t -butyl alcohol in male F344/N rats based on increased incidences of renal tubule adenoma or carcinoma (combined). There was no evidence of carcinogenic activity in female F344/N rats receiving 2.5, 5, or 10 mg/mL t -butyl alcohol. There was equivocal evidence of carcinogenic activity of t -butyl alcohol in male B6C3F1 mice based on the marginally increased incidences of follicular cell adenoma or carcinoma (combined) of the thyroid gland. There was some evidence of carcinogenic activity of t -butyl alcohol in female B6C3F1 mice based on increased incidences of

follicular cell adenoma of the thyroid gland. Exposure to t -butyl alcohol was associated with mineralization and renal tubule hyperplasia in male rats, transitional epithelial hyperplasia and increased severity of nephropathy of the kidney in male and female rats, follicular cell hyperplasia of the thyroid gland in male and female mice, and chronic inflammation and hyperplasia of the urinary bladder in male mice and to a lesser extent in female mice. Synonyms: 2-Methyl-2-propanol, 2-methylpropan-2-ol, TBA, t -butanol, tertiary butyl alcohol, t -butyl hydroxide, trimethyl carbinol, trimethyl methanol

9. Sitarek K, Berlinska B, Baranski B. (1994) Assessment of the effect of n-butanol given to female rats in drinking water on fertility and prenatal development of their offspring. Int J Occup Med Environ Health 7(4):365-370.
Female rats were given aqueous solutions of n-butanol containing 0.24, 0.8 and 4% n-butanol (0.3; 1.0 and 5.0 g/kg/day) for 8 weeks before and during gestation. The control animals received tap water. The experiment was performed in two stages. The first comprised of the assessment of the oestrous cycle before exposure and then during 4-5 and 7-8 weeks of exposure, and the second stage of the fertility of female rats and their foetal development. The duration of the cycle and its individual stages in the control and the exposed females were similar. It was found that n-butanol alcohol is a foetotoxic agent and produces developmental anomalies in a foetus's skeleton and central nervous system.

10. Swiercz R, Korsak Z, Rydzynski K. (1995) Kinetics of n-butyl alcohol and m-xylene in blood during single and combined inhalation exposure in rats. Int J Occup Med Environ Health 8(4):361-365.
The levels of m-xylene and n-butyl alcohol in blood of rats during single and combined inhalation exposure to m-xylene and n-butyl alcohol at the concentrations of 100 + 100 ppm were investigated. We found that levels of n-butyl alcohol and m-xylene in blood of animals during single exposure did not differ as compared to coexposure. It has been shown that less than additive neurotoxic and irritating respiratory tract effects of m-xylene and n-butyl alcohol mixture, observed earlier under acute and subchronic inhalation study, cannot be explained by their metabolic interaction.

11. Teeguarden JG, Deisinger PJ, Poet TS, English C, Corley RA, Barton HA, Clewell HJ, Faber WD. (2004) A Physiologically-Based Pharmacokinetic (PBPK) Model For Intravenous And Inhalation-Route Pharmacokinetics Of Butyl Acetate (BA) And Metabolites Nbutanol (BOH) And N-Butyric Acid (BOOH). Toxicologist 78(1-S):421.
Risk assessment for n-butyl acetate and metabolites n-butanol and n-butyric acid (the butyl series) can be accomplished with limited toxicity data and pharmacokinetic data for each compound through application of the “family approach” (Barton et al., 2000). The necessary quantitative and interpretive tool is a PBPK model describing the inhalation-route blood kinetics of the series members. A series of revisions of the initial model were carried through to validation of the inhalation route (BA and BOOH) for male SD rats. Rats were implanted with dual indwelling cannulae and administered BA, BOH or BOOH by IV bolus dose, IV infusion or by inhalation in a recirculating closed chamber. Hepatic, vascular and extravascular metabolic constants for metabolism were estimated by fitting the model to the blood time course data. The respiratory bioavailability of BA (100%) and BOH (~50%) was estimated from a novel closed chamber inhalation study design (Poet, 2002) involving simultaneous measurement of ventilation rates, chamber loss (uptake) and blood kinetics. The resulting PBPK model successfully reproduces the blood time course of these compounds following inhalation exposure to BA and BOH, verifying the description of the blood kinetics based on i.v. studies. This effort highlights the value of new, cost effective dosimetry based approaches to risk assessment for metabolically related compounds.

12. Teeguarden JG, Deisinger PJ, Poet TS, English JC, Faber WD, Barton HA, Corley RA, Clewell HJ, 3rd. (2005) Derivation of a human equivalent concentration for n-butanol using a physiologically based pharmacokinetic model for n-butyl acetate and metabolites n-butanol and n-butyric acid. Toxicol Sci 85(1):429-446.

The metabolic series approach for risk assessment uses a dosimetry-based analysis to develop toxicity information for a group of metabolically linked compounds using pharmacokinetic (PK) data for each compound and toxicity data for the parent compound. The metabolic series approach for n-butyl acetate and its subsequent metabolites, n-butanol and n-butyric acid (the butyl series), was first demonstrated using a provisional physiologically based pharmacokinetic (PBPK) model for the butyl series. The objective of this work was to complete development of the PBPK model for the butyl series. Rats were administered test compounds by iv bolus dose, iv infusion, or by inhalation in a recirculating closed chamber. Hepatic, vascular, and extravascular metabolic constants for metabolism were estimated by fitting the model to the blood time course data from these experiments. The respiratory bioavailability of n-butyl acetate (100% of alveolar ventilation) and n-butanol (50% of alveolar ventilation) was estimated from closed chamber inhalation studies and measured ventilation rates. The resulting butyl series PBPK model successfully reproduces the blood time course of these compounds following iv administration and inhalation exposure to n-butyl acetate and n-butanol in rats and arterial blood n-butanol kinetics following inhalation exposure to n-butanol in humans. These validated inhalation route models can be used to support species and dose-route extrapolations required for risk assessment of butyl series family of compounds. Human equivalent concentrations of 169 ppm and 1066 ppm n-butanol corresponding to the rat n-butyl acetate NOAELs of 500 and 3000 ppm were derived using the models.

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