BENZO[b]FLUORANTHENE

GENERAL BACKGROUND INFORMATION

Benzo[b]fluoranthene (BbF) is a member of the class of compounds referred to as polycyclic aromatic hydrocarbons (PAHs). PAHs contain two or more aromatic rings. PAHs are ubiquitous in nature and are both naturally occurring and man-made. Exposure to BbF can come from air, water, or soil. As a PAH, BbF is present in the emissions from industrial plants that produce coal tar, cooking plants, asphalt production plants, and home heating with wood and coal. BbF is also present in charcoal-broiled foods and cigarette smoke (ATSDR, 1990).

PHARMACOKINETICS

No data on the absorption, distribution or excretion of BbF were identified. BbF is metabolized under *in vitro* incubation conditions to phenol and dihydrodiol metabolites (Amin et al., 1982). The general metabolic pathways elucidated for benzo(a)pyrene are also active on BbF (Cooper et al., 1983; Levin et al., 1982; Grover et al., 1986). The reactive metabolites associated with the tumorigenic effects of BbF may not be the diol epoxides (Amin et al., 1982; Amin et al., 1985). As for the other PAHs, the material excreted is expected to consist primarily of dihydrodiol and phenol conjugates (Grover et al., 1986).

HUMAN TOXICOLOGICAL PROFILE

The database for human toxicity is very limited. There are no studies correlating exposure to BbF and cancer or systemic toxicity. The only data implicating BbF as a carcinogen come from carcinogenicity studies using a mixture of PAHs.

MAMMALIAN TOXICOLOGICAL PROFILE

The database on the toxicity of BbF is limited. Intratracheal administration of BbF to rats resulted in an increase in respiratory tract tumors (Deutsch-Wenzel et al., 1983). BbF has caused skin tumors in mice following dermal application (Wynder and Hoffman, 1959). The skin tumor initiating ability of BbF has been demonstrated in mice using a standard initiation/promotion protocol with either croton oil or phorbol myristate acetate as a tumor promotor (Amin et al., 1985; LaVoie et al., 1979, 1982).

GENOTOXICITY

The genotoxicity of BbF has been shown equivocally in three *in vitro* studies. BbF has been shown to be mutagenic in *Salmonella typhimurium* in the presence of an exogenous rat-liver preparation (LaVoie et al., 1979). Mutagenic activity has been reported in another similar study (Hermann, 1981). Negative results were reported by Mossanda (1979). The results cannot support an unequivocal determination regarding the genotoxicity of BbF at this time.

REFERENCES

Agency for Toxic Substance and Disease Registry (ATSDR) (1990) Toxicological profile for benzo(b)fluoranthene. U.S. Public Health Service.

Amin, S., LaVoie, E.J. and Hecht, S.S. (1982) *Identification of metabolites of benzo(a)fluoranthene.* Carcinogenesis 3:171-174.

Amin, S., Huie, K., Hussaur, N., Geddie, J.E. and Hecht, S.S. (1985) *Mutagenicity and tumor initiating activity of methylated benzo(b)fluoranthenes.* Carcinogenesis 6:1023-1025.

Cooper, C.S., Grover, P.L. and Sims, P. (1983) *The metabolism and activation of benzo(a)pyrene.* In: Bridges, J.W., Chase, L.F. eds. Progress in drug metabolism, Vol.7. John Wiley and Sons, New York, pps. 295-395.

Deutsch-Wenzel, R.P., Brune, H., Grimmer, O., Dettbarn, G. and Misfield, J. (1983) *Experimental studies in rat lungs on the carcinogenicity and dose-response relationships of eight frequently occurring environmental polycyclic aromatic hydrocarbons.* J. Natl.Cancer Inst. 71:539-544.

Grover, P.L. (1986) *Pathways involved in the metabolism and activation of polycyclic aromatic hydrocarbons.* Xenobiotica. 16:915-931.

Hermann, M. (1981) *Synergistic effects of individual polycyclic aromatic hydrocarbons and the mutagenicity of their mixtures.* Mutat. Res. 90:399-409.

LaVoie, E.J., Amin, S., Hecht, S.S., Furuya, K. and Hoffmann, D. (1979) *On the metabolic activation of the environmental carcinogens benzo(j)fluoranthene and benzo(b)fluranthene.* Proc. Am. Assoc. Ca. 20:81.

LaVoie, E.J., Amin, S., Hecht, S.S., Furuya, K. and Hoffmann, D. (1982) *Tumour initiating activity of dihydrodiols of benzo(b)fluoranthene, benzo(j)fluoranthene, and benzo(k)fluoranthene.* Carcinogenesis 3:49-52.

Levin, W., Wood, A., Chang, R.L. et al. (1982) *Oxidative metabolism of polycyclic aromatic hydrocarbons to ultimate carcinogens.* Drug Metab. Rev. 13:555-580.

Mossanda, K., Poncelet, F., Fouassin, A. and Mercier, M. (1979) *Detection of mutagenic polycyclic aromatic hydrocarbons in African smoked fish.* Food Cosmet. Toxicol. 17:141-143.

Wynder, E.L. and Hoffmann, D. (1959) *The carcinogenicity of benzofluoranthenes.* Cancer 12:1194-1199.

BENZO[k]FLUORANTHENE

GENERAL BACKGROUND INFORMATION

Benzo[k]fluoranthene (BkF) is a member of the class of compounds referred to as polycyclic aromatic hydrocarbons (PAHs). PAHs contain two or more aromatic rings. PAHs are ubiquitous in nature and are both naturally occurring and man-made. Exposure to BkF can come from air, water, or soil. As a PAH, BkF is present in the emissions from industrial plants that produce coal tar, cooking plants, asphalt production plants, and home heating with wood and coal. BkF is also present in charcoal-broiled foods and cigarette smoke (ATSDR, 1990).

PHARMACOKINETICS

No data on the absorption, distribution or excretion of BkF were identified. BkF is believed to be metabolized to phenol and dihydrodiol metabolites (ATSDR, 1990). The general metabolic pathways elucidated for benzo[a]pyrene are believed to be active on BkF. As for the other PAHs, the material excreted is expected to consist primarily of dihydrodiol and phenol conjugates (Levin et al., 1982; Cooper et al., 1983; Grover et al., 1986).

HUMAN TOXICOLOGICAL PROFILE

The database for human toxicity is very limited. There are no studies correlating exposure to BkF and cancer or systemic toxicity. The only data implicating BkF as a carcinogen come from carcinogenicity studies using a mixture of PAHs.

MAMMALIAN TOXICOLOGICAL PROFILE

The database on the toxicity of BkF is limited. The skin tumor initiating ability of BkF has been demonstrated in mice using a standard initiation/promotion protocol with either croton resin or phorbol myristate acetate as tumor promotors (Van Duuren et al., 1966; LaVoie et al., 1982). Chronic dermal application of benzo[k]fluoranthene to mice resulted in no skin tumors, suggesting that BkF alone is not a complete carcinogen (Wynder and Hoffman, 1959).

GENOTOXICITY

The genotoxicity of BkF has not been documented in *in vitro* studies. In vivo, a single topical application of BkF was reported to bind to DNA in CD-1 mouse skin (Weyland et al., 1987). Covalent binding of chemicals to DNA can result in strand breaks and DNA damage, ultimately leading to mutations (ATSDR, 1990).

REFERENCES

Agency for Toxic Substance and Disease Registry (ATSDR) (1990) Toxicological profile for polycyclic aromatic hydrocarbons. U.S. Public Health Service.

Cooper, C.S., Grover, P.L. and Sims, P. (1983) *The metabolism and activation of benzo(a)pyrene.* In: Bridges, J.W., Chase, L.F. eds. Progress in drug metabolism, Vol.7. John Wiley and Sons, New York, pp. 295-395.

Grover, P.L. (1986) *Pathways involved in the metabolism and activation of polycyclic aromatic hydrocarbons.* Xenobiotica. 16:915-931.

LaVoie, E.J., Amin, S. and Hecht, S.S. (1982) *Tumor initiating activity of dihydrodiols of benzo(b)fluoranthene, benzo(j)fluoranthene and benzo(k)fluoranthene.* Carcinogenesis 3:49-52.

Levin, W., Wood, A., Chang, R.L. et al. (1982) *Oxidative metabolism of polycyclic aromatic hydrocarbons to ultimate carcinogens.* Drug Metab. Rev. 13:555-580.

Van Duuren, B.L., Sivak, A. and Segal, A. (1966) *The tumor producing agents of tobacco leaf and tobacco smoke condensate.* JNCI 37:519.

Weyand, E.H., Rice, J.E., and LaVoie, E.J. (1987) *32P-postlabeling analysis of DNA adducts from non-alterant PAH using thin-layer and high performance liquid chromatography.* Cancer Lett 37:257-266.

Wynder, E.L. and Hoffmann, D. (1959) *The carcinogenicity of benzofluoranthenes.* Cancer 12:1194-1199.

CHRYSENE

GENERAL BACKGROUND INFORMATION

Chrysene is one of the polycyclic aromatic hydrocarbon (PAH) compounds which are formed during the combustion of organic material. Chrysene often exists in particulate form, adsorbing to existing particulate material in air. Human exposure can occur in the workplace (coal and asphalt production plants, cooking plants, smoke houses) or in the environment due to chrysene contamination of air, food, soil and water (ATSDR, 1990).

PHARMACOKINETICS

Chrysene can be absorbed by all routes of exposure (see section on Relative Absorption Factors). Its absorption is believed to be qualitatively similar to benzo[a]pyrene (ATSDR, 1990). Following absorption, chrysene distributes to all organs, reaching the highest concentration in tissues with large fat content (adipose tissue, mammary tissue, brain) (Modica et al., 1983). Chrysene undergoes metabolic biotransformation mediated by the mixed function oxidase enzyme system to form reactive intermediates hypothesized to be responsible for its toxicity. The major metabolites include trans-dihydrodiols, phenols, diol epoxides and triol epoxides (Thakker et al., 1985). The reactive metabolites are conjugated and excreted primarily in feces (Schlede et al., 1970).

HUMAN TOXICOLOGICAL PROFILE

There is no information available on threshold toxic effects of chrysene in humans. Since it is structurally similar to benzo[a]pyrene, it would be expected to produce effects similar to B[a]P following acute or chronic exposure (see Toxicity Profile on Benzo[a]pyrene).

MAMMALIAN TOXICOLOGICAL PROFILE

There is no information available on threshold toxic effects of chrysene in animals. Since it is structurally similar to benzo[a]pyrene, it would be expected to produce effects similar to B[a]P following acute or chronic exposure (see Toxicity Profile for Benzo[a]pyrene).

GENOTOXICITY

The genotoxicity of chrysene has been evaluated in in vivo and in vitro cytogenetic tests. Chrysene produced weak positive results in bacterial mutation assays, human epithelial mutation studies, cell transformation assays and in vivo cytogenetic studies (Waters et al., 1987). Metabolism of chrysene is essential to produce the observed positive responses. Chrysene is not genotoxic in all test systems, however, it is believed to be a weak mutagen (ATSDR, 1990). The carcinogenicity of chrysene has not been adequately studied. There are no reports directly correlating human chrysene exposure and tumor development. There is limited evidence that chryesene is a skin carcinogen in animals following long-term dermal application (Wynder and Hoffmann, 1959; Hecht et al., 1974).

REFERENCES

Agency for Toxic Substances and Disease Registry (ATSDR) (1990) Toxicological profile for chrysene. U.S. Department of Health and HUman Services, Public Health Service.

Hecht, S.S., Bondinell, W.E. and Hoffmann, D. (1974) *Chrysene and methylchrysene: Presence in tobacco smoke and carcinogenicity.* J. Natl. Cancer Inst. 53:1121-1133.

Modica, R., Fiume, M., Guaitani, A. and Bartosek, I. (1983) *Comparative kinetics of benz[a]anthracene, chrysene and triphenylene in rats after oral administration.* Toxicol. Lett. 18:103-109.

Schlede, E., Kuntzman, R., Haber, S. and Conney, A.H. (1970) *Effect of enzyme induction on the metabolism and tissue distribution of benzo[a]pyrene.* Cancer Res. 30:2898-2904.

Thakker, D.R., Yagi, H., Levin, W., Wood, A.H., Conney, A.H. and Jerina, D.M. (1985) *Polycyclic aromatic hydrocarbons: Metabolic activation of ultimate carcinogens.* In Anders, M.W., ed. Bioactivation of Foreign Compounds. Academic Press, New York, pps. 178-242.

Waters, M.D., Stack, H.F., Brady, A.L., Lohman, P.H., Haroun, L. and Vainio, H. (1987) Use of computerized data listings and activity profiles of genetic and related effects in the review of 195 compounds. Genetic Toxicology Division, Health Effects Research Laboratory, EPA, Reasearch Triangle Park, N.C.

Wynder, E.L. and Hoffmann, D. (1959) *A study of tobacco carcinogenesis. VII. The role of higher polycyclic hydrocarbons.* Cancer 12:1079-1086.

ACENAPHTHYLENE

GENERAL BACKGROUND INFORMATION

Acenaphthylene is a member of the polycyclic aromatic hydrocarbons (PAH). PAHs are a class of non-polar compounds that contain two or more aromatic rings. They are ubiquitous in nature and are both naturally occurring and man-made. The data on acenaphthylene are limited.

PHARMACOKINETICS

No data were found regarding the pharmacokinetics of acenaphthylene.

HUMAN TOXICOLOGICAL PROFILE

No data were found regarding the human toxicity of acenaphthylene.

MAMMALIAN TOXICOLOGICAL PROFILE

No data were found regarding the mammalian toxicity of acenaphthylene.

GENOTOXICITY

Data from a single mutagenicity assay using acenaphthylene were positive (U.S. EPA, 1982).

REFERENCES

U.S. Environmental Protection Agency (U.S. EPA) (1982) An exposure and risk assessment for polynuclear aromatic hydrocarbons (acenaphthylene). U.S. EPA Contract 68-01-6017. Office of Water Regulations and Standards. Washington, D.C.

THIS PAGE HAS BEEN INTENTIONALLY LEFT BLANK

ANTHRACENE

GENERAL BACKGROUND INFORMATION

Anthracene is a polycyclic aromatic hydrocarbon (PAH). PAHs are a class of compounds which are non-polar and contain two or more aromatic rings. They are ubiquitous in nature and are both naturally occurring and man-made. As a PAH, anthracene is found in tobacco smoke, certain foods, and the emissions from industrial or natural burning.

PHARMACOKINETICS

Little data were found regarding the pharmacokinetics of anthracene. The intestinal absorption of anthracene is less dependent on the presence of bile in the stomach than is the absorption of larger PAHs such as benzo(a)pyrene (Rahman et al, 1986).

HUMAN TOXICOLOGICAL PROFILE

Anthracene is a skin irritant and allergen (Sax, 1984). Humans exposed to anthracene in an occupational setting may demonstrate skin disorders (Clement, 1985). Anthracene has been associated with gastrointestinal tract toxicity in humans (Badiali et al, 1985). However, the usefulness of this study is limited due to confounding factors. Hematopoietic toxicity has also been observed in cancer patients who have been treated with anthracene-containing chemotherapeutics (Falkson et al, 1985). No control groups and concomitant exposure to other ingredients in the therapeutic agents prevents any definitive conclusions.

MAMMALIAN TOXICOLOGICAL PROFILE

A subchronic study where anthracene was administered to mice by gavage for at least 90 days found no treatment-related effects at doses up to 1000 mg/kg-day (USEPA, 1989).

The data on the carcinogenicity of anthracene are considered inadequate by EPA (IRIS, 1991).

GENOTOXICITY

Tests for DNA damage, mutation, chromosome effects and cell transformation in a variety of eukaryotic cell preparations have shown negative results. The majority of tests using anthracene in prokaryotes are negative, but positive results are reported in one or two tests (ATSDR, 1990; IRIS, 1991).

REFERENCES

Agency for Toxic Substances and Disease Registry (ATSDR) (1990) Toxicological summary for polycyclic aromatic hydrocarbons. U.S. Public Health Service.

Badiali, D. et al. (1985) *Melanosis of the rectum in patients with constant constipation.* Dis Colon Rectum 28:241-245.

Clement (1985) Chemical, physical and biological properties of compounds present at hazardous waste sites.

Falkson, G. Klein, B., Falkson, H. (1985) *Hematological toxicity: experience with antracyclines adn anthracenes.* Exp. Hematol 13:64-71.

Integrated Risk Information System (IRIS) (1991) U.S. Environmental Protection Agency

International Agency for Research on Cancer (IARC) (1983) *Monograph on the evaluation of carcinogenic risk of chemicals to man, anthracene.* 32:433-440.

Sax, N.I. (1984) Dangerous Properties of Industrial Materials. 6th edition. Van Nostrand Reinhold Company, N.Y.

BENZO[g,h,i]PERYLENE

GENERAL BACKGROUND INFORMATION

Benzo[g,h,i]perylene is a member of the polyaromatic hydrocarbons (PAH). PAHs constitute a class of non-polar compounds that contain two or more aromatic rings. They are ubiquitous in nature and are both naturally occurring and man-made. The data regarding benzo[g,h,i]perylene are limited. As a PAH, it is found in food (charcoal broiled meats), vegetables, tobacco smoke and soot (U.S. EPA, 1980). Exposure occurs by inhalation, ingestion and by dermal contact.

PHARMACOKINETICS

No data were found regarding the pharmacokinetics of benzo[g,h,i]perylene.

HUMAN TOXICOLOGICAL PROFILE

No data were found regarding the human toxicology of benzo[g,h,i]perylene.

MAMMALIAN TOXICOLOGICAL PROFILE

No data were found regarding the mammalian toxicity of benzo[g,h,i]perylene.

GENOTOXICITY

No data were found regarding the genotoxicity of benzo[g,h,i]perylene.

REFERENCES

U.S. Environmental Protection Agency (U.S. EPA). (1980) An exposure risk assessment of polycyclic aromatic hydrocarbons (benzo(g,h,i)perylene). U.S. EPA Contract 68-01-6017. Office of Water Regulations and Standards. Washington, D.C.

THIS PAGE HAS BEEN INTENTIONALLY LEFT BLANK

FLUORENE

GENERAL BACKGROUND INFORMATION

Fluorene is a member of the polyaromatic hydrocarbons (PAH). PAHs constitute a class of non-polar compounds that contain two or more aromatic rings. They are ubiquitous in nature and are both naturally occurring and man-made. The data on fluorene are very limited. Low levels of (5 to 67 ug/kg) have been detected in smoked meats (U.S. EPA, 1982).

PHARMACOKINETICS

No data were found regarding the pharmacokinetics of fluorene.

HUMAN TOXICOLOGICAL PROFILE

The database for the toxicological effects of fluoranthene on humans, separate from other PAHs, is limited. Toxic effects attributable to mixtures of PAHs include a variety of skin lesions and non-cancer lung diseases such as bronchitis (IARC, 1973).

MAMMALIAN TOXICOLOGICAL PROFILE

Limited information is available on the threshold effects of fluorene. An EPA study (EPA,1989) indicated that CD-1 mice exposed by gavage to up to 500 mg/kg-day of fluorene showed hypoactivity as well as a decrease in red blood cell count and packed cell volume and hemoglobin. Increases in absolute and relative liver, spleen and kidney weights was also observed. Gershbein (1975) reported that partially hepatectomized rats fed a diet of 180 mg/kg-day of fluorene for 10 days showed a statistically significant increase in liver regeneration, which is indicative of the ability to induce a proliferative response.

Fluorene is not reported to be a complete skin carcinogen (ATSDR, 1990). It was inactive as a tumor initiator when an estimated total dose of 1.0 mg was applied prior to the application of tetradecanoyl phorbol acetate (LaVoie et al, 1980).

GENOTOXICITY

There is no evidence that fluorene is genotoxic, but genotoxicity has been studied only in a few in vitro assays (ATSDR, 1990).

REFERENCES

Agency for Toxic Substances and Disease Registry (ATSDR) (1990) Toxicological profile for polycyclic aromatic hydrocarbons. U. S. Public Health Service.

Gershbein, L.L. (1975) *Liver regeneration as influenced by the structure of aromatic and heterocyclic compounds.* Res Commun Chem Pathol Pharmacol 11:445-466.

International Agency for Research on Cancer (IARC) (1983) *Monograph on the evaluation of carcinogenic risk of chemicals to man, fluorene.* 32: 419-430.

LaVoie, E.J. (1980) *Identification of mutagenic hydrodiols as metabolites of benzo(j)fluoranthene and benzo(k)fluoranthene.* Cancer Research 40:4528-4532.

U.S. Environmental Protection Agency (U.S. EPA) (1982) An exposure and risk assessment of polycyclic aromatic hydrocarbons (fluorene). U.S. EPA Contract 68-01-6017. Office of Water Regulations and Standards, Washington, D.C.

U.S. Environmental Protection Agency (EPA) (1989) Mouse oral subchronic toxicity study. Prepared by Toxicity Research Laboratories, Ltd. Muskegon, MI for the Office of Solid Waste, Washington, D.C.

PHENANTHRENE

GENERAL BACKGROUND INFORMATION

Phenanthrene is a member of the polyaromatic hydrocarbons (PAH). PAHs constitute a class of non-polar compounds that contain two or more aromatic rings. They are ubiquitous in nature and are both naturally occurring and man-made. The database on the potential health effects of phenanthrene is limited.

PHARMACOKINETICS

Little data are available regarding the pharmacokinetics of phenanthrene. The intestinal absorption of phenanthrene is less dependent on the presence of bile in the stomach than is the absorption of the larger PAHs (such as benzo(a)pyrene) (Rahman et al, 1986).

HUMAN TOXICOLOGICAL PROFILE

Phenanthrene has been shown to be a skin photosensitizer in humans (Sax, 1984).

MAMMALIAN TOXICOLOGICAL PROFILE

Phenanthrene has a reported LD 50 of 700 mg/kg in mice (Simmon et al., 1979). Rats injected intraperitoneally evidenced liver effects (Yoshikawa et al, 1987).

There is equivocal evidence for cancer from dermal application of phenanthrene in rats (IARC, 1983). Phenanthrene is not a complete skin carcinogen (ATSDR, 1990). It is neither an initiator (LaVoie et al, 1981; Roe, 1962) nor a promoter (Roe and Grant, 1964). Higgins and Yang (1962) reported no tumor production within two months after the ingestion of 200 mg of phenanthrene by rats.

GENOTOXICITY

There are limited data that suggest that phenanthrene is mutagenic (Wood et al., 1979). However, the majority of tests are negative (ATSDR, 1990).

REFERENCES

Agency for Toxic Substances and Disease Registry (ATSDR) (1990) Toxicological profile for polycyclic aromatic hydrocarbons. U. S. Public Health Service.

Higgins, L. and Yang, Y. (1962) *Induction and extinction of mammary cancer.* Science 137:257-262.

International Agency for Research on Cancer (IARC) (1983) *Monograph on the evaluation of carcinogenic risk of chemicals to man, Phenanthrene.* 32:419-430.

LaVoie, K. et al. (1981) *Mutagenicity and tumor initiating activity and metabolism of phenanthrenes.* Cancer Res. 41:3441-3447.

Rahman, A., Barrowman, J.A., Rahimtula, A. (1986) *The influence of bile on the bioavailability of polynuclear aromatic hydrocarbons from the rat intestine.* Can J Physio Pharmacol 64:1214-1218.

Roe, F.J.C. (1962) *Effect of phenanthrene on tumour-initiation by 3,4-benzpyrene.* Br J Cancer 16:503-506.

Sax, N.I. (1984) Dangerous Properties of Industrial Materials. 6th edition. Van Nostrand Reinhold Company. N.Y.

Simmon, P. et al. (1979) *Mutagenic activity of chemicals carcinogens and related compounds in the intraperitoneal host-mediated assay.* J. Natl. Cancer Inst. 62:911-918.

Wood, R. et al. (1979) *Mutagenicity and tumorigenicity of phenanthrene and chrysene epoxides and diol epoxides.* Cancer Res. 39:4069-4077.

Yoshikawa, T. et al. (1987) *Toxicity of polycyclic aromatic hydrocarbons III. Effects of beta-naphtoflavone pretreatment on hepatotoxicity of compounds produced in the ozonation or NO2-nitration of phenanthrene and pyrene by rats.* Veterm Human Toxicol. 29:113-117.

DIBENZO[a,h]ANTHRACENE

GENERAL BACKGROUND INFORMATION

Dibenzo[a,h]anthracene is a member of the polycyclic aromatic hydrocarbons (PAH). PAHs are a class of compounds which are non-polar and contain two or more aromatic rings. They are ubiquitous in nature and are both naturally occurring and man-made. The data regarding dibenzo[a,h]anthracene are very limited. As a PAH, it is found in tobacco smoke, food, and the emissions from industrial or natural burning.

PHARMACOKINETICS

Dibenzo[a,h]anthracene is metabolized similarly to benzo(a)pyrene (ATSDR, 1990). However, while the metabolic profiles of these two compounds (and other alternant PAHs) are qualitatively similar, there are differences in the levels and rates of formation of specific metabolites among tissues and cell preparations used. Sanders et al (1986) applied ^{14}C - dibenzo[a,h]anthracene to the shaved backs of mice. After 24 hours, the majority of activity was recovered from the application site, with the remainder from body tissues and excreta. In comparison, benzo(a)pyrene similarly applied was found predominantly in the excreta and body tissues, with the remainder at the application site.

HUMAN TOXICOLOGICAL PROFILE

The database for the toxicological effects of dibenzo[a,h]anthracene on humans, separate from other PAHs, is limited. Toxic effects attributable to mixtures of PAHs include a variety of skin lesions and non-cancer lung diseases such as bronchitis (IARC, 1973).

MAMMALIAN TOXICOLOGICAL PROFILE

Dibenzo[a,h]anthracene has been shown to induce skin tumors in lab animals (i.e. it is a complete carcinogen) following dermal exposure (Wyndner and Hoffman, 1959; Van Duuren et al, 1967; and Lijinsky et al, 1965). Dibenzo[a,h]anthracene ahs also demonstrated tumor initiation activity (Slaga et al. 1980).

Carcinogenic PAHs as a group has immunosupprssive effects, with the degree of immunosuppression correlated with carcinogenic potency (ATSDR, 1990). Dibenzo[a,h]anthracene was also tested for developmental effects via parenteral routes and was found to produce fetolethal effects in rats (Wolfe and Bryan, 1939).

GENOTOXICITY

Dibenzo[a,h]anthracene is mutagenic (Barfknecht et al, 1982; Rocchi et al, 1980) and produces DNA damage (Martin et al, 1978) in cultured human cells. Test results in nonhuman systems were also positve (ATSDR, 1990).

REFERENCES

Agency for Toxic Substances and Disease Registry (ATSDR) (1990) Toxicological profile for polycyclic aromatic hydrocarbons. U. S. Public Health Service.

Barfknecht, T.R. et al. (1982) *Human cell mutagenicity of polycyclic aromatic hydrocarbons components of diesel emissions*. Dev. Toxicol. Environ. Sci. 10:277-294.

Lijinsky, W.H., Garcia, B., Terracini, B. (1965) *Tumorigenic activity of hydrogenated derivatives of dibenz(ah)anthracene*. JNCI 34:1.

Martin, C.N., McDermid, A.C., Garner, R.C. (1978) *Testing of known carcinogens and noncarcinogens for their ability to induce unscheduled DNA synthesis in HeLA cells*. Cancer res. 38:2621-2627.

Rocchi, P. et al. (1980) *Polycyclic hydrocarbons induction of diptheria toxin-resistant mutants in human cells*. Carcinogenesis 1:765-767.

Sanders, C.L., Skinner, C., Gelman, R.A. (1986) *Percutaneous absorption of 7,10 ^{14}C-benzo(a)pyrene and 7,12 ^{14}C-dimethylbenz(a)anthracene in mice*. J. Environmental Pathol Toxicol Oncol 7:25-34.

Slaga, T.J., Gleason, G.L., Well, G. (1980) *Comparison of skin tumor-initiatin activities in dihydrodiols and dio-epoxide of various polycyclic aromatic hydrocarbons*. Cancer Res 40:1961-1964.

U.S. Environmental Protection Agency (U.S. EPA) (1981) An exposure and risk assessment of polycyclic aromatic hydrocarbons (dibenz(a,h)anthracene). U.S. EPA Contract 68-01-6017. Office of Water Regulations and Standards, Washington, D.C.

Van Duuren, B.L., Langseth, L. Goldschmidt, B.M. (1967) *Carcinogencity of epoxides, lactones and peroxy compounds. VI. Structure and carcinogenic activity*. JNCI 39:1217-1227.

Wolfe, J.M. and Bryan, W.R. (1939) *Effects induced in pregnant rats by injection of chemically pure carcinogenic agents*. Am J Cancer 36:359-368.

Wydner, E.L. and Hoffman, D. (1959) *A study of tobacco carcinogenesis. VII. The role of higher polycyclic hydrocarbons*. Cancer 12:1079-1086.

INDENO[1,2,3-cd]PYRENE

GENERAL BACKGROUND INFORMATION

Indeno[1,2,3,-cd]pyrene is a member of the polyaromatic hydrocarbons (PAH). PAHs constitute a class of non-polar compounds that contain two or more aromatic rings. They are ubiquitous in nature and are both naturally occurring and man-made. Indeno[1,2,3-cd]pyrene is present in cigarette smoke (IARC, 1983) as well as emissions from industrial stacks.

PHARMACOKINETICS

No data were found regarding the pharmacokinetics of indeno[1,2,3-cd]pyrene. However, its metabolism should be similar to another non-alternant PAH, benzo(b)fluoranthene (ATSDR, 1990).

HUMAN TOXICOLOGICAL PROFILE

The database for the toxicological effects of indeno[1,2,3-cd]pyrene on humans, separate from other PAHs, is limited. Toxic effects attributable to mixtures of PAHs include a variety of skin lesions and non-cancer lung diseases such as bronchitis (IARC, 1973).

MAMMALIAN TOXICOLOGICAL PROFILE

Studies on laboratoyr animals have demonstrated that indeno[1,2,3-cd]pyrene can induce skin tumors (i.e. it is a complete carcinogen) following dermal exposure (ATSDR, 1990).
It has tumor initiating activity, but is not as potent as benzo(b)fluoranthene (Rice et al, 1985).

Carcinogenic PAHs as a group are immunosuppressant, with the degree of suppression correlated with the degree of potency (ATSDR, 1990)

GENOTOXICITY

In test systems using non-human cells, indeno[1,2,3-cd]pyrene was found to be genotoxic (ATSDR, 1990).

REFERENCES

Agency for Toxic Substances and Disease Registry (ATSDR) (1990) Toxicological profile for polycyclic aromatic hydrocarbons. U. S. Public Health Service.

International Agency for Research on Cancer (IARC) (1983) *Monograph on the evaluation of carcinogenic risk of chemicals to man, Indeno(1,2,3-cd)pyrene.* 32:419-430.

Rice, J.E. et al. (1985) *On the metabolism, mutagenicity and tumor-initiating activity of ideno(123cd)pyrene.* In: Cooke, M. Dennis, A.J. eds. Polynuclear aromatic hydrocarbons: metabolisms, methods and metabolism. Proceedings of the Eighth International Symposium. Columbus, Ohio: Battelle Press, 10970-1109.

PYRENE

GENERAL BACKGROUND INFORMATION

Pyrene is a member of the polyaromatic hydrocarbons (PAH). PAHs constitute a class of non-polar compounds that contain two or more aromatic rings. They are ubiquitous in nature and are both naturally occurring and man-made. As with many of the other PAHs, pyrene has been detected in charbroiled meats and shellfish (U.S. EPA, 1982). It is found in tobacco smoke, industrial stack smoke, and smoke from forest fires.

PHARMACOKINETICS

No data were found regarding the pharmacokinetics of pyrene.

HUMAN TOXICOLOGICAL PROFILE

Pyrene is reported to be a skin irritant (Sax, 1984).

MAMMALIAN TOXICOLOGICAL PROFILE

Rats given 150 mg/kg of pyrene had changes in blood chemistry, liver and kidney damage (USEPA, 1982). A 1989 EPA study (EPA, 1989) reported nephropathy and decreased kidney weights in mice exposed to 125 mg/kg-day of pyrene by gavage for 13 weeks.

Mouse skin painting assays indicate that pyrene is neither a complete skin carcinogen, nor an initiating agent (ATSDR, 1990, IRIS, 1991).

GENOTOXICITY

The majority of genotoxic tests of pyrene are negative.
Positive results have been recorded in Salmonella typhimurium mutagenicity tests and in in vitro mammalian cell systems (ATSDR, 1990).

REFERENCES

Agency for Toxic Substances and Disease Registry (ATSDR) (1990) Toxicological profile for polycyclic aromatic hydrocarbons. U. S. Public Health Service.

Sax, N.I. (1984) Dangerous Properties of Industrial Materials. 6th Edition. Van Nostrand Reinhold Company. N.Y.

U.S. Environmental Protection Agency (U.S. EPA) (1982) An exposure and risk assessment of polycyclic aromatic hydrocarbons (pyrene). USEPA Contract 68-01-6017. Office of Water Regulations and Standards, Washington, D.C.

U.S. Environmental Protection Agency (EPA) (1989) Mouse oral subchronic toxicity study of pyrene. Prepared by Toxicity Research Laboratories, Ltd. Muskegon, MI for the Office of Solid Waste, Washington, D.C.

Integrated Risk Information System (IRIS) (1991) U.S. Environmental Protection Agency.

2-METHYLNAPHTHALENE

GENERAL BACKGROUND INFORMATION

2-Methylnaphthalene is a member of the polycyclic aromatic hydrocarbons (PAH). PAHs are a class of non-polar compounds that contain two or more aromatic rings. They are ubiquitous in nature and are both naturally occurring and man-made. This compound is used in the synthesis of organic chemicals and pesticides. The database for toxicological information is very limited.

PHARMACOKINETICS

No data were found regarding the pharmacokinetics of 2-methylnaphthalene.

HUMAN TOXICOLOGICAL PROFILE

No data were found regarding the human toxicity of 2-methylnaphthalene.

MAMMALIAN TOXICOLOGICAL PROFILE

No data were found regarding the mammalian toxicology of 2-methylnaphthalene.

GENOTOXICITY

No data were found regarding the genotoxicity of 2-methylnaphthalene.

REFERENCES

Agency for Toxic Substances and Disease Registry (ATSDR) (1990) Toxicity profile for naphthalene and 2-methylnaphthalene. U.S. Public Health Service.

THIS PAGE HAS BEEN LEFT INTENTIONALLY BLANK

Polychlorinated Biphenyls (PCBs)

POLYCHLORINATED BIPHENYLS (PCBs)

GENERAL BACKGROUND INFORMATION

The thermal stability, nonflammability, and dielectric capability of PCBs resulted in their use in electrical capacitors and transformers (NIOSH, 1986). The manufacturing, processing, distribution in commerce, and use of PCBs after January 1, 1978 was prohibited under Section 6(e) of the Toxic Substances Control Act. PCBs can be released to the environment during fires involving electrical equipment containing these compounds. PCBs are strongly adsorbed on solid surfaces, including glass and metal surfaces in laboratory apparatus, and onto soils, sediments, and particulates in the environment.

PHARMACOKINETICS

Gastrointestinal absorption of most PCB isomers is large. PCBs can also be absorbed by the inhalation and dermal routes but limited data are available (see section on Relative Absorption Factors). Distribution of PCBs follows a biphasic pattern. Initially, PCBs distribute to liver and muscle tissue. They are then redistributed to the fat, skin, and other fat-containing organs (ATSDR, 1989). PCBs are poorly metabolized in humans with major metabolites being 3- or 4-hydroxy compounds. Metabolism may proceed through formation of arene oxide intermediates (U.S. EPA, 1988). The slow metabolism of PCB congeners to more polar compounds is responsible for long biological half-lives of PCBs. Excretion occurs primarily through the feces (Goto et al., 1974).

HUMAN TOXICOLOGICAL PROFILE

Dermatologic signs are the most persistent indicator of PCB toxicity. Skin manifestations have been observed also in newborn infants of mothers exposed to high levels of PCBs and related compounds. Cases of severe chloracne were reported in a work environment in which PCB air levels were found to be between 5.2 and 6.8 mg/m^3. The workers developing chloracne had been exposed for 2 to 4 years. Other analyses revealed worker complaints of dry sore throat, skin rash, gastrointestinal disturbances, eye irritation, and headache at work area concentrations of 0.013 to 0.15 mg PCB/m^3. Higher blood PCB levels are associated with higher serum triglyceride and/or cholesterol levels, as well as high blood pressure. Air PCB concentrations as low as 0.1 mg/m^3 can produce toxic effects, and exposure to levels producing no overt toxicity can affect liver function. Recovery after termination of exposure occurs but is slow and depends upon the amount of PCBs stored in adipose tissue (Clayton and Clayton, 1981). Human exposures to PCBs resulting in toxic effects have almost all resulted from the ingestion of rice oil contaminated with "Kanechlor 400" in Japan (resulting in Yusho or rice oil disease) or from industrial exposure. Clinical symptoms of poisoning

included acne-like skin eruptions (chloracne), eyelid edema, conjunctival discharge, skin and nail pigmentation, and hyperkeratosis. Yusho patients are estimated to have ingested approximately 0.07 mg/kg/day for at least 50 days. The rice oil was found to be contaminated with polychlorinated dibenzofuran, which is believed to have played a significant role in the observed toxicity (Bandiera et al., 1984; Kashimoto et al., 1981). As suggested by laboratory experiments with Rhesus monkeys, fetal and newborn primates, including humans, may be particularly susceptible to PCBs. Fein et al. (1984) studied the effects of low-level chronic exposure to PCBs in pregnant women and their newborn offspring from consumption of Lake Michigan fish. Low levels of PCBs were reported to cause decreases in birth weight, head circumference, and gestational age of the newborn. PCBs were apparently transmitted to the fetus across the placenta and to the newborn through breast milk. Behavioral deficiencies, including immaturity of reflexes and depressed responsiveness, were reportedly observed in infants exposed to PCBs. Jacobson et al. (1984) correlated maternal consumption of PCB-contaminated fish with behavioral abnormalities in newborns, including autonomic immaturity and depressed responsiveness. The authors likened these responses to similar effects in laboratory animals.

MAMMALIAN TOXICOLOGICAL PROFILE

PCBs are only slightly toxic in acute exposures to laboratory animals. LD_{50} values for rats, rabbits, and mice are generally in the range of 1 to 10 g/kg body weight (U.S. EPA, 1980). Nonhuman primates seem to be particularly sensitive to PCB-induced reproductive effects (U.S. EPA, 1980). Dietary exposures of cynomolgus and Rhesus monkeys to 200 ug of Aroclor 1254/kg-day, 5 days per week for 28 months, resulted in symptoms of enlarged tarsal glands, conjunctivitis, loss of eyelashes, progressive detachment of fingernails, exuberant nail beds, hyperplasia of biliary ducts, hepatocellular enlargement and necrosis, and normocytic anemia (Tryphonos et al., 1986a; Tryphonos et al., 1986b). Effects were less pronounced in cynomolgus monkeys.

Monkeys that were fed diets containing 1.0 ppm of Aroclor 1016 for approximately 7 months prior to mating and during pregnancy delivered infants with reduced birth weights (Barsotti and Van Miller, 1984). Fetal mortality occurred at >2.5 ppm (0.1 mg/kg/day) of Aroclor 1248 in the diet in other studies with monkeys (Allen and Barsotti, 1976; Barsotti et al., 1976; Allen et al., 1980). In rats, a dose of 269 ppm of Aroclor 1254 given continuously in the food over the duration of pregnancy caused a decrease in the number of impregnated rats that delivered litters. Pups that were born were underweight, and most died within 7 days of birth. Two lower doses (26 and 2.5 ppm) caused altered neurobehavioral and somatic ontogeny (Overmann et al., 1987). PCBs have been shown to be teratogenic in mice. Cleft palate, dilated kidney pelvis, and thymus hypoplasia were observed. The ED50 (effective dose for 50% of the animals) for formation of cleft palate was a single 100 mg/kg dose, with peak sensitivity occurring on the twelfth day of gestation (d'Argy et al., 1987).

Immunological effects (decreased IgM, IgG induction) were noted in monkeys following a 27 month exposure at a dose of 0.005 mg/kg/day (Tryphonos et al., 1989).

GENOTOXICITY

Most genotoxicity assays of PCBs have been negative. The majority of microbial assays of PCB mixtures and various congeners show no evidence of mutagenic effects (U.S. EPA, 1980). The carcinogenic effects of PCBs have been studied in rats and mice. In a study conducted by Kimbrough et al. (1975) rats were exposed via the diet to 100 ppm Aroclor 1260 for 21 months. Hepatocellular carcinomas were observed in 26 of the 184 treated rats but only in one of the 173 controls. Neoplastic nodules were not found in controls but occurred in 144/184 of treated rats. The National Cancer Institute (NCI, 1978) reported a high incidence of hepatocellular proliferative lesions in male and female Fischer 344 rats fed three dose levels of Aroclor 1254 for 104-105 weeks, but, in part due to the small number of animals tested, carcinogenicity was not statistically demonstrable. Norback and Weltman (1985) fed a diet containing relatively high concentrations Aroclor 1260 (100 ppm for 16 months followed by 50 ppm for an additional 8 months) to Sprague-Dawley rats. In the PCB-exposed group, neoplastic nodules were observed at 12 months followed by trabecular carcinoma at 15 months and adenocarcinoma at 24 months (52/93). In the control rats, the incidence of hepatocellular neoplasms was low (1/81). Metastases to distant organs was not observed and mortality in the PCB exposed animals was not increased. The incidence of these slow-growing hepatocellular neoplasms was strikingly higher in female rats than in male rats.

PCBs (Clophen C) have also been shown to be cocarcinogenic. When PCBs were mixed with diethylnitrosamine (DENA), twice as many tumors were observed as were observed in animals treated with DENA alone (Brunn, 1987).

Based on the positive evidence for carcinogenicity of Aroclor 1254, Aroclor 1260, Kaneclor 500, and Clophen A-30 and A-60 in animals, along with adequate evidence in humans, the U.S. EPA has placed these PCBs in categroy B2 - probable human carcinogen (U.S. EPA, 1988).

REFERENCES

Agency for Toxic Substances and Disease Registry (ATSDR) (1989) Toxicological profile for selected PCBs. U.S. Public Health Service.

Allen, J.R., Barsotti, D.A. and Carstens, L.A. (1980) *Residual effects of polychlorinated biphenyls on adult nonhuman primates and their offspring.* J. Toxicol. Environ. Health 6:55-66.

Allen, J.R. and Barsotti, D.A. (1976) *The effects of transplacental and mammary movement of the PCBs on infant rhesus monkeys.* Toxicology 6:331.

Bandiera, S., Farrell, K., Mason, G., Kelley, M., Romkes. M., Bannister, R. and Safe, S. (1984) *Comparative toxicities of the polychlorinated dibenzofuran (PCDG) and biphenyl (PCB) mixtures which persist in Yusho victims.* Chemosphere 13:507-512.

Barsotti, D.A., Marlar, R.J. and Allen, J.R. (1976) *Reproduction dysfunction in Rhesus monkeys exposed to low levels of polychlorinated biphenyls (Aroclor 1248).* Food Cosmet. Toxicol. 14:99.

Barsotti, D.A. and Van Miller, J.P. (1984) *Accumulation of a commercial polychlorinated biphenyl mixture (Aroclor 1016) in adult rhesus monkeys and their nursing infants.* Toxicology 30:31-44.

Brunn, H., Schmidt, E., Reinecher, M., Manz, D. and Eigenbrodt, E. (1987) *Histology and histochemistry of the liver of chickens after DENA-induced hepatocarcinogenesis and ingestion of low chlorinated biphenyls.* Arch. Toxicol. 60:337-342.

Clayton, F.D. and Clayton, F.E. (eds.). (1981) Patty's Industrial Hygiene and Toxicology. Volume 2B, Toxicology, Third Revised Edition. John Wiley and Sons, New York, NY. pp. 3845-3869.

d'Argy, R., Dencker, L., Klasson-Wehler, E., Bergman, A. Darnerud, P.O. and Brandt, I. (1987) *3,3',4,4'-Tetrachlorobiphenyl in pregnant mice: Embryotoxicity, teratogenicity, and toxic effects on the cultured embryonic thymus.* Pharmacol. Toxicol. 61:53-57.

Fein, G., Jacobson, J.L., Jacobson, S.W. and Schwarz, P. (1984) Intrauterine exposure of humans to PCBs (Polychlorinated Biphenyls): Newborn effects. EPA-600/3-84-060.

Goto, M., Sugiura, K., Hattori, M., Miyagawa, T. and Okamura, M. (1974) *Metabolism of 2,3-dichlorobiphenyl-^{14}C and 2,4,6-trichlorobiphenyl-^{14}C in the rat.* Chemosphere 5:227-232.

Jacobson, J.L., Schwartz, P.M., Fein, G.G. and Dowler, J.K. (1984) *Prenatal exposure to an environmental toxin; A test of the multiple effects model.* Dev. Psychol. 20:523-532.

International Agency for Research on Cancer (IARC) (1982) Monographs on the evaluation of the carcinogenic risk of chemicals to humans. Polychlorinated biphenyls and polybrominated biphenyls. Vol 18. Lyon, France.

Kashimoto, T., Tung, T-C., and Ohi, G. (1981) *Role of polychlorinated dibenzofuran in Yusho (PCB poisoning).* Arch. Environ. Health 36:321-326.

Kimbrough, R.D., Squire, R.A., Linder, R.E., Strandburg, J.D., Montali, R.D. and Burse, V.W. (1975) Prepared by PCB Risk Assessment Work Force. In Appendix A, U.S. EPA, 1981. Draft Environmental Impact Statement for the Hudson River PCB Demonstration Reclamation Project.

National Cancer Institute (NCI) (1978) Bioassay of Aroclor 1254 for Possible Carcinogenicity.

National Institute for Occupational Safety and Health (NIOSH) (1986) *Polychlorinated biphenyls (PCBs): Potential health hazards from electrical equipment fires or failures. Current Intelligence Bulletin 45.*

Norback, D.H. and Weltman, R.H. (1985) *Polychlorinated biphenyl induction of hepatocellular carcinoma in the Sprague-Dawley rat.* Environ. Health Perspect. 60:97-105.

Overmann, S.R., Kostas, J., Wilson, L.R., Shain, W. and Bush, B. (1987) *Neurobehavioral and somatic effects of perinatal PCB exposure in rats*. Environ. Res. 44:56-70.

Tryphonos, L., Charbonneau, S., Tryphonas, H., Zawidzka, Z., Mes, J., Wong, M. and Arnold, D.L. (1986a) *Comparative aspects of Aroclor 1254 toxicity in adult cynomolgus and Rhesus monkeys: A pilot study*. Arch. Environ. Contam. Toxicol. 15:159-169.

Tryphonos, L., Arnold, D.L., Zawidzka, Z., Mes, J., Charbonneau, S. and Wong, J. (1986b) *A pilot study on adult Rhesus monkeys (M. mulatta) treated with Aroclor 1254 for two years*. Toxicol. Pathol. 14:1-10.

Tryphonos, L., et al. (1989) *Immunotoxicity Studies of PCB (Arochlor 1254) in the Adult Rhesus (Macca mulatta) Monkey – Preliminary Report*. Int. J. Immunopharmacol. 11:199-206.

U.S. Environmental Protection Agency (U.S. EPA) (1980) Ambient water quality criteria for polychlorinated biphenyls. EPA-440/5-80-068. Office of Water Regulations and Standards, Washington, DC.

U.S. Environmental Protection Agency (U.S. EPA) (1988) Drinking water criteria document for polychlorinated biphenyls (PCBs). EACO-CIN-414.

THIS PAGE HAS BEEN INTENTIONALLY LEFT BLANK

Metals

ARSENIC

GENERAL BACKGROUND INFORMATION

The toxicity of arsenic depends upon its chemical form along with the route, dose, and duration of exposure. In general, arsenites (As^{+3}) are potentially more toxic than arsenates, soluble arsenic compounds are potentially more toxic than insoluble compounds, and inorganic arsenic compounds are potentially more toxic than organic derivatives (U.S. EPA, 1985).

PHARMACOKINETICS

Absorption from the gastrointestinal tract is dependent upon the solubility of the specific arsenic compound and the dose. Absorption from the respiratory tract is also dependent upon the specific arsenic compound, along with particle size (see section on Relative Absorption Factors).

HUMAN TOXICOLOGICAL PROFILE

Depending upon dose and exposure route, arsenic is an irritant of the skin, mucous membranes, and the gastrointestinal tract. Acute toxicity from the ingestion of higher doses of arsenic may result in vomiting, diarrhea, convulsions, a severe drop in blood pressure, and cardiovascular effects. The lethal dose for humans is reported to be 1.0 to 2.6 mg/kg-bw (Vallee et al., 1960). Acute toxicity from inhalation exposure to arsenic adsorbed to particulate matter may result in conjunctivitis and pharyngitis. Subchronic effects included hyperpigmentation (melanosis), multiple arsenical keratoses, sensory-motor polyneuropathy, persistent chronic headache, lethargy, gastroenteritis, and mild iron deficiency anemia. Inhaled arsenic compounds have been reported to be associated with skin lesions, cardiovascular and respiratory effects, and peripheral neuropathy (Stokinger, 1981; IARC, 1980). Chronic oral exposure of humans to inorganic arsenic compounds has been reported to cause skin lesions, peripheral vascular disease, and peripheral neuropathy (Silver and Wainman, 1952). The incidence of blackfoot disease, a peripheral circulatory disease characterized by gangrene of the extremities, has reportedly been related to the presence of arsenic in the drinking water of residents of the southwest of Taiwan (Tseng, 1977). The symptoms of chronic inhalation exposure to arsenic compounds are similar to those associated with chronic oral toxicity.

MAMMALIAN TOXICOLOGICAL PROFILE

Oral LD_{50} values for trivalent arsenic vary from 15 to 293 mg/kg in rats and from 10-150 mg/kg in other test species (U.S. EPA, 1984). Chronic toxicity data from arsenic exposure to rats cannot be extrapolated to man as the rat is able to store this compound bound to hemoglobin in red blood cells (Lanz et al., 1950). This binding results in extremely slow excretion by rats compared to other species (Mealey et al., 1959). For this reason, dogs have been used to obtain experimental toxicity information. Studies of the subchronic oral toxicity of diets containing sodium arsenite or sodium arsenate in dogs report that arsenite is potentially more toxic than arsenate. The NOEL (no observed effect level) was reported to be 50 mg/kg-diet for both substances (Byron et al., 1967). Schroeder and Balassa (1967) studied the chronic oral toxicity of arsenic on growth and survival in mice. Ingestion of water containing As^{+3} at 5 mg/L over two years is reported to have resulted in decreased survival and reduced median life span in male and female mice. No information regarding chronic inhalation exposure of experimental animals to arsenic could be located in the available literature. Animal studies to test the teratogenic potential of arsenic have been performed. Matsumoto et al. (1973) reported decreased fetal weight in oral doses of up to 40 mg-arsenate/kg-bw/day administered to pregnant mice for three consecutive days. Diets containing up to 100 mg-arsenite/kg-diet, however, were reported to have had no effect on offspring (Kojima, 1974). No data regarding the teratogenicity of inhaled arsenic could be found in the literature.

GENOTOXICITY

Nearly all results of gene mutation studies for arsenic (III) and arsenic (V) compounds have been negative. Arsenite and arsenate also have been inactive in gene-specific mutation assays in yeast and in cultured mammalian cells. In contrast, arsenic (III), arsenic (V), arsenite and arsenate have been found to result in chromosome aberrations and sister chromatid exchanges in cultured animal and human cells tested in vitro (ATSDR, 1987). There is limited evidence that occupational exposure to arsenic may cause chromosome changes in humans (Beckman et al., 1977). Beckman et al. (1977) reported an increase in gaps, chromatid aberrations and chromosome aberrations from mine workers at a smelter in northern Sweden.

The majority of tests in which experimental animals were exposed orally to a variety of arsenic compounds produced negative results regarding carcinogenicity (Hueper and Payne, 1962; Byron et al., 1967). A few studies have, however, reported tumorigenic effects of arsenic treatment (Schrauzer et al., 1978). Mixed results were reported in arsenic inhalation studies (Ishinishi et al., 1977; Ivankovic et al., 1979). Epidemiological studies conducted in the U.S. have failed to correlate the incidence of skin cancer with arsenic in drinking water (Morton et al., 1976; Goldsmith et al., 1972). A dose-response relationship between the

occurrence of skin cancer and arsenic consumption in the drinking water of Taiwanese, however, was reported by Tseng et al. (1977). Arsenic exposure at certain doses may produce a pattern of skin disorders, hyperpigmentation, and keratosis that may develop into basal or squamous cell carcinoma (U.S. EPA, 1985). Several epidemiological studies of workers occupationally exposed to arsenic have reported a correlation between this exposure and mortality due to respiratory cancer (Higgins et al., 1982; Enterline and Marsh, 1982; Brown and Chu, 1983). Based upon epidemiological data, the EPA has classified arsenic as Group A -Human Carcinogen.

REFERENCES

Agency for Toxic Substances and Disease Registry (ATSDR) (1987) Toxicological profile for arsenic. U.S. Public Health Service.

Beckman, G. et al., (1977) *Chromosome aberrations in workers exposed to arsenic.* Environ. Health Perspect. 19:145.

Brown, C.C. and Chu, K.C. (1983). *Implications of the multistage theory of carcinogenesis applied to occupational arsenic exposure.* J. Natl. Cancer Inst. 70:455-463.

Byron, W.R., Bierbower, G.W., Brouwer, J.B. and Hansen, W.H. (1967) *Pathological changes in rats and dogs from two-year feeding of sodium arsenite or sodium arsenate.* Toxicol. Appl. Pharmacol. 10:132-147.

Enterline, P.E. and Marsh, G.M. (1982) *Mortality among workers exposed to arsenic and other substances in a copper smelter.* Am. J. Epidemiol. 116:895-910.

Goldsmith, J.R. et al. (1972) *Evaluation of health implications of elevated arsenic in well water.* Water Res. 6:1133-1136.

Higgins, I., Welch, K. and Burchfiel, C. (1982) Mortality of Anaconda smelter workers in relation to arsenic and other exposures. Dept. of Epidemiology, Univ. of Michigan, Ann Arbor, MI.

Hueper, W.C. and Payne, W.W. (1962) *Experimental studies in metal carcinogenesis. Chromium, nickel, iron, arsenic.* Arch. Environ. Health 5:445.

IARC (International Agency for Research on Cancer). (1980) Arsenic and arsenic compounds. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans. WHO, Lyon, France. 23:39-142.

Ishinishi, N., et al. (1977). *Preliminary experimental study on carcinogenicity of arsenic trioxide in rat lung.* Environ. Health Perspect. 19:191-196.

Ivankovic, S., Eisenbrand, G. and Preesman, R. (1979) *Lung carcinoma induction in BD rats after single intratracheal instillation of an arsenic containing pesticide mixture formerly used in vineyards.* Int. J. Cancer 24:786-788.

Kojima, H. (1974) *Studies on developmental pharmacology of arsenite. II. Effect of arsenite on pregnancy, nutrition, and hard tissue.* Fol. Pharmacol. Japon. 70:149-163.

Lantz, H., Wallace, P.W. and Hamilton, J.G. (1950) *The metabolism of arsenic in laboratory animals using* As^{74} *as trace.* Univ. Calif. Pub. Pharmacol. 2:263-282.

Mealey, J., Bronwell, G.L. and Sweet, W.H. (1959) *Radioarsenic in plasma, urine, normal tissues, and intracranial neoplasms.* Arch. Neurol. Psychiatry 81:310-320.

Morton, W., Starr, G., Pohl, D., Stoner, J., Wagner, S. and Weswig, P. (1976) *Skin cancer and water arsenic in Lane County, Oregon.* Cancer 37:2523-2532.

Schrauzer, G.N., White, J.E., McGinness, J.E., Schneider, C.J. and Bell, L.J. (1978) *Arsenic and cancer: Effects of joint administration of arsenite and selenite on the genesis of mammary adenocarcinoma in inbred female C3H/ST mice.* Bioorg. Khim. 9:245-253.

Schroeder, H.A. and Balassa, J.J. (1967) *Arsenic, germanium, tin, and vanadium in mice: Effects on growth, survival and tissue levels.* J. Nutr. 92:245-252.

Silver, A.S. and Wainman, P.L. (1952) *Chronic arsenic poisoning following use of an asthma remedy.* JAMA 150:584.

Stokinger, H.E. (1981) The Metals: Arsenic. In: Patty's Industrial Hygiene and Toxicology, Vol. II, 3rd ed., G.D. Clayton and F.E. Clayton, Ed.; John Wiley and Sons, Inc., NY. pp. 1517-1531.

Tseng, W.P. (1977) *Effects and dose-response relationships of skin cancer and Blackfoot Disease with arsenic.* Environ. Health Perspect. 19:109-119.

U.S. Environmental Protection Agency (EPA) (1985) Health advisories for 52 chemicals which have been detected in drinking water. Office of Drinking Water. NTIS PB860118338.

U.S. Environmental Protection Agency (EPA) (1984) Health effects assessment for arsenic. ECAO-HO20. Prepared for the Office of Emergency and Remedial Response by the Environmental Criteria and Assessment Office.

Vallee, B.L., Ulmer, D.D. and Wacker, W.E.C. (1960) *Arsenic toxicology and chemistry.* Arch. Ind. Health 21:132-151.

CADMIUM

GENERAL BACKGROUND INFORMATION

Cadmium typically exists in the environment as a salt of the +2 valence state or as a metal. It forms no stable organic compounds. Cadmium releases are generally associated with mining, smelting, manufacturing operations, and from the disposal of alkaline batteries containing cadmium (Doull, 1980; U.S. EPA, 1981).

PHARMACOKINETICS

Cadmium is absorbed by all routes of exposure (see section on Relative Absorption Factors). Absorption through the gastrointestinal tract is low, respiratory absorption more efficient and dermal absorption relatively insignificant (ATSDR, 1989). Absorbed cadmium is widely distributed throughout the body, with the major portion of the body burden located in liver and kidney (Sumino et al., 1975). The distribution of cadmium is linked to the distribution of metallothionein, a low-moleculer-weight protein, rich in cadmium-binding sites. Cadmium is not known to undergo any direct metabolic conversions in vivo. The principle excretory route for absorbed cadmium is urinary. Excretion is slow, accounting for the long half-life of cadmium in the body (17-38 years) (ATSDR, 1989).

HUMAN TOXICOLOGICAL PROFILE

Cadmium is a local respiratory tract irritant. Systemic symptoms occur in a few hours after an acute exposure to cadmium dust or fumes. Upper respiratory tract irritation is followed by coughing, chest pain, sweating, and chills. These symptoms resemble nonspecific upper respiratory infection (Sittig, 1985). Within 24 hours severe pulmonary irritation may develop, with progressively increasing pain in the chest, dyspnea, pulmonary edema, cough, and generalized weakness. Chronic exposure to cadmium fumes may result in emphysema-like lung damage (Sittig, 1984). Renal dysfunction may ensue (Friberg, 1950). Bernard and Lauwerys (1984) observed that the gastrointestinal tract is adversely affected by acute oral exposure with such symptoms as nausea, vomiting, salivation, abdominal pain, cramps, and diarrhea. The principal effects of chronic cadmium exposure are osteomalacia and osteoporosis (Itai Itai disease) secondary to glomerular and tubular necrosis in the kidney. The Itai Itai ("ouch-ouch") disease is endemic areas in Japan, which have been contaminated with mining wastes containing cadmium. Victims display the osteomalacia and osteoporosis as primary symptoms, as well as protein, sugar and amino acids not normally found in the urine. Other chronic effects include immunosuppression and decreases in measures of respiratory fitness (ventilation capacity, vital capacity, forced expiratory volume, etc.) (U.S. EPA, 1981).

MAMMALIAN TOXICOLOGICAL PROFILE

Several subchronic and chronic oral toxicity studies have been conducted in animals. Koller et al. (1975) and Fitzhugh and Meiller (1941) conducted feeding studies using mice and rats, respectively. The first group of researchers reported immunological impact manifested by a decrease in the number of lymphocytes secreting antibodies (to sheep red blood cells) as well as some renal effects. The second set of authors observed hematological symptoms expressed as marked anemia. Yuhas et al. (1979) conducted a drinking water study using Sprague-Dawley male rats. Decreased weight gain was observed at the highest dose level. In addition, the authors identified increases in cadmium content and decreases in the zinc content of the bone. Renal dysfunction or otherwise generalized adverse effects on the kidney have been reported in a number of long-term cadmium ingestion studies (Friberg et al., 1974; Kijikawa et al., 1981; Schroeder et al., 1964; Kanisawa and Schroder, 1969). In addition, the latter two research groups have observed renal and cardiac arteriosclerosis.

GENOTOXICITY

Results of mutagenicity tests in bacteria and yeasts have been inconclusive. Positive results have been obtained in mutation assays in Chinese hamster cells and in mouse lymphoma cells. Conflicting results have been obtained in assays of chromosomal aberrations in human lymphocytes treated in vitro or obtained from exposed workers. Cadmium treatment in vitro or in vivo appears to result in aneuploidy in germ cells of mice or hamsters (ATSDR, 1989). Reports of elevated prostate cancer in cadmium workers have been evaluated as insufficient evidence of the carcinogenic action of the compound (U.S. EPA, 1985), but the elevated risk of lung cancer observed by Thun et al. (1985) is more convincing. Thus, the carcinogenic potential of inhaled cadmium should be viewed as limited, but suggestive. Although ingestion of cadmium may result in kidney effects, no carcinogenic response has been demonstrated for this route.

REFERENCES

Agency for Toxic Substances and Disease Registry (ATSDR) (1989) Toxicological profile for cadmium. U.S. Public Health Service.

Bernard, A. and Lauwerys, R. (1984) *Cadmium in the human population*. Experimenti 40:143-152.

Doull, J., Klaasen, C.D. and Amdur, M.D. (1980) Casarett and Doull's Toxicology, 2nd ed., MacMillan Publishing Co., Inc. New York.

Fitzhugh, O.G. and Meiller, F.H. (1941) *The chronic toxicity of cadmium*. J. Pharm. Exp. Ther. 72:15.

Friberg, L. (1950) *Health hazards in the manufacture of alkaline accumulators with special reference to chronic cadmium poisoning*. Acta. Med. Scand. 138(Suppl. 240): 1-124.

Friberg, L., Piscator, M., Nordberg, G.F. and Kjellstrom, T. (1974) Cadmium in the Environment, 2nd ed., CRC Press, Boca Raton, FL.

Kanisawa, M. and Schroeder, H.A. (1969) *Life term studies on the effect of trace elements on spontaneous tumors in mice and rats*. Cancer Res. 29:892-895.

Kijikawa, K., Nakanishi, I. and Kuroda, K. (1981) *Morphological changes of the kidney and bone of rats in chronic cadmium poisoning*. Exp. Molec. Pathol. 34:9-24.

Koller, L.D., Exon, J.H. and Roan, J.G. (1975) *Antibody suppression by cadmium*. Arch. Environ. Health 30:598.

Schroeder, H.A., Balassa, J.J. and Vinton, W.H. (1964) *Chromium, lead, cadmium, nickel, and titanium in mice: Effects on mortality, tumors and tissue levels*. J. Nutr. 83:239-250.

Sittig, M. (1985) Handbook of Toxic and Hazardous Chemicals and Carcinogens. Noyes Publication; Park Ridge, NJ.

Sumino, K., Hayakawa, K., Shibata, T. and Kitamura, S. (1975) *Heavy metals in normal Japanese tissues*. Arch. Environ. Health 30:487-494.

Thun, M.J., Schnorr, T.M., Smith, A., Halperin, W.E. and Lewen, R.A. (1985) *Mortality among a cohort of U.S. cadmium production workers - an update*. J. Natl. Cancer Inst. 74:325-333.

U.S. Environmental Protection Agency (EPA) (1981) Health assessment document for cadmium. Environmental Criteria and Assessment Office. EPA-600/8-81/023.

U.S. Environmental Protection Agency (EPA) (1985) Cadmium contamination of the environment: an assessment of nationwide risk. Office of Health and Environmental Assessment. EPA-440/4-85-023.

Yuhas, E.M., Miya, T.S. and Schnell, R.C. (1979) *Dose-related alterations in growth and mineral deposition by chronic oral cadmium administration in the male rat*. Toxicology 12:19-29.

THIS PAGE HAS BEEN INTENTIONALLY LEFT BLANK

CHROMIUM

GENERAL BACKGROUND INFORMATION

Chromium is used in plating for corrosion resistance and decorative purposes (appliances, tools, automobiles, etc.), in the manufacture of alloys (including stainless steel and heat resistant alloys), and in printing, dyeing, photography, tanning, and numerous other industrial applications (ATSDR, 1989).

PHARMACOKINETICS

Absorption studies of chromium compounds indicate that it is absorbed by all routes of exposure (see section on Relative Absorption Factors) with chromium (VI) compounds being more readily absorbed than chromium (III) compounds. Once absorbed, chromium is rapidly distributed to all organs, including the developing fetus. Chromium VI is readily reduced to Cr III in vivo. Excretion occurs primarily through the kidneys via urine (ATSDR, 1989).

HUMAN TOXICOLOGICAL PROFILE

In humans, the respiratory tract is the primary system of concern for chromium toxicity. Renal damage has also been observed. Hexavalent chromium has been shown to be highly toxic, causing ulceration of nasal mucosa and carcinoma of the lung following long-term occupational exposure. Cases of acute poisoning in man have been reported from the medical use of chromic acid.

Chronic exposures of workers in chromium-related industries have been observed to result in skin and nasopharyngeal irritations. Both Cr(III) an Cr(VI) can cause allergic contact dermatitis and irritation (Samitz and Shrager, 1966). Chromium was shown to be an allergen in recurrent contact dermatitis of the feet (Correia and Brandao, 1986). Hexavalent forms are responsible for effects on the upper respiratory system, including ulceration and perforation of the nasal septum, chronic rhinitis, and pharyngitis. Lindberg and Hedenstierna (1983) reported that subjective and objective evidence of adverse nasal effects were found at exposure levels of 2 to 20 ug Cr(VI)/m^3 but not at less than 1 ug/m^3. They also reported that workers exposed to 2 to 20 ug Cr(VI)/m^3 had slight transient decreases in measures of pulmonary mechanics (e.g., forced vital capacity, FVC) with recovery (no changes) seen by two (non-exposed) days later.

MAMMALIAN TOXICOLOGICAL PROFILE

In laboratory animals, Cr compounds are of low oral acute toxicity. Hexavalent chromium is more acutely toxic than Cr(III), with kidney failure being the primary symptom. The LC_{50}

in rats for inhalation of sodium chromate(VI) was reported as 33 mg Cr/m^3/4H, and the LD_{50}'s for oral and dermal exposures were given as 16.7 mg Cr/kg and 514 mg Cr/kg, respectively (Gad et al., 1986). Chromium was found to localize in the proximal renal tubules when intraperitoneal doses of potassium dichromate were administered to rats 5 times weekly for 8 months (Berry et al., 1978). Low level hexavalent chromium exposure increases respiratory defense mechanisms while they are inhibited by long-term, high level exposure (Glaser et al., 1985). Chromium salts have been shown to be teratogenic and embryotoxic in mice and hamsters following intravenous or intraperitoneal injection. However, these are unnatural routes of administration for assessing effects of environmental exposures, and further research is needed (U.S. EPA, 1984).

GENOTOXICITY

Both Cr(III) and Cr(VI) have been shown to interact with DNA in bacterial systems. Cr(III) is generally considered to be a relatively inactive genotoxic agent since it is unable to cross cell membranes. It was recently shown, however, to cause chromosomal aberrations in human lymphocytes (Friedman et al., 1987). Hexavalent chromium has consistently caused transformations and mutations in a wide variety of in vitro assays (Bianchi and Lewis, 1985). Chromosomal damage has been observed in lymphocytes cultured from workers exposed to chromium. The epidemiologic studies of respiratory cancer in chromate production workers provide the bulk of the evidence for chromium carcinogenicity. Studies of chromate production facilities in the United States, Great Britain, and Japan have all found an association between occupational exposure to chromium and lung cancer (U.S. EPA, 1984). Workers were exposed to both Cr(VI) and Cr(III), and it is unclear whether Cr(VI) alone is the etiologic agent or whether Cr(III) is implicated as well. The U.S. EPA (1984) concluded that in rats, only calcium chromate had consistently produced lung tumors by several routes of administration, and that other Cr(VI) compounds produced local sarcomas or lung tumors in rats at the site of administration (subcutaneous, intraperitoneal, intermuscular, intrabroncheal, and intratracheal). Trivalent chromium compounds have not been found to be carcinogenic by any route of administration, but these compounds have not been studied as extensively.

REFERENCES

Agency for Toxic Substances and Disease Registry (ATSDR) (1989) Toxicological profile for chromium. U.S. Public Health Service.

Berry, J.P., Houdry, J., Galle P. and Laquie, G. (1978) *Chromium concentration by proximal renal tubule cells:an ultrastructural microanalytical and cytochemical study.* J. Histochem. Cytochem. 26:651-657.

Bianchi, B. and Lewis, A.G. (1985) *Mechanisms of chromium genotoxicity.* In: Merian, E., Fre, R.W., Hardi, W. and Schlatter, C. (eds). Carcinogenic and Mutagenic Metal Compounds : Environmental and Analytical Chemistry, and Biological Effects. Gordon and Breach Science Publishers, London.

Correia, S., and Brandao, F.M. (1986) *Contact dermatitis of the feet.* Derm. Beruf. Umwelt. 34:102-106.

Friedman, J., Shabtai, F., Levy, L.S. and Djaldetti, M. (1987) *Chromium chloride-induced chromosomal aberrations in human lymphocytes via indirect action.* Mutat. Res. 191:207-210.

Gad, S.C., Powers, W.J., Dunn, B.J., Hoffman, G.M., Siino, K.M. and Walsh, R.D. (1986) *Acute toxicity of four chromate salts.* In: Serrone, D.M., ed. Chromium Symposium 1986: An Update. Pittsburgh, PA: Industrial Health Foundation, Inc., pp. 43-56.

Glaser, U., Hochrainer, D., Kloppel, H. and Kuhnen, H. (1985) *Low-level chromium (VI) effects on alveolar macrophages and immune functions in Wistar rats.* Arch. Toxicol. 57:250-256.

Lindberg, R.G. and Hedenstierna, L. (1983) *Chrome plating: Symptoms, findings in the upper airways and effects on lung function.* Arch. Environ. Health 38:367-374.

Samitz, M.H. and Shrager, J. (1966) *Patch test reactions to hexavalent and trivalent chromium compounds.* Arch Dermatol. 94:304-306.

U.S. Environmental Protection Agency (U.S. EPA) (1984) Health assessment document for chromium. Final Report EPA-600/8-83-014F. Environ. Criteria and Assessment Office, Res.Triangle Park, N.C.

THIS PAGE HAS BEEN INTENTIONALLY LEFT BLANK

Copper

CAS No.: 7440-50-8
Synonyms: bronze powder, gold bronze

A. Physical and Chemical Properties

Chemical Formula:	Cu
Form:	Reddish, lustrous, ductile, malleable metal; face-centered cubic structure; available as ingots, sheets, wire, or powder
Chemical Class:	Metal
Atomic Weight:	63.55
Boiling Point:	2595°C
Melting Point:	1083°C
Specific Gravity:	8.94
Solubility in Water:	Most copper salts are insoluble except copper sulfate, copper nitrate and cupric chloride
Solubility in Organics:	None
Organic Carbon Partition Coefficient:	NA
Log Octanol/Water Partition Coefficient:	
Vapor Pressure:	1 mm at 1,628°C
Vapor Density:	NA
Henry's Law Constant:	NA
Bioconcentration Factor:	

B. Regulations and Standards

Safe Drinking Water Act
- Maximum Contaminant Level Goal (MCLG for Drinking Water (mg/L): 1.3
- Maximum Contaminant Level (MCL) for Drinking Water (mg/L): NA

Clean Water Act
- Ambient Water Quality Criteria (mg/L)
  - Human Health
    - Water and Fish Consumption: NA
    - Fish Consumption Only: NA
  - Aquatic Organisms (mg/L)
    - Fresh Water

Stokinger, H.E. 1981. The metals. In: Patty's Industrial Hygiene and Toxicology. Clayton, G.D., and F.E. Clayton, eds. Vol. 2A. New York: John Wiley and Sons. Pp. 1605-149.

Taylor, A., and V. Marks. 1978. Cobalt: A review. J. Hum. Nutr. 32:165-177.

Wehner, A.P., R.H. Bush, R.J. Olson, and D.K. Craig. 1977. Chronic inhalation of cobalt oxide and cigarette smoke by hamsters. Am. Ind. Hyg. Assoc. 38:338-345.