Literature Search Product

for

Biphenyl

(CAS No. 92-52-4)

In Support of Summary Information on the
Integrated Risk Information System (IRIS)
Prepared by the Oak Ridge Institute for Science and Education
Project 06-21

August 3, 2007

Search Strategy and Presentation of Results

The Statement of Work provided by EPA called for a literature search not limited by time. An initial search was conducted in PubMed using the terms biphenyl OR 92-52-4 AND toxic*, resulting in >1700 hits. Using the CASNR alone resulted in 197 hits.

A Toxline search was conducted using CASNR 92-52-4, resulting in >29,900 hits. By adding suitable limitations such as "toxic", "genotoxic", "developmental", etc., and associating the term "biphenyl" with its CASNR, the number of hits was reduced to 1755. Both PubMed and Toxline automatically search for synonyms, of which the most common is diphenyl. The combined hits from PubMed and Toxline were combined in an EndNote database, checked for duplicates, and subsequently all material showing the CASNR for biphenyl, or the word biphenyl alone as a keyword, were labeled "Selected-ORISE".

Additional searches of Biosis and Embase (in Dialog) were conducted using the terms 92-52-4 and toxic, toxico?, toxicit?, chronic, subchronic, acute, oral, inhale?, inhalation, dermal, intravenous, cancer?, carcinog?, carcinoma?, oncogene?, tumor?, neoplasm?, mutag?, mutat?, genotox?, fetotox?, embryotox?, teratology?, teratogen?, reproductive, developmental, neurotox?, immunotox?, pharmacokinetic?, pharmacodynamic?, PBPK, metabolism, epidemiol?, human study, and human studies. These searches yielded a limited number of useful hits that were added to the database.

The reference section of the 1999 CICAD for biphenyl was compared to the ORISE database on biphenyl, and another 35, mostly older, references were added. A commercial heat transfer fluid exists, known as therminol vp-1, dowtherm A, dinil, dinyl, or diphyl (CAS no. 8004-13-5), a mixture of 73.5% diphenyl ether and 26.5% biphenyl. An additional search was conducted that resulted in 40 additional references added to the database. The resulting database has 2024 entries, of which 789 contain the keyword or CASNR for biphenyl. These entries were scanned for toxicological relevance, leaving 303 hits that were given the keyword "LSP". Also included in this LSP are studies on the main metabolites of biphenyl, 2- and 4-hydroxybiphenyl.

The following Literature Search Product presents those 303 references categorized as suggested in the 2006 IRIS Toxicological Review template. General overview articles or summary documents prepared by other agencies are listed before Chapter 2. A limited number of references was listed in more than one section when they appeared applicable to either. In Chapter 3, 2 references were placed in an initial general section because they refer to more than one of the categories Uptake, Distribution, Metabolism, Excretion, or PBPK.

Yellow highlights were added to all references that the individual members of the research team consider central to this IRIS Toxicological Review. Studies of potential interest for the diphenyl ether/biphenyl mixture are shown with cyan highlights. ORISE considers this mixture as potentially relevant because, despite the comparatively low percentage of biphenyl in the mixture, the other constituent, diphenyl ether, has very low toxicity and is otherwise used as a flavoring agent (International Chemical Safety Cards). References not highlighted represent various categories: those that contain one of the CASRNs without evident relevance to the project as judged from title and/or abstract, abstracts to which a full peer-reviewed publication exists, and references that may be used as needed to extract additional information. For the time being ORISE has procured only highlighted references; other may be added upon request of the EPA Chemical Manager.

Secondary material (review articles or overviews from other agencies) applying to several or all of Chapters 2–4.

Health effects of selected chemicals. Vol. 4-5. Diphenyl Ether (Benzene, 1,1-oxybis) (1996) (1999) Nord 15:179–190.
There was no evidence that diphenyl ether is a human health hazard under ordinary conditions of manufacture, handling or use. In the use as a heat transfer agent, leaks in the heating system frequently occur resulting in exposure of workers to diphenyl ether via inhalation. The outstanding odor and taste would cause contamination to be readily detected and also excessive ingestion unlikely. Diphenyl ether has a low oral and dermal toxicity. Undiluted diphenyl ether irritates skin, but the EC-irritation criteria are not met. However, if exposure is prolonged, the irritation may be severe. Animal data on eye irritation is incomplete. The mild eye irritation has not been scored according to EC-criteria. Subacute inhalation study revealed ocular and nasal irritation. Also the eutectic mixture containing diphenyl ether caused irritation of the respiratory tract and eye. Therefore classification as Xi; R 36/37/38 is proposed. Diphenyl ether showed no mutagenic activity. Pure diphenyl ether has not been tested for reproduction toxicity. Therminol VP-1 (the eutectic mixture of diphenyl ether (73.5%) and diphenyl (26.5%) was not embryotoxic, fetotoxic or teratogenic at maternal toxicity levels. The NOEL for maternal toxicity was 50 mg/kg body weight/day

ACGIH (American Conference of Governmental Industrial Hygienists). (2001) Biphenyl. In: Documentation of the threshold limit values and biological exposure indices. 7th edition. American Conference of Governmental Industrial Hygienists, Cincinnati, OH.
A TLV-TWA of 0.2 ppm (1.3 mg/m3) is recommended for occupational exposure to biphenyl. This value is intended to minimize the potential for irritation of nasal mucosa and respiratory difficulties identified in rats and mice exposed by inhalation to biphenyl dust. Limited data from worker exposure to biphenyl indicate that transient nausea, vomiting, bronchitis occur and, more seriously, central and peripheral nerve damage occur at heavy, chronic exposures. Sufficient data were not available to recommend Skin, SEN, or carcinogenicity notations or a TLV-STEL

Ames, BN; Gold, LS. (1998) The prevention of cancer. Drug Metab Rev 30(2):201–223.
BIOSIS COPYRIGHT: BIOL ABS. RRM LITERATURE REVIEW HUMAN ONCOLOGY CARCINOGENS CANCER DIET PESTICIDES RISK ASSESSMENT NEOPLASTIC DISEASE

Ames, BN; Gold, LS. (1998) The causes and prevention of cancer: the role of environment. Biotherapy (Dordrecht) 11(2-3)–ÿ.
BIOSIS COPYRIGHT: BIOL ABS. The idea that synthetic chemicals such as DDT are major contributors to human cancer has been inspired, in part, by Rachel Carson's passionate book, Silent Spring. This chapter discusses evidence showing why this is not true. We also review research on the causes of cancer, and show why much cancer is preventable. Epidemiological evidence indicates several factors likely to have a major effect on reducing rates of cancer: reduction of smoking, increased consumption of fruits and vegetables, and control of infections. Other factors are avoidance of intense sun exposure, increases in physical activity, and reduction of alcohol consumption and possibly red meat. Already, risks of many forms of cancer can be reduced and the potential for further reductions is great. If lung cancer (which is primarily due to smoking) is excluded, cancer death rates are decreasing in the United States for all other cancers combined. Pollution appears to account for less than 1% of human cance

Anon. (1987) Programme for the prevention of harmful health effects of workplace chemicals. Summary toxicological evaluations. Berufsgenossenschaft der chemischen Industrie, Gaisbergstrasse 11, Postfach 101480, D-W-6900 Heidelberg, Germany.
This booklet presents summary toxicological evaluations of 27 chemical products. The full evaluations are published in the series Toxikologische Bewertungen. Each summary gives: name, Chemical Abstracts Service Registry Number, synonyms, formula, physical and chemical properties, results of tests on animals (acute and chronic toxicity, pharmacokinetics and metabolism, reproductive effects, mutagenicity, carcinogenicity, cutaneous effects), effects in man and exposure limits. Two of the summaries (benzotrichloride and 5-nitro-2-aminotoluene) have been updated since publication of this booklet (see CIS 91-000)

Apol, A; Thoburn, TW. (1986) Health hazard evaluation report, Boise Cascade, Vancouver, Washington. Hazard Evaluations and Technical Assistance Branch, National Institute for Occupational Safety and Health, U. S. Department of Health and Human Services, Cincinnati, Ohio; Report No. HETA-85-462-1748.
An authorized representative of the Association of Western Pulp and Paper Workers requested an investigation be made of employee exposure to diethylenetriamine (111400) (DETA), hexamethylene-diisocyanate (822060) (HDI),

and other chemicals in use during the production of carbonless paper at the Boise Cascade (SIC-2641) facility in Vancouver, Washington. This facility makes paper from pulp and carbonless paper by applying the appropriate coatings to the paper. Possible exposures to biphenyl (92524) and butyl-biphenyls, formaldehyde (50000), phenol (108952), and petroleum solvents were also investigated. Medical interviews were conducted with 65 employees. All the breathing zone and area samples for DETA in the coater preparation department were lower than detectable concentrations of 0.01 and 0.07 parts per million (ppm). Concentrations of biphenyl were less than detectable concentrations of 0.02ppm. Butyl-biphenyl concentrations were 0.12 and 0.29ppm. HDI concentrations ranged from 0.7 to 4.5 micrograms/cubic meter in the breathing zone samples for coater and assistant coater operators. DETA concentrations were less than 0.06ppm. In four cases, pulmonary problems were determined which may have been related to past diisocyanate exposure. The authors recommend that workers with asthma sensitization be medically monitored and evaluated and that contact and inhalation exposures be reduced by the use of personal protective clothing and increased ventilation

Bach, PH; Hardy, TL. (1985) Relevance of animal models to analgesic-associated renal papillary necrosis in humans. Kidney Int 28(4):605–613.

Bascom, R; Bromberg, PA; Costa, DA; et al. (1996) Health effects of outdoor air pollution. Am J Respir Crit Care Med 153(1):3–50.
BIOSIS COPYRIGHT: BIOL ABS. RRM LITERATURE REVIEW HUMAN ANIMAL OZONE NITROGEN OXIDES CARBON MONOXIDE METALS CHEMICALS CARCINOGENS GENOTOXICITY IMMUNOLOGIC EFFECTS ALTERED INFECTIVITY INFLAMMATION MORALITY MORBIDITY EPIDEMIOLOGY

Bedford, CT. (1979) Industrial chemicals and miscellaneous organic compounds. In: Hathaway, D; eds. Foreign compound metabolism in mammals. A specialist periodical report. London: Chemical Society; pp. 495–523.
PESTAB. The metabolism of industrial chemicals and other miscellaneous compounds are discussed according to their structural classifications. The major categories outlined include the aliphatic, aromatic, and heteroaromatic compounds, and some organometallic and inorganic substances. The metabolism of biphenyl by pigs, rabbits, rats and guinea pigs and by liver microsomes of rabbits, rats and guinea pigs is examined. The metabolism of naphthalenes by laboratory animals and man occurs mainly by glucuronic acid conjugation. PCB binding to rat liver microsomal fractions has been reported and some urinary metabolites have been identified. In vivo and in vitro studies on the metabolism of organotin compounds have established that microsomally induced C-hydroxylation occurs, and the a

BUA (Beratergremium fuer umweltrelevante Altstoffe). (1992) Biphenyl (1,1'-biphenyl) (July 1990). Beratergremium fuer umweltrelevante Altstoffe (BUA). Vol. 50 (1992).
Ecological aspects: Degradation: Biphenyl is biologically degradable under aerobic conditions: BOD28 values of 59% degradation without adaptation and 100% after adaptation are stated for activated sludge. Mineralization by activated sludge organisms was detected; the values recorded after 5 days were 8% in one case and 15% in another. Bacterium populations occurring naturally in waters mineralized biphenyl: the degradation rate in seawater during the first 21 days was 0.32-1.51 ug/l x day, in river water the degradation reached 100% after 4 days. Bacteria isolated from soil also degraded biphenyl, up to 7 metabolites being detected, and some species were able to grow on biphenyl as their sole source of carbon and energy. Many fungi have been found to metabolize biphenyl (detection of hydroxylation products); in one case biphenyl was degraded to benzoic acid; in another the hydroxybiphenyls were converted into sulphonic acid derivatives, which accumulated in the medium after 120 hours. No investigations of anaerobic degradation by microorganisms have been reported. Hydroxybiphenyls have also been found as metabolites in amphibia (frogs), fish (trouts) and birds (chickens). Hydrolysis of biphenyl under environmental conditions is considered to be unlikely. No data on this have been published. The mean half-life for photochemical oxidative degradation in the troposphere is about 2 days. No figures are available for the photochemical degradation of free biphenyl in water. Anaerobic degradability tests in water and photochemical degradability tests of free biphenyl in water are not required, since these degradation processes are of no relevance because of their good biodegradability in aerobic zones. Accumulation: At a log Pow of approximately 4, bioaccumulation is likely. This has been demonstrated by investigations: a log BCF of 3.41 was measured for activated sludge after 5 days and a log BCF of 3.43 for the green alga Chlorella fusca after 1 day (both values calculated on dry weight). For the yeast fungus Rhodotorula rubra a log BCF at equilibrium (< 15 min exposure) of 2.39 - 2.57 was recorded. The log BCF after 1.7 hours for the salt water lamellibranch Mytilus edulis was 1.75, calculated on fresh weight, in other salt water lamellibranches (Crassostrea virginica and Rangia cuneata) concentrations of 0.3 and 0.1 mg/kg respectively, calculated on fresh weight, were measured. The log BCF at equilibrium for the rainbow trout (Salmo gairdneri) was 2.59 - 2.69, while the values for the golden orfe (Leuciscus idus) were 2.05 after 1 day and 2.45 after 3 days (all values calculated on fresh weight). Data on the

bioaccumulation of biphenyl in higher terrestrial organisms are not available. According to the calculated soil sorption coefficients biphenyl may be considered to be immobile in soil. In spite of this immobility, appreciable geoaccumulation under aerobic conditions is unlikely in view of the microbial degradability. Ecotoxic effects: In an O2 consumption test with Pseudomonas putida no harmful effect was observed within a period of 30 minutes at an input of 1,000 mg/l (predissolved in ethanol). In the case of Photobacterium phosphoreum an EC 50 in respect of bioluminescence of 1.9 mg/l was measured after exposure for 30 minutes. At 6.3 mg/l biphenyl had no lethal effect on ciliata after 18 hours in one case and 24 hours in another. In another test slight inhibition of the cellular proliferation was seen after 43 hours at 5.6 mg/l. Unicellular green algae showed a 50% reduction of their photosynthesis rate in the presence of biphenyl after 3 hours at 1.28 mg/l in one case and at 3.86 mg/l in another. Depending on whether a closed and more or less tight test vessel was used with a continuous flow method or a static method, and also on the test time (24 or 48 hours), the LC 50 value for Daphnia magna was 0.36 to 4.7 or 27 mg/l, while the NOEC after 48 hours in the closed continuous flow system was 0.04 mg/l. In a reproduction test with Daphnia magna in the closed continuous flow apparatus the NOEC after 21 days was found to be 0.17 mg/l. The mussel Mytilus edulis has a 40-minute EC 50 of 0.3 mg/l (effect on the food intake). The inducibility of budding of the jellyfish Aurelia aurita is impaired after exposure for 14 days to biphenyl at concentrations 96-hour LC 50 values of 1.5 - 5 mg/l are stated for fish. The cellular proliferation of 49 mould fungus species was inhibited by biphenyl vapour after 3 and 7 days; in 37 species the inhibition after 7 days was 70 to 100%. In Penicillium digitatum 17 and 80 mg biphenyl/m3 air caused, respectively, 50% and 100% inhibition of the cellular proliferation. When the biphenyl was distributed in the nutrient medium (100 mg/kg) the cellular proliferation of 14 mould fungus species was inhibited to up to 100% after only 2 days; on the other hand, all 22 yeast fungus species tested showed little or no inhibition after 4 days - in as far as determination was possible. In the severely inhibited fungus species the sporogenesis was additionally suppressed; in some species, furthermore, the spore germination after 1 day was inhibited to the extent of 74 to 100%. At the stated concentrations biphenyl did not kill the fungi. In Penicillium digitatum and Diplodia natalensis the occurrence of biphenyl-resistant mutants was observed after exposure for several weeks and more than 10 days respectively. In a dietary study with birds (Agelaius phoeniceus) a LD 50 of 96 mg biphenyl/kg bodyweights was determined. Data on the effects of biphenyl on ecosystems are not available. Toxicological aspect: In animal toxicity tests biphenyl was absorbed well through the gastrointestinal tract and presumably also via lung and skin. The major metabolite is 4-hydroxybiphenyl. The other metabolites a

BUA (Beratergremium fuer umweltrelevante Altstoffe). (1994) Biphenyl. Beratergremium fuer umweltrelevante Altstoffe (BUA). Vol. 133.

BUA (Beratergremium fuer umweltrelevante Altstoffe). (1996) Supplementary reports II - m-dichlorobenzene; bromomethane; 1,3,5-trichlorobenzene; N,N-diethylaniline; styrene; biphenyl; o/m-chloroaniline; nitrobenzene. Gesellschaft Deutscher Chemiker (GDCh) - Advisory Committee on Existing Chemicals of Environmental Relevance (BUA). S. Hirzel Verlag, P.O. Box 10 10 61, 70009 Stuttgart, Germany, 157 pages.
This document comprises translations of supplementary reports, finalized between June 1993 and April 1994, relating to eight substances evaluated in earlier BUA reports. The new data relate mainly to the results of animal studies carried out following recommendations in the original reports. No human effects are reported

Chu, I; Villeneuve, DC; Rousseaux, CG. (1994) Toxicology of coal liquefaction products: an overview. J Appl Toxicol 14(4):241–256.
BIOSIS COPYRIGHT: BIOL ABS. RRM LITERATURE REVIEW MAMMALIA HEAVY DISTILLATE MIDDLE DISTILLATE LIGHT DISTILLATE ACUTE TOXICITY SHORT-TERM TOXICITY SUBCHRONIC TOXICITY DERMAL EXPOSURE ORAL EXPOSURE INHALATION EXPOSURE TERATOLOGIC EFFECT MUTAGENIC EFFECT CARCINOGENIC POTENTIAL TOXICODYNAMICS

CLARK, CR; MARSHALL, TC; MERICKEL, BS; et al. (1979) Toxicological assessment of heat transfer fluids proposed for use in solar energy applications. Toxicol Appl Pharmacol 51:529-535.

Cramer, G; Ford, R; Hall, R. (1978) Estimation of toxic hazard: a decision tree approach. Food Cosmet Toxicol 16(3):255–276.
HEEP COPYRIGHT: BIOL ABS. A procedure for making a significant part of the safety evaluation process rational, public and explicit, is proposed. It uses currently available toxicological data to validate the procedure, which consists of a decision tree of 33 questions, each answered yes or no. Each answer leads to another question or to final classification into 1 of 3 classes (I, II and III) reflecting a presumption of low, moderate or serious toxicity. The tree is organized into branches dealing with major chemical classifications and is intended for use with all ingested, structurally defined organic and metallo-organic substances. Answering the questions requires chemical or biochemical training and relies primarily on features of chemical structure. Occurrence in body tissues and fluids

and natural occurrence in food are also involved. The logic of the tree rests heavily on known data on metabolism and toxicity. The classification according to presumptive toxicity can be combined with knowledge of human intake to provide for each substance a protection index, which can be used to establish priorities and to define tentatively the extent of appropriate testing. The procedure is applied to a large number of pesticides, drugs, food additives and industrial and environmental chemicals of known biological properties. So fat it has not resulted in any underestimation of toxicity, and it may provide a practical means for discriminating effectively among different levels of probable hazard

Dow Corning Corp. (1979) Comparative acute inhalation health hazard assessment with Dow Corning x2-1162, dowtherm a, dowtherm g, and therminol 66 heat transfer fluids, with cover letter dated 4/20/94. Submitted under TSCA Section 8D; EPA Document No. 86940001301; NTIS No. OTS0558082.

Eastman Kodak. (1981) Toxicity and health hazard summary with cover letters. Submitted under TSCA Section 8D; EPA Document No. 878214405; NTIS No. OTS0206548.

Elkins, HB. (1959) Organic compounds. Part I: hydrocarbons. In: Anonymous; eds. Chemistry of Industrial Toxicology. New York, NY: John Wiley and Sons, Inc.; pp. 98–111.
The toxicological properties of hydrocarbons are reviewed. The gaseous compounds act as asphyxiants and also as very weak narcotics, the volatile liquid hydrocarbons are more strongly narcotic and the higher members are irritating. Substances covered in detail include paraffins, olefins, acetylene (74862), naphthenes (91203), and the aromatic hydrocarbons benzene (71432), toluene (108883), xylene (1330207), coal-tar naphthas, naphthalene, styrene (100425), anthracene (120127), diphenyl and terpenes. Concentrations of some compounds which may occur during work operations are given, with narcotic concentrations and tests for exposure. Particular emphasis is placed on benzene because of its cumulative toxic effects

Hamilton, A; Hardy, HL. (1974) Aromatic hydrocarbons. In: Anonymous; eds. Industrial toxicology. 3rd edition. Acton, Massachusetts: Publishing Sciences Group, Inc; pp. 271–276.
The toxicity of aromatic hydrocarbon solvents is reviewed. Benzene (71432) is the primary raw material for styrene (100425) used in the rubber (9006046) industry. It is a central nervous system depressant causing narcosis at high doses. Acute symptoms of benzene poisoning are nonspecific and include lightheadedness, headache, excitement, respiratory paralysis, and death. Chronic response involves disturbance of the hematopoietic system. Clinical manifestations are insiduous at onset and diagnosis is difficult. Purpura and agranulocytosis are major hematopoietic injuries along with anemia, leukopenia, thrombocytopenia, hypoplastic, and hyperplastic bone marrow changes. Benzene also causes leukemia of various forms, of which the myelogenic form is most common. Benzene poisoning can be prevented by control of atmospheric concentrations to 25 parts per million (ppm) for an 8 hour exposure. Diagnosis is through urinary sulfate and phenol determination and abnormal chromosomal patterns, which are specific to each form of leukemia. Toluene (108883) and xylene (1330207) are less volatile and toxic than benzene in the solvent sample. However, humans exposed to 200ppm toluene showed fatigue, nausea, confusion, lack of self control, incoordination, and staggering gait. Toluene does not produce injury to the bone marrow except in rare cases, and death due to glue sniffing is attributed to lethal cardiac arrythmia following sensitization to high toluene concentrations. Xylenes are similar to toluene in their toxicity. Diphenyl (92524) and diphenyl-oxide (101848), based as heat transfer media and fungistatic agents cause thermal burns, and irritation of eyes and upper respiratory airways. Symptoms of poisoning include polyneuritis, electrocardiographic changes and hepatic cellular and function abnormalities. Naphthalene (91203) is used as an intermediate in the dye and plastic industries. Exposure to this compound results in lenticular opacity, eye irritation, profuse sweating, and hemolytic anemia, especially in individuals with erythrocytic deficiencies

Institut national de recherche et de sécurité. (2000) Diphenyl. Institut national de recherche et de sécurité, 30 rue Olivier-Noyer, 75680 Paris Cedex 14, France, CD-ROM CD 613, May, 3p.
Chemical safety information sheet. Synonyms: biphenyl; phenylbenzene. Toxicity: irritation of conjunctive and respiratory mucous membranes; skin diseases; skin absorption. Chronic toxicity: carcinogen; skin and nasal septum ulcers; renal damage (ingestion). Exposure limits (France): TWA = 1.5mg/m³ (0.2ppm). Complete datasheet collection on CD-ROM analysed under CIS 01-201.

IPCS (International Programme on Chemical Safety). (1999) Concise International Chemical Assessment Document (CICAD) 6: Biphenyl. Available online at http://www.inchem.org/documents/cicads/cicads/cicad06.htm.

Kirwin, CJ; Galvin, JB. (1993) Ethers. CLAYTON, G D AND F E CLAYTON (ED) PATTY'S INDUSTRIAL HYGIENE AND TOXICOLOGY, VOL II, PART A: TOXICOLOGY, 4TH EDITION XVII+945P JOHN WILEY

AND SONS, INC : NEW YORK, NEW YORK, USA; CHICHESTER, ENGLAND, UK ISBN 0-471-54724-7 ; 0 (0) 1993 445-525 .
BIOSIS COPYRIGHT: BIOL ABS. RRM BOOK CHAPTER HUMAN LABORATORY ANIMAL EXPOSURE INDUSTRIAL EXPOSURE OCCUPATIONAL RISK USA

Koch Chemical Co. (1982) Koch material safety data and product information sheets on biphenyl, ethyltoluene and 1,2,4-trimethylbenzene with attachments and cover letter dated 071282. Submitted under TSCA Section 4A; EPA Document No. 40-8258072; NTIS No. OTS0514284.

Macintosh, F. (1945) The toxicity of diphenyl and o-phenyl-phenol. Analyst 70:334–335

Marquardt, P. (1973) [Pathogens and toxic foreign substances in foodstuffs]. Z Allgemeinmed 49(12):551–557. (German).
HEEP COPYRIGHT: BIOL ABS. Additives such as dyes, preservatives, antioxidants and stabilizers are found in processed food. Boric acid compounds, used as preservatives, cause intestinal and kidney disorders in humans with as little as 1 g. Dimethylaminoazobenzene caused liver cancer in animals when given chronically in nontoxic dosages and the food of animals containing 25% ascorbic acid, caused heavy damage and death. Parascorbic acid leads to gastroenteritis and other disorders when taken orally, and when taken chronically, becomes carcinogenic. Sulfites disturb thiamine and vitamin B-1, and the WHO has set a maximum allowable intake at 0.38 mg/kg of body weight, although they occur in wine at up to 1.5 mg/kg. Diphenyl and o-phenylphenol are acutely toxic to rabbits, rats, dogs and apes. Nitrosamines, which are highly carcinogenic, are formed in the body by the mixture of cycasin and the already present amines and amides. The 160-200 types of Aspergillus flavus produce 30 aflatoxins, some of which have caused death in turkeys. The European Free Trade Association has set the maximum allowable Sn intake level for humans at 250 mg/kg, but Sn intake level for humans at 250 mg/kg, but Sn solder containing 40-70% Pb is used in the manufacture of cans. Up to 0.05-0.09 mg/day of Hg is supposedly allowable and the normal concentration is 4 mug/ml of blood, but healthy fish eaters in Sweden have had up to 60 mug and sick fish eaters have shown values 130 and over. The effects of some chemicals can only be seen through observation of several generations of test animals

MIC Envir Sci; Monsanto Co. (1983) Toxicity summary sheet: biphenyl. Submitted under TSCA Section 4A; EPA Document No. 40-8359191; NTIS No. OTS0510133.

Monsanto Co. (1987) Health and safety studies on monochlorobenzene and therminol with cover letter dated 062287. Submitted under TSCA Section 8D; EPA Document No. 86870000410; NTIS No. OTS0513158.

Parke, DV; Lewis, DF. (1992) Safety aspects of food preservatives. Food Addit Contam 9(5):561–577.
BIOSIS COPYRIGHT: BIOL ABS. RRM HUMAN FOOD PRODUCTS FOOD ADDITIVES ANTIOXIDANTS FOOD SAFETY METHODS

Santodonato, J; Bosch, S; Meylan, W; et al. (1985) Monograph on human exposure to chemicals in the workplace: diphenyl. Center for Chemical Hazard Assessment, Syracuse Research Corporation, Syracuse, New York; No. SRC-TR-85-158; Sponsored by National Cancer Inst., Bethesda, MD. Div. of Cancer Etiology; NIOSH/00164921.
This report summarizes and evaluates toxicologic information relevant to an occupational hazard assessment of diphenyl (92524), including chemical and physical properties, production and use, extent of occupational exposure, pharmacokinetics, animal carcinogenicity and mutagenicity, and epidemiological studies. Currently, diphenyl is mainly a by product from the hydrodealkylation of toluene (108883), used to manufacture benzene (71432). Diphenyl is used as a heat transfer fluid in combination with diphenyl-oxide (101848), as a dye carrier in the production of polyester fabrics, as a fungicide, and as a raw material for synthesis of alkylated diphenyls. While industrial hygiene data are extremely limited, one Finnish report, where diphenyl was impregnated in paper as a fungicide, has measured average concentrations as high as 10 parts per million (ppm); instantaneous levels as high as 19.5ppm have been reported. Inhalation is not a major route of absorption. The low odor threshold of 0.83 parts per billion would be an effective warning indicator. In the workplace, skin penetration may be the most important route of absorption. Diphenyl is probably well absorbed by all routes in animals, with some tendency for bioaccumulation. Hydroxylation is involved in the major metabolic pathway, although metabolite structures are species specific. Metabolites are primarily excreted in urine. Results of three oral administration studies in rats and mice are negative for carcinogenicity. This is supported by short term genotoxicity assays. However, slight mutagenic activity is demonstrated by one study in yeast, and sister chromatid exchange has been demonstrated in cultured mammalian cells. While several case reports of acute poisoning and death have been published,

epidemiological data are not available. Hepatic dysfunction and neurological impairment is indicated by one cross sectional study of the health status of 22 occupationally exposed cases

SANOTSKII, IV. (1997) Long-term (gonadotropic, embryotropic, mutagenic, ageing) effects of exposure to solvents. Meditsina Truda I Promyshlennaya Ekologiya 0(3):17–20.
BIOSIS COPYRIGHT: BIOL ABS. Experiments, clinical and hygienic research revealed multiple long-term effects caused by various chemical solvents. Systematic study covered the solvents' influence on reproductive function (gonads, fetus, descendants) and helped to set safety standards for putting some solvents into production. Individual solvents appeared to accelerate natural aging. Important notion is that up to date epidemiologic research incompletely covered relationship between changes of health state and quantitative parameters (active concentrations/doses) of chemical hazards

Smyth, HF. (1931) Toxicity of certain benzene derivatives and related compounds. J Indust Hyg 13:87– 96.
Studies to determine the toxicity of certain benzene (71432) derivatives and related compounds are reviewed. Industrially and toxicologically, the most important benzene derivatives are the nitro, amino, diamino, and chlorine compounds of benzene and toluene (108883). The nitro and amino compounds affect the blood and the central nervous system. Diamines are toxic and phenylenediamines used in hair dyes have been responsible for several cases of poisoning. The animals used in the experiments were white rats, guinea-pigs, and rabbits. Studies were carried out using guanidine (113008) and guanidine derivatives, aniline (62533) and aniline derivatives and compounds, diphenyl (92524) and diphenyl derivatives, nitrobenzene (98953), phenylnaphthylamines , and tolulenediamines . In all of these compounds, the level of toxicity depended on the amount of dosage. In studies with animals, the one pathologic lesion seen was a tendency to extravasation of blood in the lungs with the severity of the lesion paralleling the severity of the poisoning. The data reveal little danger of poisoning with any compounds having a minimum lethal dose of over 0.25gm/kilo. However, this applies only to solids or liquids taken by mouth. Fat or lipoid soluble substances are more toxic by skin absorption and vapor inhalation

U.S.EPA. (1984) Health and environmental effects profile for 1,1-biphenyl. Environmental Criteria and Assessment Office, Office of Health and Environmental Assessment, Office of Research and Development, Cincinnati, OH; EPA/600/x-84/147. Available from the National Technical Information Service, Springfield, VA; NTIS PB88-137831.
TD3: The Health and Environmental Effects Profile for 1,1'-biphenyl was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents. Quantitative estimates have been presented provided sufficient data are available. 1,1'-Biphenyl has been determined to be a systemic toxicant. An Acceptable Daily Intake (ADI), defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect, for 1,1'-biphenyl is .05 (mg/kg bw/day) for oral exposure

U.S.EPA. (1990) Health and environmental effects document for 1,1-biphenyl. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC.

Vettorazzi, G. (1977) State of the art of the toxicological evaluation carried out by the Joint Food and Agriculture Organization World Health Organization Expert Committee on Pesticide Residues: Part 3. Miscellaneous pesticides used in agriculture and public health. In: GUNTHER, FAA; Gunther, JD; eds. Residue reviews. Residues of pesticides and other contaminants in the total environment. Vol. 66. New York, NY: Springer-Verlag; pp. 137–184.
HEEP COPYRIGHT: BIOL ABS. HUMAN PLANT ANIMAL

2. CHEMICAL AND PHYSICAL INFORMATION

IPCS (International Programme on Chemical Safety). (1999) Concise International Chemical Assessment Document (CICAD) 6: Biphenyl. Available online at http://www.inchem.org/documents/cicads/cicads/cicad06.htm.

Partition coefficients of biphenyl, diphenyl oxide and dowtherm a between 1-octanol and water -- another look (1983) Epa/Ots Doc #878213735.

NLM (National Library of Medicine). (2007) HSDB Database: Biphenyl (CASRN 92-52-4). Available online at http://toxnet.nlm.nih.gov/cgi-bin/sis/search/f?./temp/~uc2w6z:1

O'Neil, MJ; Heckelman, PE; Koch, CB; et al., eds. (2006) The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals. 14th ed. Whitehouse Station, NJ: Merck and Co., Inc.; p. 9867.

3. TOXICOKINETICS

Bridges, J. (1980) Monooxygenase reactions glucuronic acid and sulphate conjugation in isolated hepatocytes. Toxicology 18(3): 195–204.
PESTAB. A review is presented of the use of isolated hepatocytes in drug metabolism studies. Topics include passage across the plasma membrane and metabolism by cytochrome P-450. The role of substrate lipophilicity is considered. Excretion of metabolites and the relationship between Phase 1 and Phase 2 metabolism are also described. Studies using biphenyl as a substrate show that addition of classical metabolic inhibitors such as rotenone or 2,4-dinitrophenol dramatically modify the ratio of free phenol to its conjugates. 2,4-Dinitrophenol (2 x 10-4 M) increased the total amount of 4-hydroxybiphenyl formed compared with the control, while decreasing the total amounts of glucuronic acid and sulfate conjugates. Other topics discussed include the effects of cofactor levels and external factors on drug metabolizing activity, and tissue and species comparisons of drug metabolizing activities

Philpot, R; Anderson, M; Eling, T. (1977) Uptake accumulation and metabolism of chemicals by the lung. In: BAKHLE, YSA; Vane, J; eds. Lung biology in health and disease. Vol. 4. Metabolic functions of the lung. New York, NY: Marcel Dekker, Inc; pp. 123–171.
HEEP COPYRIGHT: BIOL ABS. REVIEW RAT GUINEA-PIG DOG RABBIT MONKEY DRUGS TOXIC SUBSTANCES POLLUTION CARCINOGENESIS

3.1. ABSORPTION

Dow Tox Res Lab. (1983) Acute oral lethality, percutaneous absorption and inhalation toxicity of biphenyl 99. Submitted under TSCA Section 8D; EPA Document No. 878213747; NTIS No. OTS0206456.

University of Cincinnati. (1946) Final report on the physiological response of experimental animals to the absorption of diphenyl, and several resins, elastomers and plastics with cover letter (sanitized). Submitted under TSCA Section 8D; EPA Document No. 878213563; NTIS No. OTS0206411.

3.2. DISTRIBUTION

Dencker, L; Danielsson, BR. (1987) Transfer of drugs to the embryo and fetus after placentation. In: Nau, H; Scott, WJ; eds. Pharmacokinetics in teratogenesis. Vol. 1. Interspecies comparison and maternal-fetal drug transfer. Boca Raton, FL: CRC Press, Inc; pp. 55–70.
BIOSIS COPYRIGHT: BIOL ABS. RRM HUMAN TOXICITY METALS ANESTHETIC GASES OCCUPATIONAL EXPOSURE

Pelkonen, O. (1977) Transplacental transfer of foreign compounds and their metabolism by the foetus. Prog Drug Metab 2(119):161.
PESTAB. Aspects of the placental transfer of foreign compounds and their metabolism by the fetus are reviewed in terms of the drugs and other xenobiotics likely to be encountered and the mechanism by which they are handled in

various species. The human fetus is exposed, via the maternal organism, to many foreign substances; correlation of this fact with observed fetal damage is extremely difficult. Harmful effects may be caused directly by the xenobiotic compound or by a more active metabolite. Pesticides are among the environmental pollutants that are being examined for harmful effects to the fetus. The ability of the human fetus to oxidize foreign compounds mainly resides in the liver and adrenal glands, which possess cytochrome P-450-linked electron-transport chains. Some conjugation reactions are well developed in the fetus during the first half of pregnancy, whereas glucuronic acid conjugation seems to be somewhat deficient. Drug metabolism develops much later in fetuses of common laboratory animals than in human fetuses, predominantly after birth. The ability of the human fetus to oxidize foreign compounds seems to closely parallel to active steroid-hydroxylation characteristic of the human fetus. Possible consequences of the fetal drug metabolizing capacity are accumulation of water-soluble metabolites, formation of toxic intermediates, and interactions between steroids and antibiotics

3.3. METABOLISM

Ackland, MJ. (1993) Correlation between site specificity and electrophilic frontier values in the metabolic hydroxylation of biphenyl, di-aromatic and CYP2D6 substrates: a molecular modelling study. Xenobiotica 23(10):1135–1144.
1. A series of biphenyl, di-aromatic and CYP2D6 substrates known to undergo metabolic aromatic hydroxylation was derived from the literature, several animals species were represented. 2. Molecular orbital calculations were performed on the substrates using the AM1 semi-empirical force field and the electrophilic frontier values (f((E))) plotted for each available aromatic site. 3. A qualitative correlation was observed between the sites of oxidation and high f((E)) values, suggesting the role of frontier orbitals in the metabolic hydroxylation of these substrates. 4. The mechanistic implications for the involvement of frontier orbitals in aromatic hydroxylation are discussed. It is proposed that electron abstraction occurs in the region of high electron density to form a radical cation. Hydrogen abstraction by Fesup 4sup +Osup - then occurs followed by oxygen rebound. 5. The method can be helpful in indicating regio-specificity in the metabolic hydroxylation of bi-phenyls, related di-aromatic compounds and possibly CYP2D6 aromatic substrates

Baty, JD. (1979) Species, strain, and sex differences in metabolism. In: Hathaway, D; eds. Foreign compound metabolism in mammals. A specialist periodical report. London: Chemical Society; pp. 159–189.
PESTAB. Many species, strain and sex differences in the metabolism of foreign compounds have been documented. This brief review of some species differences includes comparisons of catabolic reactions, conjugation, biliary excretion and enzyme activity. The pharmacogenetics of sex and strain differences are also outlined. DDT metabolism was different in CF-1 mice and the Syrian hamster. The major urinary metabolites in both species were conjugates of bis(p-chlorophenyl)acetic acid. The mouse urine also contained small amounts of DDE. Minor qualitative differences and substantial quantitative differences were noted in the hydroxylation patterns of biphenyl in the rat, rabbit and guinea pig. The main metabolite in these three species was 4-hydroxybiphenyl. In studies on 16 strains of mice, piperonyl butoxide lengthened hexobarbitone sleeping times, but had no effect on zoxazolamine paralysis times. Pretreatment of the mice with either phenobarbital or piperonyl butoxide had no effect on warfarin survival. A genetic influence in plasma protein binding has been found for the binding of racemic warfarin

Bend, J; Hook, GE; Easterling, RE; et al. (1972) A comparative study of the hepatic and pulmonary microsomal mixed-function oxidase systems in the rabbit. J Pharmacol Exp Ther 183(1):206–217

Benford, D; Bridges, J; Parke, DV. (1980) Activation of hepatic microsomal biphenyl 2-hydroxylation by corticosteroids. Xenobiotica 10(5):329–336.

Benford, D; Bridges, J; Boobis, A; et al. (1981) The selective activation of cytochrome P-450 dependent microsomal hydroxylases in human and rat liver microsomes. Biochem Pharmacol 30(12):1702–1703

Benford, D; Bridges, J. (1983) Tissue and sex differences in the activation of aromatic hydrocarbon hydroxylases in rats. Biochem Pharmacol 32:309–313.

Borlakoglu, J; John, P. (1989) Cytochrome P-450-dependent metabolism of xenobiotics. A comparative study of rat hepatic and plant microsomal metabolism. Comp Biochem Physiol C 94(2):613–617.
1. A comparison was made between rat hepatic and plant microsomal cytochrome P-450 and cytochrome P-450 linked enzymic activities. 2. The results show that, compared with plant microsomes, rat hepatic microsomal protein

concentrations were 165-fold higher, and rat hepatic cytochrome P-450 concentration were 32-fold higher. 3. Rat hepatic Cytochrome P-450 linked enzyme activities were 1765-fold and 25-fold greater when compared with plant microsomes using aldrin and biphenyl as substrates, respectively. 4. Rats metabolised biphenyl to 2- and 4-hydroxybiphenyl, whereas plants produced only the latter metabolite. 5. Pretreatment of rats and plant tissues with biphenyl, Aroclor 1248 and the sodium salt of phenobarbital increased significantly the microsomal protein concentrations, and enzyme activities linked to cytochrome P-450. 6. Unlike rat microsomes, those of plants were unable to metabolise halosubstituted biphenyls at measurable rates

Borlakoglu, J; Wilkins, J. (1993) Correlations between the molecular structures of polyhalogenated biphenyls and their metabolism by hepatic microsomal monooxygenases. Comp Biochem Physiol C Comp Pharmacol Toxicol 105(1):113–117.
BIOSIS COPYRIGHT: BIOL ABS. 1. Collation of the data presented in the preceding papers (references 4,5) showed a significant correlation ($r = 0.83$; $P < 0.001$) between the molecular mass (and hence the extent of halosubstitution) of halogenated biphenyls and their rate of hydroxylation by hepatic microsomal monooxygenases. 2. There was no relationship between the extent of polyortho halosubstitution of biphenyl and the rate of metabolism. 3. A marginal correlation ($r = 0.33$; $P < 0.001$) was found when the number of adjacent unsubstituted meta-para positions were linked on the rate of metabolism of PCBs. This structural feature facilitates microsomal oxidation. 4. The results support the proposal that PCBs with meta-para hydrogen atoms are less enriched in tissues of animals and humans as this structural features favours their metabolism by P450 isoenzymes

Bridges, J; Burke, M. (1971) Factors affecting the in vitro interaction of biphenyl with P-450 in the hamster. Chemico-Biological Interactions 3:314–315.
Factors affecting the in-vitro interaction of biphenyl (92524) with cytochrome-P-450 in hamsters were discussed. The results of studies to find suitable incubation conditions for investigating the in-vitro metabolism of biphenyl in hamsters were presented. It was known that biphenyl was metabolized in most mammalian species primarily to the more water soluble 2-hydroxy and 4-hydroxy derivatives. The 2 and 4-hydroxylation reactions had different pH optima in phosphate buffers. In untreated hamsters, the optimum pH values for 2 and 4 hydroxylation were 7.8 and 7.4, respectively. Neither optima was altered by phenobarbitone pretreatment, whereas 3-methylcholanthrene (MC) shifted the optimum pH for 4-hydroxylation to 8.0. The optimum pH for 2-hydroxylation was not affected by MC. The relative rates of 2 and 4-hydroxylation at their respective pH optima for control hamsters, phenobarbitone, and MC pretreated animals were 25 to 1, 70 to 1, and 2.5 to 1. Various agents generally used to dissolve biphenyl and other lipid/soluble drugs, prior to adding them to microsomal incubates, interacted with microsomal cytochrome-P-450. For example, ethanol was shown to be a type 2 compound, provoking maximum increases in absorbance at 422 nanometers (nm) and a maximum decrease at 390nm. Biphenyl in the presence of ethanol mediated a type 1 spectral change, maximal increase in microsomal absorption at 390nm and a decrease at 422nm. Tween-30 diminished the magnitude of the biphenyl mediated spectral change. Tergitol modified the biphenyl spectral change such that the 422nm trough was unaffected whereas the 390nm peak was lost. The authors note that the influence of substrate soluble agents should be considered when evaluating spectral dissociation constants

Burke, M; Bridges, J. (1975) Biphenyl hydroxylations and spectrally apparent interactions with liver microsomes from hamsters pretreated with phenobarbitone and 3-methylcholanthrene. Xenobiotica 5(6)–376.
HEEP COPYRIGHT: BIOL ABS. Metabolism of (14-C)biphenyl (an agricultural fungistat) by hamster liver microsomes was studied by TLC, fluorimetry and difference absorption spectrophotometry. 4-Hydroxybiphenyl (major metabolite) and 2-hydroxybiphenyl (minor) accounted for at least 83 percent of total biphenyl metabolism. Small quantities of 2,2'- and 4,4'-dihydroxybiphenyl metabolities were also tentatively identified. Biphen

Burke, M; Prough, R. (2002) Assay of underivatized biphenyl metabolites by high-pressure liquid chromatography. Anal Biochem 83:466–473.
Biphenyl and its hydroxylated derivatives were separated and assayed by high-pressure liquid chromatography, using a microbondapack-nh-2 column eluted with isooctane-acetonitrile-isoamyl alcohol (100:4:4), into which was incorporated 10% ethanol toward the end of the separation. The retention times, in minutes, were biphenyl (92524), 1.0; 2-hydroxybiphenyl (90437), 4.0; 3-hydroxybiphenyl, 6.3; 4-hydroxybiphenyl, 7.6; 2.2'-dihydroxybiphenyl, 12.9; and 4.4'-dihydroxybiphenyl, 15.0. Using this method to assay biphenyl metabolites formed in-vitro and in-vivo. It was found that control rat or rabbit liver homogenate or microsomes formed as the only major metabolite, 4-hydroxybiphenyl. This was also the only significant biphenyl metabolite in acid hydrolyzed rat urine, with trace amounts of 2-hydroxy and 4,4'-dihydroxybiphenyl. Liver microsomes of 3-methylcholanthrene (56495) treated rats, however, formed the 2,3,4-hydroxybiphenyls

Chatz, U; Janik, F. (1988) Mixed-function oxidase activities and cytochrome p-450 contents in livers of rats treated with diethylene glycol. Naunyn Schmiedebergs Arch Pharmacol 337(Suppl.):R18.
BIOSIS COPYRIGHT: BIOL ABS. RRM ABSTRACT AMINOPYRINE-N-DEMETHYLASE ETHYLMORPHINE-N-DEMETHYLASE CHLORPROMAZINE-N-DEMETHYLASE DIPHENYLOXAZOLE HYDROXYLASE ETHOXYCOUMARIN O-DEETHYLASE CHLORPROMAZINE-5-OXIDASE NITROANISOLE O-DEALKYLATION ANILINE HYDROXYLATION BIPHENYL 4 HYDROXYLATION 3 4 BENZO-A-PYRENE HYDROXYLATION ACETANILIDE 4 HYDROXYLATION DOSE

Creaven, PJ; Parke, DV. (2001) The stimulation of hydroxylation by carcinogenic and non-carcinogenic compounds. Biochem Pharmacol 15:7–16.
The effects of drugs and polycyclic hydrocarbons on the rate and pattern of hydroxylation of biphenyl (92524) were investigated in-vitro and in-vivo. Animals were pretreated with 20-methyl-cholanthrene (56495) (MCA), 1,2,5,6-dibenzanthracene (53703) (DBA), 3,4,9,10-dibenzpyrene (189559), 3,4,8,9-dibenzpyrene (189640), 22-methyl-cholanthrene (17012894), 1,2,3,4-dibenzpyrene (191300), 1,2,4,5-dibenzpyrene (192654), 1,2,6,7-dibenzpyrene (192518), 3,4-benzpyrene (50328) (BP), meprobamate (57534), nikethamide (59267), or phenobarbitone (50066). Compounds were administered as a single intraperitoneal dose to Wistar-albino-rats and albino-ICI-mice 24 hours before the experiments. Drug administration was by repeated injection by subcutaneous or intraperitoneal routes. In in-vitro experiments, pretreated animals were killed and biphenyl-2-hydroxylase and biphenyl-4-hydroxylase activities of liver microsomal preparations were determined. In-vivo, biphenyl was administered orally or intraperitoneally to rats pretreated with BP or phenobarbitone. Urine was collected for 48 hours and 2-hydroxybiphenyl and 4-hydroxybiphenyl were determined spectrofluorometrically. In-vitro, the drugs increased 4-hydroxylation of biphenyl; MCA, DBA, and BP stimulated only 2-hydroxylation; 1,2,6,7-dibenzpyrene stimulated neither. Other hydrocarbons stimulated one or the other in varying degrees. In-vivo, following biphenyl administration, animals receiving no pretreatment excreted 5 times as much 4-hydroxybiphenyl as 2-hydroxybiphenyl. Pretreatment with BP stimulated biphenyl-2-hydroxylase activity only, while pretreatment with phenobarbitone produced a moderate stimulation of 4-hydroxylation of biphenyl. Pretreatment of mice with phenobarbitone slightly inhibited both 2-hydroxylation and 4-hydroxylation. The authors conclude that there is a positive correlation between the carcinogenicity of polycyclic hydrocarbons and the induction of hepatic microsomal enzymes

Deliconstantinos, G. (1988) Effect of phenobarbital and 3-methylcholanthrene on biphenyl hydroxylations and fluidity of rat liver microsomal membranes. In Vivo 2(6):393–398.
The metabolism of biphenyl by rat liver microsomes after administration of phenobarbital and 3-methylcholanthrene was studied. Phenobarbital increased the activity of biphenyl-4-hydroxylase and 3- methylcholanthrene increased the activity of both biphenyl-4-hydroxylase and biphenyl-2-hydroxylase as compared to non-treated (control) rats. Phenobarbital increased the lipid fluidity while 3-methylcholanthrene increased the lipid rigidity of microsomal membranes labeled with 1,6-diphenyl-1,3,5-hexatriene (DPH), as indicated by the steady-state fluorescence anisotropy [(ro/r)-1]-1. Arrhenius plots of [ro/r)-1]-1 indicated that the lipid phase separation of the control membrane at 22.1 +/- 1.1 degrees was reduced in phenobarbital treated (14.5 +/- 0.8 degrees) and increased in 3-methylcholanthrene treated rats (32.7 +/- 2.2 degrees). Arrhenius plots of biphenyl-4-hydroxylase and biphenyl-2-hydroxylase activities exhibited a break point at 21.8 +/- 1.1 degrees and 32.1 +/- 2.1 degrees, respectively, suggesting differences in the interactions of the enzymes with their annular lipids. It is suggested that biphenyl-4-hydroxylase requires a liquid state of its lipid microenvironment to be fully active, while biphenyl-2-hydroxylase a gel state of its lipid microenvironment. These studies provide a basis for postulating that a "non-genomic" mechanism of phenobarbital and 3-methylcholanthrene induces cytochrome P-450 dependent monoxygenases

Dent, J; Graichen, M; Schnell, S; et al. (1980) Constitutive and induced hepatic microsomal cytochrome P-450 monooxygenase activities in male Fischer 344 and CD rats: A comparative study. Toxicol Appl Pharmacol 52(1):45–53.
HEEP COPYRIGHT: BIOL ABS. The hepatic microsomal mixed function monooxygenase system (MFO) is the major enzyme system responsible for the activation and deactivation of xenobiotics. To compare the hepatic MFO system in Fischer-344 (F-344) and CD (Sprague-Dawley) rats, hepatic microsomes were prepared from control, phenobarbital (3 20 mg/kg)-pretreated male F-344 and CD rats (49 days old). Both control and phenobarbital-treated F-344 rats had significantly lower microsomal epoxide hydratase activity than corresponding preparations from CD rats. The pattern of benzo(a)pyrene metabolism was significantly different between the strains. Microsomes from F-344 rats produced less dihydrodiols and quinones than the corresponding preparations from CD rats. The spectral characteristics of cytochrome P-450 in hepatic microsomes from both control and phenobarbital-treated F-344 rats were significantly different from those observed in CD rat hepatic microsomes. The lambdamax for the reduced cytochrome P-450 CO complex occurred at a slightly longer wavelength and the reduced ethylisocyanide difference

spectra 430/455 nm peak ratios were larger by about 70%. No significant strain differences were detected in control rats or rats pretreated with either phenobarbital or 3-methylcholanthrene regarding to microsomal protein, benzphetamine-N-demethylase, NADPH-cytochrome c reductase, biphenyl-4-hydroxylase, biphenyl-2-hydroxylase, arylhydrocarbon hydroxylase, ethoxycoumarin- or ethoxyresorufin-O-deethylase activities. Differences apparently do exist in the in vitro hepatic microsomal metabolism of xenobiotics in these 2 strains of rats. These differences may be of importance regarding the susceptibility of the 2 strains of rats to various toxic agents.

Fry, JR; Wiebkin, P; Kao, J; et al. (1978) A comparison of drug-metabolizing capability in isolated viable rat hepatocytes and renal tubule fragments. Xenobiotica 8(2)–120.
HEEP COPYRIGHT: BIOL ABS. The metabolism of a number of xenobiotics (ethoxycoumarin, biphenyl, benzo(a)pyrene, 4-methylumbelliferone and benzoic acid) was investigated in isolated viable rat hepatocytes and kidney tubule fragments in suspension. The level of Phase I metabolism was very low in the kidney cells although such cells possess appreciable Phase II metabolic capacity. These findings are discussed in relation to the physiological role of cytochrome P-450 and the conjugating enzymes, and the value of intact cell systems in assessing inter-organ differences in xenobiotic metabolism

Garle, MJ; Fry, JR. (1989) Detection of reactive metabolites in-vitro. Toxicology 54(1):101–110.
BIOSIS COPYRIGHT: BIOL ABS. RRM DEPLETION ASSAY GLUTATHIONE MICROSOMAL MONOOXYGENASE METABOLISM IPRONIAZID NAPHTHALENE THIOACETAMIDE ACROLEIN HEXACHLOROBUTADIENE MENADIONE ALLYL ALCOHOL

Graham, PS; Hellyer, RO; Ryan, AJ. (1970) Inhibition of drug metabolism enzymes by some naturally occurring compounds. Biochem Pharmacol 19:759–768.
IPA COPYRIGHT: ASHP The ability of a series of naturally occurring pyrethrin synergists to inhibit various pathways of drug metabolism has been studied in the rat and mouse. The compounds were effective in vitro inhibitors of the oxidative metabolism of aniline, aminopyrine, diphenyl and hexobarbital by liver preparations. In vivo inhibition of hexobarbital oxidation in the mouse as shown by an increase in sleeping times was also observed. Some considerations of structure-activity relationships are discussed

Gram, T; Litterst, C; Sikic, B; et al. (1976) Comparative aspects and differential influence of physiological pharmacological and pathological alterations on hepatic and pulmonary drug metabolism. Hoppe-Seyler's Z Physiol Chem 357(8):1029.
HEEP COPYRIGHT: BIOL ABS. ABSTRACT RABBIT RAT KIDNEY MIXED FUNCTION OXIDASES BENZPHETAMINE DEMETHYLASE BI PHENYL HYDROXYLASE CYTOCHROME C REDUCTASE ANILINE HYDROXYLASE CYTOCHROME P-450 UDP GLUCURONYL TRANSFERASE GLUTATHIONE S ARYL TRANSFERASE AMINOPYRINE DEMETHYLASE CARBON TETRA CHLORIDE

Halpaap, K; Horning, E; Horning, M. (1977) Metabolism of biphenyl by the epoxide diol pathway. Pharmacologist 19(2):169.
HEEP COPYRIGHT: BIOL ABS. ABSTRACT RAT INTRA PERITONEAL ADMINISTRATION GAS CHROMATOGRAPHY MASS SPECTROMETRY

Halpaap, K; Horning, M; Horning, E. (1978) Metabolism of biphenyl in the rat. J Chromatogr 166(2):479–490.
HEEP COPYRIGHT: BIOL ABS. The metabolism of biphenyl in the rat was studied by using gas chromatographic and mass spectrometric methods. The free and conjugated urinary metabolites were characterized. Eight new metabolites were isolated. A dihydrodiol and 2 hydroxydihydrodiols were characteristic for the epoxide-diol pathway. There were 2 dihydroxybiphenyls, a trihydroxybiphenyl, a trihydroxymethoxybiphenyl and 4,4'-dihydroxy-3-methylthiobiphenyl. The mass spectra of the trimethylsilyl derivatives of the metabolites exhibited characteristic doubly charged and metastable ions

Halpaap, K; Horning, E; Horning, M. (1978) Effects of beta-naphthoflavone and phenobarbital pretreatment on the metabolism of biphenyl in the rat. Fed Proc Fed Am Soc Exp Biol 37(3):465.
PESTAB. In continuation of our work on the metabolism of biphenyl we have studied the effect of induction with beta-naphthoflavone and phenobarbital in male Sprague-Dawley rats. In earlier studies the activities of biphenyl-2-hydroxylase and -4-hydroxylase were measured. In our investigation, rats were administered beta-naphthoflavone (80 mg/kg, po) 48 hr before administration of biphenyl (30 mg/kg, ip). In the phenobarbital studies the rats were administered phenobarbital for three days (60 mg/kg, po) prior to the biphenyl injection. We have identified and quantified several urinary metabolites of biphenyl with the use of GC-MS methods. After induction with beta-naphthoflavone, a cytochrome P448 inducer, significant changes were observed in the urinary profile when

compared to the non-induced rat. There was a marked increase in the formation of 3,4-dihydroxybiphenyl. There was only a small increase in the formation

Halpapp-Wood, K; Horning, E; Horning, M. (1981) The effect of 3-methylcholanthrene, Aroclor 1254, and phenobarbital induction on the metabolism of biphenyl by rat and mouse 9000 g supernatant liver fractions. Drug Metab Dispos 9(2):103–107.
The effects of 3-methylcholanthrene (56495) (MC), Aroclor-1254 (11097691), and phenobarbitol (50066) (PB) on liver microsomal metabolism of biphenyl (92524) were studied in Sprague-Dawley-rats and in Ha-mice. The metabolism analysis of livers from noninduced and induced animals was carried out by open tubular capillary gas chromatography and by gas chromatography/mass spectrometry. The major metabolite of biphenyl in all cases was 4-hydroxybiphenyl (92693), and only very small amounts of diols were observed before induction. After induction with MC, and increase was observed in all monohydroxybiphenyls for rat liver supernatant fractions, and the diols were present in greater amounts. The effect of Aroclor-1254 induction was similar to that observed for MC induction, but induction by PB showed very little effect. For the mouse, induction with MC resulted in an increase in all monohydroxybiphenyls and an increase in the diols. Induction with Aroclor-1254 resulted in an increase in 2-hydroxybiphenyl formation, but not in 4-hydroxylation. Very little change was observed after PB induction. The authors conclude that the effects of MC and Aroclor-1254 induction on biphenyl metabolism are similar in the rat, but not in the mouse

Halpapp-Wood, K; Horning, E; Horning, M. (1981) Effect of phenobarbital and beta-naphthoflavone induction on the metabolism of biphenyl in the rat and mouse. Drug Metab Dispos 9(2):97–102.
HEEP COPYRIGHT: BIOL ABS. The effects of induction by beta-naphthoflavone (BNF) and by phenobarbital (PB) on the metabolism of biphenyl were studied in the rat (Sprague-Dawley) and the mouse (C57BL/6Tex and DBA/2Tex). Marked changes were observed after BNF induction. A major pathway of metabolism in C57BL/6 mice after induction was biphe

Hamid, MR; Bachmann, E; Metwally, SA. (1985) Interaction of capsaicin with mixed function oxidases: ex-vivo and in vivo studies. J Drug Res 16(1-2):29–36.
IPA COPYRIGHT: ASHP The effect of subcutaneous administration of capsaicin on the ex-vivo metabolism of diphenyl (biphenyl) in rats and the in vivo effect of the drug on drug metabolism using a hexobarbital sleeping time model are described. Capsaicin produced marked activation of drug metabolizing enzymes

Haugen, D. (1980) Biphenyl metabolism by rat liver microsomes: regioselective effects of inducers solvents and inhibitors. Fed Proc 39(6):Abstract 1818.
HEEP COPYRIGHT: BIOL ABS. ABSTRACT 3 METHYL CHOLANTHRENE PHENO BARBITAL METHANOL ACETONE DI METHYL SULFOXIDE 7 8 BENZO FLAVONE 1 BENZYL IMIDAZOLE

Haugen, D. (1981) Biphenyl metabolism by rat liver microsomes: regioselective effects of inducers, inhibitors, and solvents. Drug Metab Dispos 9(3):212–218.
Examination of the regioselective metabolism of biphenyl was explored as a means of characterizing different forms of cytochrome P-450 in microsomal and purified mono-oxygenase systems. In the present study the effects of the inducers phenobarbital and 3-methylcholanthrene, the inhibitors 7,8-benzoflavone and 1-benzylimidazole, and the solvents methanol, acetone, and dimethyl sulfoxide on the 2-, 3-, and 4-hydroxylation of biphenyl and the O-deethylation of 7-ethoxycoumarin by rat liver microsomes were examined. Phenobarbital pretreatment primarily induced 2- and 3-hydroxylation, the latter most dramatically. 3-Methylcholanthrene pretreatment induced 2- and 3-hydroxylation to similar extents. The inhibitors and solvents had regioselective effects on biphenyl metabolism that were characteristic of the uninduced, phenobarbital-induced, and 3-methylcholanthrene-induced microsomes. The presence of multiple forms of cytochrome P-450 in uninduced microsomes is indicated by the regioselective effects of the solvents and the inhibitors. The 3-methylcholanthrene-dependent increases in 2- and 3-hydroxylation appear due to induction of a single form of cytochrome P-450, as indicated by similar dose-response relationships and similar changes in sensitivity to the inhibitors. The phenobarbital-dependent increases in 2- and 3-hydroxylation appear due to the induction of two forms of cytochrome P-450, as indicated by different changes in sensitivity to the effects of dimethyl sulfoxide and 7,8-benzoflavone. The results indicate that examination of the regioselectivity of biphenyl metabolism is a useful approach for characterizing microsomal mono-oxygenases, and they suggest that the approach may also be useful in the characterization of purified mono-oxygenase systems

Hazleton Labs. (1956) Chronic oral administration metabolic studies on dogs. Submitted under TSCA Section 8D; EPA Document No. 878213568; NTIS No. OTS0206411.

Hoensch, HP; Hutt, R; Hartmann, F. (1979) Biotransformation of xenobiotics in human intestinal mucosa. Environ Health Perspect 33: 71-78 .
PESTAB. Various foreign compounds including halogenated hydrocarbons, biphenyls, and aromatic hydrocarbons are biotransformed and detoxified by drug metabolizing enzymes, particularly the monooxygenases, located in the liver and in the small intestine. The content of cytochrome P-450 and monooxygenase and NADPH-cytochrome reductase activities were determined using specimens of human small intestine and jejunal biopsy material obtained from patients. Cytochrome P-450 content in surgical samples ranged from 30 to 120 pmol/mg protein. Monooxygenase activity ranged from 60 to 110 pmol/min-mg protein. Patients with total villous atrophy demonstrated no detectable monooxygenase activity, and only low enzyme rates were found in patients with a partial villous atrophy. Patients with steatorrhea and normal histology demonstrated mucosal monooxygenase activities that were higher than patients with villous atrophy, but were still only half of that observed in normal controls. It was concluded that the monooxygenase activity in the human small intestine depends on the morphological integrity of the mucosa, and that the enzyme rates were reduced when malassimilation was present. These factors are predicted to influence the absorption of xenobiotics from the intestinal tract

Hook, GER; Bend, J; Hoel, D; et al. (1972) Preparation of lung microsomes and a comparison of the distribution of enzymes between subcellular fractions of rabbit lung and liver. J Pharmacol Exp Ther 182(3): 474–490

Hook, GER; Fowler, BB; Orton, T; et al. (1975) Stimulation and suppression of hepatic and extrahepatic microsomal mixed-function oxidases (MFOs) by 2,3,7,8-tetrachlorodibenzo-p-dioxin. Toxicol Appl Pharmacol 33(1): 138 1975.
PESTAB. TCDD is one of the most toxic compounds known to man. The ability of TCDD to alter hepatic microsomal MFOs, although perhaps unrelated directly to the toxic action of the compound, is without precedent as far as dose-response relationships are concerned and indicates that the ingestion of minute amounts of TCDD could radically alter the metabolism of other simultaneously ingested foreign compounds such as drugs or chemicals of environmental origin. The response of microsomal MFOs following oral ingestion of TCDD was investigated in both hepatic and extrahepatic tissues of the rat, rabbit, and guinea pig. Cytochrome P-450 concentrations and benzpyrene hydroxylase activities were increased in rat liver microsomes by oral doses of less than 1 mug TCDD/kg. However, N-demethylase and testosterone 2beta-and 16alpha-hydroxylase activities of hepatic microsomes from male rats were suppressed. The stimulating effect of TCDD on rat hepatic microsomes was considerably more persistent than the suppressive effect. Following a single oral dose of only 25 mug TCDD/kg, benzpyrene hydroxylase of male rat liver microsomes remained signficantly elevated after 73 days but the suppression of benzphetamine N-demethylase had gone by 35 days. In microsomes from extrahepatic tissues of the rat, MFO stimulation by TCDD occurred only in the kidney. However, UDP-glucuronyl transferase was increased in microsomes from the lung, kidney, intestine, and brain but not testes. The response of the rabbit and guinea pig to TCDD differed considerably from that of the rat. Benzpyrene hydroxylase was unaffected in hepatic microsomes from guinea pig and suppressed in microsomes from rabbit liver. Benzphetamine N-demethylase was also suppressed in rabbit liver microsomes. The only pulmonary microsomal MFO responsive to TCDD was biphenyl 4-hydroxylase of the rabbit and guinea pig. Suppression of MFO activity was not observed in any of the extrahepatic tissues studied and may be confined to only certain hepatic systems. The results indicate that the most dramatic TCDD effects on microsomal MFOs are limited to the liver and kidney. (Author abstract by permission, Abstract No. 39)

Hook, GER; Haseman, JK; Lucier, G. (1975) Induction and suppression of hepatic and extrahepatic microsomal foreign-compound-metabolizing enzyme systems by 2,3,7,8-tetrachlorodibenzo-p-dioxin. Chem -Biol Interactions 10(3): 10(3):199–214.
PESTAB. The effect of dioxins on hepatic and extrahepatic foreign-compound-metabolizing enzyme systems in microsomes from rats, rabbits, and guinea pigs were investigated. The N-demethylation of benzphetamine, amino-pyrine, and ethylmorphine was suppressed following dioxins treatment in hepatic microsomes from C-D male albino rats, but not from pregnant C-D rats. Both cytochrome P-450 and benzpyrene hydroxylase were significantly stimulated in hepatic microsomes from both male and female rats at doses as small as 1 mg dioxins/kg body weight. Benzpyrene hydroxylase of male rat liver microsomes remained significantly elevated for 73 days after a single oral dose of 25 mg/kg body weight. The suppression of benzphetamine N-demethylase was gone after 35 days. The effect of age on these enzymes was determined. Benzpyrene hydroxylase was unaffected in hepatic microsomes from Hartley albino New Zealand rabbit liver. Benzphetamine N-demethylase was also suppressed in rabbit liver microsomes. The only lung enzyme responsive to dioxins was biphenyl 4-hydroxylase of the rabbit and guinea pig

Hook, GER; Orton, T; Moore, J; et al. (1975) 2,3,7,8-Tetrachlorodibenzo-p-dioxin-induced changes in the hydroxylation of biphenyl by rat liver microsomes. Biochem Pharmacol 24(3)–340.

HEEP COPYRIGHT: BIOL ABS. Biphenyl 2-and 4-hydroxylase activities and cytochrome P-450 concentrations in microsomes were increases by oral doses of less than 1 mug TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin, a contaminant of the herbicide 2,4,5-T)/kg. Female rats were more sensitive than male rats to the inductive effects of TCDD, since highly significant increases in biphenyl-hydroxylating activities were observed at the dose level of 0.2 mug TCDD/kg in female but not in male rats. The inductive effect was very persistent: biphen

Hook, JB; McCormack, KM; Kluwe, WM. (1978) Renal effects of 2,3,7,8-Tetrachlorodibenzo-p-dioxin. In: Anonymous; eds. Pentachlorophenol: chemistry, pharmacology, and environmental toxicology, environmental science research. Vol. 12. pp. 381–388.
The effect of 2,3,7,8-tetrachlorodibenzo-p-dioxin (1746016) (TCDD) pretreatment on the nephrotoxicity of chloroform (67663) was studied in mice. ICR-mice were injected with 1.6 or 16 micrograms per kilogram TCDD. Seventy two hours later, selected animals were killed and renal and hepatic microsomal aryl-hydrocarbon-hydroxylase, epoxide-hydratase, biphenyl-2-hydroxylase, biphenyl-4-hydroxylase, and serum-glutamic-oxaloacetic-transaminase (SGOT) activities were determined. Blood urea nitrogen (BUN) was measured. Relative kidney and liver weights were determined. The other mice were challenged with 0.5 to 25 microliters per kilogram chloroform. Twenty four hours later, the animals were killed and the relative liver and kidney weights were measured. TCDD significantly increased renal and hepatic enzyme activities. Neither BUN nor SGOT were increased. TCDD increased relative liver weight, but had no effect on relative kidney weight. Chloroform had no effect on relative kidney or liver weights in control mice. In TCDD treated animals, chloroform increased the relative liver weight, but had no effect on relative kidney weight. No potentiation was observed. The authors conclude that TCDD has profound metabolic effects on the kidney as well as the liver. These metabolic changes do not appear to be accompanied by physiological changes. TCDD has no effect on the acute toxicity of chloroform. Comparing these results with those of previous studies in rats, the observed changes in kidney function induced by TCDD are probably due to a decline in the general health of the animals

Jansen, E; DeFluiter, P. (1992) Detection of the enzymatic activity of cytochrome P-450 enzymes by high-performance liquid chromatography. J Chromatogr Biomed Appl 580(1-2):325–346.
BIOSIS COPYRIGHT: BIOL ABS. The reactions catalyzed by the various cytochrome P-450 enzymes are reviewed with respect to the analysis of products by high-performance liquid chromatography (HPLC). Especially biotransformation reactions of purified cytochrome P-450 enzymes in a reconstituted system and in microsomes mainly of rat liver origin are considered. Emphasis is put on the specificity of product formation due to the individual isozymes of cytochrome P-450. It is shown that the presence of eight cytochrome P-450 isozymes can be monitored and determined by specific product formation after HPLC analysis, which is an important parameter in toxicological studies

Jones, R; Mendis, D; Parke, DV. (1977) The effect of an NADPH-regenerating system on biphenyl metabolism in isolated rat hepatocytes. Biochim Biophys Acta 500(1):124–131.
HEEP COPYRIGHT: BIOL ABS. Biphenyl 4-hydroxylation was studied in isolated rat hepatocytes. There was an inter-relationship between 4-hydroxylase activity and glucuronidase activity, removal of 4-hydroxybiphenyl by conjugation being necessary to stimulate a 2nd phase of hydroxylation. Addition of an NADPH-regenerating system resulted in an initial depression of both processes, but later their activities were enhanced. This action could not be explained by the presence of non-viable cells

Laitinen, M; Watkins, J, III. (1986) Mucosal biotransformations. In: Rozman, K; Hanninen, O; eds. Gastrointestinal toxicology. New York, NY: Elsevier Science Publishing Co. Inc.; pp. 169–192.
BIOSIS COPYRIGHT: BIOL ABS. RRM REVIEW RABBIT RAT MOUSE GUINEA-PIG FASTING DIET TOXICITY XENOBIOTICS

Lum, PY; Walker, S; Ioannides, C. (1985) Foetal and neonatal development of cytochrome P-450 and cytochrome P-448 catalysed mixed function oxidases in the rat: induction by 3-methylcholanthrene. Toxicology 35:307–317.
The effect of age on the development of the polycyclic aromatic hydrocarbon induced cytochrome-P-448 and the phenobarbital induced cytochrome-P-450 was studied in Wistar-rats. Fetal and neonatal development of these cytochromes were investigated in rat livers from animals given a single intraperitoneal (ip) injection of 20 milligrams per kilogram (mg/kg) 3-methylcholanthrene (56495). Cytochrome-P-450 activity was monitored by following the N-demethylation of benzphetamine, and O-deethylation of ethoxyresorufin reflected cytochrome-P-448 activity. Developmental patterns of cytochrome-P-450 and cytochrome-P-448 activities differed markedly. As the animals grew, cytochrome-P-450 activity rose while that of cytochrome-P-448 was suppressed. Cytochrome-P-448 was the predominant form in the fetal and neonatal livers but was gradually replaced by cytochrome-P-450 in adult animals. The ip injection of 3-methylcholanthrene enhanced the O-deethylation of ethoxyresorufin and the 2-

hydroxylation of biphenyl at all ages post partum. Extent of induction increased with age and no plateau was achieved even at 14 weeks following birth. Modest increases in total cytochrome-P-450 concentrations were observed at all ages but were statistically significant only in the older animals. The authors conclude that the inducibilities of cytochrome-P-450 and cytochrome-P-448 appear to be age dependent and that markedly different developmental patterns occur for cytochrome-P-450 and cytochrome-P-448

Matsubara, T; Prough, R; Burke, M; et al. (1974) The preparation of microsomal fractions of rodent respiratory tract and their characterization. Cancer Res 34(9):2196–2203.
HEEP COPYRIGHT: BIOL ABS. A method for preparing rodent (rat and hamster) lung microsomes using normal differential centrifugation methods is described which allows the spectral characterization of these lung fractions. Procedures were established to quantitate the microsomal cytochromes b5 and P-450 in microsomes, which contain appreciable amounts of contaminating Hb and methemoglobin. Physical biochemical characterizations of the rodent lung microsomal cytochromes include reduced-minus-oxidized difference spectra, low temperature difference spectra, substrate-binding difference spectra and enzymatic cytochrome P-450 reduction studies. The lung microsomal cytochromes are similar to those found in liver microsomes except that their specific content is 20-40 fold lower than in liver. The lung microsomal fraction appears to use NADH more effectively as an electron donor to reduce cytochrome P-450 than liver microsomal fractions. Administration i.p. of 3-methylcholanthrene induced the rodent lung microsomal cytochrome P-450-dependent mixed-function oxidase system by increasing the specific content of cytochrome P-450 and shifted the difference-absorption maximum of the CO derivative of reduced cytochrome P-450 from 450 nm-448 nm. Phenobarbital treatment was without effect on the content of cytochrome P-450. Although benzphetamine demethylase and biphenyl hydroxylase activities in lung microsomes from 3-methylcholanthrene-induced animals are as high as the activities of normal liver, lung benzo(a)pyrene hydroxylase is 400-fold less active than the comparable liver hydroxylase of control animals and induced lung benzo(a)pyrene hydroxylase is 100-fold less active than the hydroxylase of liver microsomes from carcinogen-treated rats

McPherson, F; Bridges, J; Parke, DV. (1975) In vitro enhancement of hepatic microsomal biphenyl 2-hydroxylation by carcinogens. Nature 252(5483):488–489.
PESTAB. The in vitro incubation of some chemically dissimilar compounds which are carcinogenic to rat hepatic microsomes in the presence of NADPH produced a selective increase in biphenyl 2-hydroxylation, but had no significant effect on biphenyl 4-hydroxylation. Non-carcinogens do not enhance either hydroxylase. These observations may be the result of a direct effect of the carcinogens themselves, or may be mediated by the formation of active metabolites. These results indicate that the study of the in vitro enhancement of biphenyl 2-hydroxylase in hepatic microsomes in the presence of a NADPH-regenerating system may prove a basis for a preliminary screening system which, in conjunction with other such tests, may be of considerable value in detecting potential carcinogens

McPherson, F; Bridges, J; Parke, DV. (1974) The enhancement of biphenyl 2-hydroxylation by carcinogens in vitro. Biochem Soc Trans 2(4):618–619.
PESTAB. Hepatic microsomal preparations from adult male Syrian hamsters or adult male Wistar rats were added to a regenerating system containing glucose 6-phosphate, glycose 6-phosphate dehydrogenase, and one of a variety of carcinogens or noncarcinogens. After 5 min incubation, biphenyl was added and the incubation continued for 5 more min. A number of carcinogens, including butter yellow, dimethylnitrosamine, aflatoxin B1, 3-methylcholanthrene, 2-acetamidofluorene, and safrole produced a significant elevation in biphenyl 2-hydroxylation but had no effect on or slightly inhibited biphenyl 4-hydroxylation. Noncarcinogenic compounds such as phenobarbitone, nikethamide, aniline, and 1,2,3,4-dibenzpyrene did not increase biphenyl 2-hydroxylation. Other microsomal drug-metabolizing enzymes (p-nitroanisole demethylase, nitroreductase, aniline hydroxylase, and cytochrome P-450 reductase) were unaffected by the presence of carcinogens. The results suggest that enhanced biphenyl 4-hydroxylation, but not enhanced biphenyl 2-hydroxylation, requires de novo microsomal enzyme synthesis

McPherson, F; Bridges, J; Parke, DV. (1976) Studies on the nature of the in vitro enhancement of biphenyl 2-hydroxylation provoked by some chemical carcinogens. Biochem Pharmacol 25(12):1345–1350.
HEEP COPYRIGHT: BIOL ABS. Studies on the metabolism of (14C)biphenyl and 2-hydroxy and 4-hydroxybiphenyls confirm that preincubation of fresh hepatic microsomal preparations from rats or hamsters with chemical carcinogens such as safrole, benz(a)pyrene and 2-acetamidofluorene and an NADPH regenerating system produces an increase in the levels of 2-hydroxybiphenyl, through a specific increase in its formation from biphenyl. These data also support the validity of the fluorimetric assay method for monitoring this reaction. The addition of estradiol or glutathione to the incubation mixture and the use of various preincubations and time periods with the carcinogens and NADPH prior to adding biphenyl indicate that production of an active metabolic of the carcinogens is probably a prerequisite for the in vitro enhancement of biphenyl-2-hydroxylase to occur. The lack of effectiveness of EDTA in enhancing biphenyl-2-hydroxylase and the complete destruction of this enhancement by short-term

storage of microsomal preparations at -20ê suggests that the phenomenon is different from that of degranulation of the endoplasmic reticulum by carcinogens

McPherson, F; Bridges, J; Parke, DV. (1976) The effects of benzopyrene and safrole on biphenyl 2-hydroxylase and other drug-metabolizing enzymes. Biochem J 154(3):773–780.
HEEP COPYRIGHT: BIOL ABS. A study was made of the nature and specificity of the increase in biphenyl 2-hydroxylase activity after preincubation of liver microsomal preparations with various carcinogens in vitro. This enhancement of enzyme activity in vitro was investigated in mouse, hamster and rat, and although the rat appears to be atypical in the variation of the pattern of 2- and 4-hydroxylation with age, similar enhancements were detectable in each species examined. An increase in biphenyl 2-hydroxylase activity was apparent 2h after intraperitoneal administration of safrole or benzopyrene to mature Wistar albino rats and appeared to be similar in nature to that observed after preincubation of liver microsomal preparations with the same chemical in vitro. Investigation of other drug-metabolizing enzyme systems suggests that the enhancing effects of carcinogens in vitro are specific for biphenyl 2-hydroxylase. No correlation between the enhancement of biphenyl 2-hydroxylase and inhibtion of biphenyl 4-hydroxylase was apparent.

Meyer, T; Aarbakke, J; Scheline, RR. (1976) The metabolism of biphenyl. I. Metabolic disposition of 14C-biphenyl in the rat. Acta Pharmacol Toxicol 39(4):412–418.
PESTAB. The nature of biphenyl metabolites and their major routes of excretion were studied in the rat. Male albino rats were given 14C-biphenyl (p.o. 100 mg/kg, 0.7-1.0 muCi). The extent of radioactivity excretion in the urine diminished greatly after 48 hr. The mean total excretion during the 96 hr period was 84.8% of the dose. The mean total 96 hr fecal excretion of radioactivity was 7.3%, of which 5.8% was detected in the first 24 hr. Only trace amounts of radioactivity were detected in expired air. After 4 days the total amount remaining in the animals was 0.6%, of which 0.1% was in peritoneal fat, 0.3% in gastrointestinal tract and its contents, 0.1% in skeletal muscles and 0.1% in the genital tract. Both acidic and phenolic metabolites of biphenyl were noted in the rat urine. The presence of amphoteric metabolites was also suggested. Therefore, biphenyl is converted through oxidative metabolic reactions in the rat to phenols and acids

Meyer, T; Scheline, RR. (1976) The metabolism of biphenyl. II. Phenolic metabolites in the rat. Acta Pharmacol Toxicol 39(4):419–432.
PESTAB. Phenolic metabolites from biphenyl were studied in male albino rats who had been injected with doses of 100 and 400 mg/kg of various biphenyl compounds. The total amount of phenols in rat urine 96 hrs after biphenyl administration was 29.5%. The most prominent metabolites were 4-hydroxy- and 4,4'-dihydroxybiphenyl, with the latter being the main one. Several previously unknown metabolites of biphenyl were also detected. The new metabolites found were 3,4'-dihydroxybiphenyl, 3,4,4'-trihydroxybiphenyl and its 3- and 4-O-methyl ethers. The two monomethylated derivatives of 3,4-dihydroxybiphenyl, while previously reported in rabbits, have now been found also in rats. The amount of phenols of biphenyls origin in the 24 hr bile from rats was 5.2% of the dose, with 4-hydroxy-, 4,4'-dihydroxy-, and 3,4,4'-trihydroxy-biphenyl as major metabolites. These results indicate that biliary metabolites are subsequently reabsorbed only to an insignificant degree. The pattern of metabolites excreted in the 24 hr fecal studies were similar to the bile studies. In the feces phenolic metabolites were the main types of metabolites excreted.

Meyer, T; Larsen, J; Hansen, EV; et al. (1976) The metabolism of biphenyl. III. Phenolic metabolites in the pig. Acta Pharmacol Toxicol 39(4):433–441.
PESTAB. Phenolic metabolites of biphenyl were studied in the pig, the dose being 100 mg/kg, for each of several biphenyl compounds. The total urinary excretion of phenols in 4 days was 27.6% of the dose administered. Most of this total (19%) was 4-hydroxybiphenyl. Other metabolites included 2-hydroxybiphenyl and 4,4'-dihydroxybiphenyl, comprising 2.7 and 2.0%, resp., of the dose. Remaining metabolites accounted for less than 1% of the administered dose. The total 96 hr recovery from male pigs was 44.8% of the dose, while the corresponding value for the female pigs was 27.6%. No fecal excretion of phenolic metabolites was detected. This study showed that pigs are poor biliary excretors of hydroxylated biphenyls in comparison with the rat. The absence of the entero-hepatic component in the metabolism of biphenyl in pigs explains why the urinary excretion of biphenyl metabolites in a neomycin-treated pig was not decreased when compared to that found in normal animals. Quantitative differences in the species pigs and rats indicate that minor amounts of di- and tri-hydroxylated biphenyls were encountered in the pig in contrast to the rat. Also, 2-hydroxybiphenyl was a more important metabolite of biphenyl in the pig than in the rat

Meyer, T. (1977) The metabolism of biphenyl: IV. Phenolic metabolites in the guinea pig and the rabbit. Acta Pharmacol Toxicol Suppl 40(2) :193–200.

HEEP COPYRIGHT: BIOL ABS. The phenolic metabolites of biphenyl in guinea pigs and rabbits were qualitatively and quantitatively analyzed as trimethylsilyl (TMS) ethers by combined gas chromatography/mass spectrometry and gas chromatography, respectively. The parent compound was hydroxylated to monohydroxylated biphenyls and minor amounts of dihydroxylated derivatives, and the main route of body clearance appeared to be by the urine in both species. In the urine of guinea pigs, 32.9% of the dose was detected 96 h after dosing, while the major part (29.5%) was eliminated during the 1st day as conjugates. The main metabolite was 4-hydroxybiphenyl (25.5%). During the 1st 24 h fecal recovery was 20.3% of the dose, and most of this (14.3%) consisted of biphenyl itself. Biliary excretion of the metabolites of biphenyl origin amounted to 3.3% of the dose during the 1st day, and 4-hydroxybiphenyl was the major metabolite. In the urine of rabbits 49.1% of the dose was recovered 96 h after dosing, and most of this (25.4 and 15.9%, respectively) was eliminated during the 1st 2 days as conjugates. The major metabolite was 4-hydroxybiphenyl (35.3%). On the 1st day fecal recovery was 1.6%, of which 1.4% was detected as biphenyl itself. Less than 1% of the dose was found in the 7 h rabbit bile, and exclusively as 4-hydroxybiphenyl. The experiments show that qualitative and quantitative differences in the metabolism of biphenyl exist between the guinea pig and the rabbit even though 4-hydroxybiphenyl was the most prominent metabolite of biphenyl in both species

Miller, MS; Huang, MT; Williams, G; et al. (1983) Effects of betamethasone on the in vitro and in vivo 2-hydroxylation of biphenyl in the rat. Drug Metab Dispos 11(6):556–561.
The in vitro addition of betamethasone to rat liver microsomes caused a concentration-dependent stimulation of biphenyl 2-hydroxylation. At a 100 microM concentration of betamethasone, the formation of 2-hydroxybiphenyl was increased by approximately 4-fold in microsomes from 28-day-old rats and 10-fold in liver microsomes from 5-day-old rats. The steroid had little or no effect on the hydroxylation of biphenyl in the 3- or 4-position except at the highest concentration tested (1 mM), where a 20-30% inhibition was observed. The ip injection of 0.01 to 10 mumol of betamethasone to 5-day-old rats had little or no effect on the total body metabolism of 0.01 to 3.5 mumol of biphenyl-2-3H to 2-hydroxybiphenyl as measured by 3H2O formation. Although betamethasone had no effect on the 2-hydroxylation of biphenyl in the intact rat, this reaction was stimulated 4- to 9-fold by the addition of 100 microM betamethasone to hepatocyte monolayer cultures

Mole, ML; Sanders, L; Oglesby, LA. (1988) High-performance liquid chromatographic assay of biphenyl metabolism by hepatocytes cultured in an embryo/hepatocyte co-culture medium. Anal Biochem 175(1):74–84.
A high-performance liquid chromatographic method has been modified for the evaluation of both Phase I and II metabolism of biphenyl by hepatocytes maintained in an embryo/hepatocyte co-culture medium. Extracts of the media, before and after hydrolysis of conjugates, are directly injected onto the HPLC and the major hydroxylated metabolites plus unmetabolized biphenyl are detected by fluorescence after separation under gradient or isocratic conditions. The method is almost free of interferences and is relatively simple and rapid. In the case of the monohydroxylated derivatives, the minimum media concentrations which can be measured are 7 to 20 nM (0.07 to 0.2 pmol on-column). Recoveries from culture medium to which known amounts of biphenyl and metabolites had been added were quantitative (90-103%) and the reproducibility good (interassay CV less than 5%). The assay was applied to cultures of hepatocytes derived from rabbit and from phenobarbital induced and noninduced rat

Mole, ML; Kavlock, RJ; Beyer, PE; et al. (1991) Effect of hepatocyte source on metabolic profile of biphenyl in an in-vitro developmental toxicity assay. Abstr Pap Am Chem Soc 202(1-2):AGRO 21. (abstract).
BIOSIS COPYRIGHT: BIOL ABS. RRM ABSTRACT RAT RABBIT HAMSTER

Nagata, K; Martin, BM; Gillette, JR; et al. (1990) Isozymes of cytochrome P-450 that metabolize naphthalene in liver and lung of untreated mice. Drug Metab Dispos 18:557–564.
The characteristics of naphthalene (91203) metabolizing cytochrome-P-450 isozymes in mouse liver and lung were examined. Cholate solubilized microsomes obtained from the livers of untreated male CD-1-mice were analyzed by sodium-dodecyl-sulfate polyacrylamide gel electrophoresis. Four P-450 isozymes designated cytochrome-P-450m50a (P450m50a), cytochrome-P-450m50b (P450m50b), cytochrome-P-450m51a (P450m51a), and cytochrome-P-450m51b (P450m51b) were determined. The ability of hepatic P450m50b and P450m51a to react with benzphetamine (156081), ethylmorphine (76584), 7-ethoxycoumarin (31005024), naphthalene, biphenyl (92524), and testosterone (58220) was investigated by determining their turnover numbers. The turnover number for P450m51a was very large for the N-demethylation of ethylmorphine. The turnover numbers of P450m50b for the hydroxylation of naphthalene and biphenyl were very high. P450m50b and P450m51a showed little reactivity toward the other substrates. Mixtures of naphthalene, glutathione (70188), and glutathione-S-transferase (GST) were incubated with P450m51a and P450m50b. The mixtures were analyzed for naphthalene/glutathione conjugates. P450m51a formed all three known glutathione-S-yl naphthalene conjugates in approximately equal amounts. P450m50b formed primarily trans(R)-hydroxy-2(R)-glutathionyl-1,2-dihydronaphthalene (NAGSH2). Mouse lung

and liver microsomes were incubated with naphthalene, glutathione, and GST in the presence or absence of antibodies raised against P450m50b (antiP450m50b) and cytochrome-P-450c (antiP450c). AntiP450m50b significantly inhibited formation of NAGSH2. AntiP450c significantly inhibited formation of the other two conjugates. The authors suggest that P450m50b is the major P450 isozyme in mouse lung and liver that catalyzes the metabolism of naphthalene

Pacifici, GM; Vannucci, L; Bencini, C; et al. (1991) Sulphation of hydroxybiphenyls in human tissues. Xenobiotica 21:1113–1118.
The kinetics of sulfotransferase activity were studied in-vitro in human liver, ileum, colon, lung, kidney, urinary bladder and brain. Tissue specimens were obtained at surgery and were free from pathological changes. Cytosolic fractions were prepared from the tissues and incubated with three substrates. o-Hydroxybiphenyl (90437), m-hydroxybiphenyl (580518) and p-hydroxybiphenyl (92693) were used as substrates. The results showed that in-vitro sulfation of hydroxybiphenyls occurs in hepatic and extrahepatic tissues although the rate of sulfation has a marked tissue dependence. With a single hydroxybiphenyl isomer as substrate, the Michaelis Menten constant (Km) of sulfotransferase was similar in different tissues. The rate of sulfation ranged from more than 100 fold in different tissues and the highest and lowest activities of sulfotransferase were found in the liver and brain, respectively. The Km of sulfotransferase was not tissue dependent but was dependent on the isomer of hydroxybiphenyl. The Km varied over a 500 fold range and the highest and lowest values of Km were found with p-hydroxybiphenyl and m-hydroxybiphenyl respectively

Parke, DV. (1977) The activation and induction of biphenyl hydroxylation and chemical carcinogenesis. In: Ullrich, V; Roots, I; Hildebrandt, A; Estabrook, R; Conney, A; eds. Microsomes and drug oxidations. New York, NY: Pergamon Press; pp. 721–729.
PESTAB. Observations are presented which suggest that the activation of biphenyl hydroxylase represents a highly specific change in the physico-chemical state of the endoplasmic reticulum, produced by interaction with carcinogenic chemicals or their metabolites and resulting in a change in the nature of cytochrome P450 which, although apparently reversible, is not repeatable. Further evidence suggests that the activation of biphenyl 2-hydroxylase following the administration of carcinogens in vivo or the incubation of microsomal preparations with carcinogens plus NADPH in vitro leads to the metabolic activation of the carcinogen and formation of a highly reactive metabolite which, in addition to alkylating the nuclear DNA, also damages the endoplasmic reticu

Parkinson, A; Safe, S. (1981) The cytochrome P-450-mediated metabolism of biphenyl and the 4-halobiphenyls. Adv Exp Med Biol 136 Pt A:745–752

Parkinson, A; Safe, S. (1982) Cytochrome P-450-mediated metabolism of biphenyl and the 4-halobiphenyls. Biochem Pharmacol 31(10):1849–1856.
HEEP COPYRIGHT: BIOL ABS. The in vitro metabolism of biphenyl, 4-fluoro-, 4-chloro-, 4-b

Paterson, P; Fry, JR. (1985) Influence of cytochrome P-450 type on the pattern of conjugation of 4-hydroxybiphenyl generated from biphenyl or 4-methoxybiphenyl. Xenobiotica 15:493– 502.
The effects of beta-naphthoflavone (6051872) on 4-methoxybiphenyl (613376) and biphenyl (92524) metabolism were studied in rats. Male Wistar-rats were pretreated with 0 to 80 milligrams per kilogram (mg/kg) beta-naphthoflavone. Forty hours later, the animals were killed and hepatocytes and liver microsomes were isolated. After incubation with 4-methoxybiphenyl or biphenyl, the rate of production of 4-hydroxybiphenyl (92693) was measured. Hepatic microsomes from rats pretreated with 0 or 40mg/kg beta-naphthoflavone and incubated with biphenyl or 4-methoxybiphenyl were treated with metyrapone (54364), alpha-naphthoflavone (604591), or ethanol (64175) and the effects on 4-methoxybiphenyl-O-demethylase (MBPD) and biphenyl-4-hydroxylase (BPOH) activity were investigated. The rate of formation of 4-hydroxybiphenyl from 4-methoxybiphenyl in hepatocytes and microsomes from non pretreated rats was essentially the same as that from biphenyl in hepatocytes and microsomes from rats pretreated with beta-naphthoflavone. MBPD and BPOH activities in microsomes from rats not pretreated with beta-naphthoflavone were essentially the same. MBPD activity was inhibited by metyrapone to a significantly greater extent than BPOH activity. BPOH activity, however, was inhibited to a greater extent by ethanol and alpha-naphthoflavone than MBPD activity. Hepatocytes were incubated with biphenyl with or without beta-naphthoflavone pretreatment and the pattern of conjugation of 4-hydroxybiphenyl was determined. In non pretreated rats, sulfate and glucuronic-acid conjugates of 4-hydroxybiphenyl were formed in approximately equal amounts, each presenting 41 to 44 percent of the total 4-hydroxybiphenyl formed. In the pretreated rats, the sulfate conjugate represented only 22 percent of the total 4-hydroxybiphenyl formed while the glucuronic-acid conjugate represented 60 percent of the total. The authors conclude that the difference in cellular metabolism between biphenyl and 4-methoxybiphenyl is due to competition between beta-naphthoflavone and biphenyl or their metabolites for common

metabolic pathways. The type of cytochrome-P-450 involved in forming 4-hydroxybiphenyl does not affect the pattern of conjugation

Pelkonen, O; Moilanen, M-L. (1979) The specificity and multiplicity of human placental xenobiotic-metabolizing monooxygenase system studied by potential substrates, inhibitors and gel electrophoresis. Med Biol (Helsinki) 57(5):306–312.
HEEP COPYRIGHT: BIOL ABS. The specificity of the placental monooxygenase system to metabolize foreign compounds was studied by using different potential substrates and inhibitors and by performing electrophoresis of placental microsomes. Placental preparations from smokers catalyzed benzo(a)pyrene hydroxylation, 7-ethoxycoumarin O-deethylation and 2,5-diphenyloxazole hydroxylation, but not biphenyl hydroxylation at 2-, 3- or 4-C, aldrin epoxidation to dieldrin or coumarin hydroxylation or aminopyrine N-demethylation. Enzyme activities were inhibited by alpha-naphthoflavone, but to a much lesser extent by SKF 525-A (proadifen hydrochloride) or metyrapone. Correlations between the metabolism of benzo(a)pyrene, 7-ethoxycoumarin and 2,5-diphenyloxazole were highly significant. There was a clear difference in Michaelis-Menten constant of 7-ethoxycoumarin O-deethylatin between placentas from smokers and nonsmokers. Gel electrophoresis revealed that protein bands of placental microsomes in the region of cytochrome P-450 enzymes were less prominent than those of rat liver microsomes, a finding that accorded with the relative amounts of cytochrome P-450. There were no consistent differences in the electrophoretic pattern between placentas of viable benzo(a)pyrene hydroxylase activities. Results show that the human placental monooxygenase system is restricted in substrate specificity, that there may be a qualitative difference between smokers and nonsmokers and that the increase in several enzyme activities by cigarette smoking cannot be detected by the standard gel electrophoresis

Powis, G; Jardine, I; Van Dyke, R; et al. (1988) Foreign compound metabolism studies with human liver obtained as surgical waste relation to donor characteristics and effects of tissue storage. Drug Metab Dispos 16(4):582–589.
BIOSIS COPYRIGHT: BIOL ABS. RRM PHARMACOKINETICS TOXICOKINETICS CYTOCHROME P-450 BENZO-A-PYRENE HALOTHANE BIPHENYL 4-HYDROXYLASE 4 HYDROXYBIPHENYL UDP-GLUCURONOSYLTRANSFERASE CYTOSOLIC THIOPURINE METHYLTRANSFERASE THERMOSTABLE PHENOLSULFOTRANSFERASE THERMOLABILE PHENOLSULFOTRANSFERASE 5 FLUOROURACIL DEHYDROGENASE

Powis, G; Melder, DC; Wilke, TJ. (1989) Human and dog, but not rat, isolated hepatocytes have decreased foreign compound-metabolizing activity compared to liver slices. Drug Metab Dispos 17:526–531.
The metabolism of biphenyl (92524) by rat, dog, and human hepatocytes and liver slices was studied in-vitro. Hepatocytes prepared from the livers of male Fischer-344-rats were incubated with biphenyl for up to 3 hours, and the extent of conversion to free and total hydroxybiphenyl, hydroxybiphenyl-sulfate (OHBPS), or hydroxybiphenylglucuronide (OHBPG) was determined. Hepatocyte viability was determined by the trypan-blue dye exclusion (TBE) test. Hepatocyte TBE was significantly, positively correlated with the total hydroxybiphenyl concentration. The free hydroxybiphenyl/total hydroxybiphenyl ratio was significantly, negatively correlated with TBE. Hepatocytes having TBEs of less than 85 percent formed mostly free hydoxybiphenyl. Hepatocytes having TBEs of greater than 90 percent formed mostly OHBPS. The rates of biphenyl metabolism by hepatocytes prepared by the perfusion and slice digestion procedures did not differ significantly except for a 29 percent decrease in the rate of formation of OHBPG in hepatocytes prepared by the slice digestion technique. Rat, dog, and human hepatocytes prepared by the slice digestion technique were incubated with biphenyl and the extent of metabolism was determined. Hepatocyte viability was assessed by the TBE test. A similar experiment was performed with rat, dog, and human liver slices. The total amounts of hydroxybiphenyl produced by dog and human hepatocytes were only 21 and 4 percent, respectively, of that formed by rat hepatocytes. The ratios of free to total hydroxybiphenyl formed by the hepatocyte preparations were: rat, 0.19; dog, 0.46; and human, 0.63. The TBEs for all preparations ranged from 87 to 91 percent. The rates of biphenyl metabolism in liver slices were similar for all species. The ratios of free to total hydroxybiphenyl formed by the preparations were: rat, 0.11; dog, 0.21; and human, 0.26. The authors conclude that isolated hepatocyte preparations do not always reflect the xenobiotic metabolizing activity of intact livers

Prough, R; Burke, MD. (1975) The role of NADPH-cytochrome c reductase in microsomal hydroxylation reactions. Arch Biochem Biophys 170(1):160–168

Rahimtula, A; O'Brien, P. (1974) Hydroperoxide catalyzed liver microsomal aromatic hydroxlylation reactions involving cytochrome p-450. Biochem Biophys Res Commun 60(1):440–447.
HEEP COPYRIGHT: BIOL ABS. RAT RABBIT BI PHENYL BENZ PYRENE COUMARIN ANILINE SUBSTRATES XENOBIOTICS METABOLISM CATALASE PEROXIDASE

Stuehmeier, G. (1980) Metabolism of biphenyl in cobalt pretreated mice. Naunyn Schmiedebergs Arch Pharmacol 311(Suppl.):R21.
HEEP COPYRIGHT: BIOL ABS. ABSTRACT CYTOCHROME P-450 CYTOCHROME P-448 PHENO BARBITAL 4 HYDROXYLATION

Stuehmeier, G; Legrum, W; Netter, KJ. (1982) Does cobalt pretreatment of mice induce a phenobarbitone-type cytochrome P-450? Xenobiotica 12(5):273–282.
1. Pretreatment of male C57BL/6JHan mice with 40 mg/kg cobaltous chloride for two days, or three days pretreatment with 80 mg/kg phenobarbitone led to an increase of biphenyl-4-hydroxylation of similar magnitude. 2-Hydroxylation remains unaffected in both cases. 2. The time course shows an equivalent decrease in 2- and 4-hydroxylation for 6 h, when microsomal Co concn, reaches its maximum. Thereafter 4-hydroxylation increases to reach the enhanced values. 3. Kinetic analysis of biphenyl 2- and 4-hydroxylation reveals distinct differences. The apparent Km for 4-hydroxylation decreases in Co-pretreated mice but remains constant in phenobarbitone-pretreated animals. Also, the ratio of 4- to 2-hydroxylation in microsomes from phenobarbitone-treated animals remains unchanged for substrate concn. of 10(-5) to 2 X 10(-3) m, but for Co-pretreatment this ratio increases markedly from 2 to 5, with increasing substrate concn. 4. Increasing concn. of the competitive inhibitor, metyrapone, reveal a greater susceptibility of microsomal cytochrome P-450 from Co-treated mice than normal or phenobarbitone-induced animals. In contrast, deprivation of reducing equivalents in vitro in the presence of metyrapone shows similarities between microsomes from cobalt- and phenobarbitone-pretreated mice

Sukach, AN; Petrenko, AI; Belous, AM. (1991) [Role of albumin in the biotransformation of biphenyl by isolated rat hepatocytes]. Ukr Biokhim Zh 63(6):57–61.
The role of albumin in biotransformation of biphenyl, a lipophilic xenobiotic, by isolated rat hepatocytes has been studied. It is shown that in the absence of albumin biphenyl is quickly and almost completely bound by cells. The rate of formation of 4-hydroxybiphenyl, the reaction product, depends on the substrate concentration (in the range 8.5-70 microM) and conforms with the Mikhaelis-Menten equation. An increase in the biphenyl concentration in the incubating medium to 140 microM induces no changes in the rate of its biotransformation. Serum albumin, while binding biphenyl, also reduces its effective concentration in a cell, which prevents the cytochrome-P-450-dependent monooxygenase system of hepatocytes from the inhibiting effect of high concentrations of the xenobiotic

Toftgard, R; Nilsen, O; Ingelman-Sundberg, M; et al. (1980) Correlation between changes in enzymatic activities and induction of different forms of rat liver microsomal cytochrome P-450 after phenobarbital-, 3-methylcholanthrene and 16a-cyanopregnenolone treatment. Acta Pharmacol Toxicol 46:353–361.
The different forms of rat liver microsomal cytochrome P-450 (RLvMc P-450) were characterized by sodium dodecyl sulfate (SDS)-polyacrylamide gel electrophoresis after induction by 16 alpha-cyanopregnenolone (PCN), phenobarbital (50066) (PB), and 3-methylcholanthrene (56495) (3-MC). The induced forms were correlated to the in-vitro metabolism of biphenyl (92524), benzo(a)pyrene (50328) (BP), and the steroids 4-androstene-3,17-dione, and 5-alpha-androstane-3-alpha-17-beta-diol. Two forms were induced with apparent molecular weights of 54,000 (RLvMc P-450(54)) and 50,000 (RLvMc P-450(50)) by an 80 milligram per kilogram (mg/kg) intraperitoneal injection of PB into rats. A 20mg/kg intraperitoneal injection of 3-MC induced RLvMc P-450(55) and RLvMc P-450(50) was mainly associated with the formation of BP-4,5-dihydrodiol and 7-alpha-hydroxy-4-androstene-3,17-dione. The RLvMc P-450(55) and the RLvMc P-450(58) were mainly associated with the formation of 2-hydroxybiphenyl and 3-hydroxybiphenyl and BP-7,8-dihydrodiol. The RLvMc P-450(54) was partially associated with the formation of BP-4,5-dihydrodiol and several metabolites of 5-alpha-androstane-3-alpha-17-beta-diol. The authors suggest that the broad range of reactions that can be catalyzed by each of the different forms of cytochrome-P-450 may result from a wide substrate specificity possessed by these enzymes, or may occur because the different forms have the same molecular weight and cannot be separated by SDS-polyacrylamide gel electrophoresis

Tong, S; Ioannides, C; Parke, DV. (1977) Enhancement of 2-hydroxylation in vitro of biphenyl by organochlorine insecticides. Biochemical Society Transactions 5:1374–1377.
The carcinogenic potential of DDT (50293) and its major metabolites, DDE (72559) and DDD (72548), were examined in male albino-Wistar-rats, 6 week old male CF-1-mice, and adult polecat-ferrets. The activities of biphenyl 2 and 4-hydroxylase were determined in hepatic microsomal suspensions prepared from sacrificed animals. The insecticides were added to the incubation mixture to give a final concentration of 0.5 molar. Protein was also measured. Results were compared with the biphenyl model system for identification of carcinogens. Both DDT and DDD enhanced the 2-hydroxylation of biphenyl in-vitro with microsomal fractions from the three different animal species. DDE, however, had either no effect or caused a decrease in enzyme activity. The enhancement of biphenyl 2-hydroxylase by these organochlorine insecticides was found to be concentration dependent, with maximum stimulation occurring at a final concentration of 3 millimolar of insecticide. In the biphenyl system, preincubation of

carcinogens with hepatic microsomal suspension and an NADPH generating system resulted in stimulation of the 2-hydroxylation of biphenyl with little or no effect on the 4-hydroxylation. The authors conclude that DDT and DDD, but not DDE, result in activation of the biphenyl 2-hydroxylase enzyme system, with its associated indication of damage to the endoplasmic reticulum and potential of carcinogenesis

Tucker, A; Tang, T. (1979) Effects of phenobarbital and methylcholanthrene on hepatic mixed-function-oxidase activities in hamsters. J Environ Pathol Toxicol 2(3):613–624.
HEEP COPYRIGHT: BIOL ABS. The effects of the inducers phenobarbital (PB) and 3-methylcholanthrene (MC) on hamster liver mixed-function oxidase activities were studied. Both inducers increased the content of cytochrome P-450 in the microsomes, aminopyrine demethylase activity, and biphenyl 4-hydroxylase activity when given for 8 days. The ability of liver homogenates from treated animals to activate compounds to mutagens was tested using the Salmonella/microsome test. Neither inducer appreciably altered mutagenicity of 2-acetylaminofluorene, benzidine, benzo(a)pyrene, aflatoxin B1 or sterigmatocystin. Mutagenicity of MC was increased when homogenates from MC-treated hamsters were used as a source of activating enzymes and this mutagenicity could be correlated with increased biphenyl 2-hydroxylase activity

Turner, JC; Green, RS. (1974) Effect of hexachlorobenzene on microsomal enzyme systems. Biochem Pharmacol 23(17):2387–2390.
PESTAB Male rats were fed for 10 days on a diet containing 333 ppm hexachlorobenzene. Increased microsomal protein levels were noted compared to control rats. On a per g liver basis, the levels of aniline hydroxylase, biphenyl 4-hydroxylase, biphenyl 2-hydroxylase, 4-nitroanisole O-demethylase, esterase, cytochrome P-450 and cytochrome b(SUB)5 all increased compared with the control values. On a per mg microsomal protein basis, biphenyl 2-hydroxylase, 4-nitroanisole O-demethylase and cytochrome P-450 levels increased several-fold compared with the control values. It is suggested that, by inducing the 2-hydroxylation reaction, hexachlorobenzene might cause preferential ortho-hydroxylation, as do some carcinogenic polycyclic hydrocarbons, and that in some circumstances this could lead to the formation of carcinogens. (Author abstract by permission)

Wiebkin, P; Fry, JR; Jones, C; et al. (1976) The metabolism of biphenyl by isolated viable rat hepatocytes. Xenobiotica 6(12): 725–743.
HEEP COPYRIGHT: BIOL ABS. The metabolism of biphenyl by isolated viable rat hepatocytes was studied and a tentative scheme of metabolism proposed which involves initial hydroxylation at t

Wiebkin, P; Fry, JR; Jones, C; et al. (1978) Biphenyl metabolism in isolated rat hepatocytes: effect of induction and nature of the conjugates. Biochem Pharmacol 27:1899–1907.
The metabolism of biphenyl (92524) was studied in isolated rat hepatocytes. Rats were pretreated with sodium-phenobarbitone (57307) (phenobarbitone) or 3-methylcholanthrene (56495) (MC) or left untreated. Approximately 20 hours later, they were killed, livers were removed, and hepatocytes were isolated. Hepatocytes were incubated with 70 micromolar (microM) biphenyl for up to 45 minutes (min). Aliquots were taken and analyzed for metabolites. Sulfate and glucuronide freely conjugated 4-hydroxybiphenyl (92693) (4OHBP) were the major metabolites produced in hepatocytes from untreated rats. 4-Hydroxybiphenyl-sulfate (4OHBPS) was the major conjugated metabolite. The major conjugate produced by hepatocytes from phenobarbitone and MC pretreated rats was 4-hydroxybiphenyl-glucuronide (19132913) (4OHBPG). Production of 4OHBPS was similar to that seen in untreated rats. Production of free and conjugated 2-hydroxybiphenyl (90437) (2OHBP) and 3-hydroxybiphenyl (580518) was markedly increased by MC, but not by phenobarbitone pretreatment. 2OHBP and 3OHBP reached maximum concentrations after 10min of incubation. Their concentrations decreased to low values by 45min, at which time the concentration of conjugated metabolites had increased. To investigate this lag, rat hepatocytes were preincubated with 0.7microM 4-methylumbelliferone for 60min, then incubated with 70microM biphenyl. The rate of formation of 4OHBPG was significantly increased, whereas the rate of formation of 4OHBPS was relatively unaffected. Hepatocytes were incubated with 7 to 70microM 4OHBP or 7 to 140microM 2OHBP and the effects on 4OHBP or 2OHBP glucuronidation and sulfation were investigated. Sulfate formation was the major conjugating pathway at low 4OHBP or 2OHBP concentrations; however, at high substrate concentrations glucuronidation became the major pathway. The authors suggest that there may be close association of the sulfation enzymes with the surface of the endoplasmic reticulum of hepatocytes

Wiebkin, P; Schaeffer, B; Longnecker, D; et al. (1984) Oxidative and conjugative metabolism of xenobiotics by isolated rat and hamster acinar cells. Drug Metab Dispos 12(4):427–431.
Isolated rat and hamster acinar cell suspensions possess the ability to carry out the cytochrome P-450-dependent O-deethylation of 7-ethoxycoumarin, 2-,3-, and 4-hydroxylation of biphenyl and 3-hydroxylation of benzo(a)pyrene. Rat and hamster acinar cells isolated from 5,6-benzoflavone-pretreated animals oxidize all three substrates at

measurable rates. These rates are considerably lower (16-210-fold in the rat and 290-2670-fold in the hamster) than those in incubations using hepatocytes isolated from 5,6-benzoflavone-pretreated animals. Hydroxylation of biphenyl at the 2-, 3-, and 4-positions proceeds at similar rates in rat acinar cells. The rate of 3-hydroxybiphenyl formation is barely detectable in hamster acinar cells where the rates of 2- and 4-hydroxybiphenyl formation are slower than in the rat. No detectable oxidation products of 7-ethoxycoumarin, biphenyl, or benzo(a)pyrene are found with acinar cells of either species isolated from untreated and phenobarbital-pretreated animals. The O-deethylation of 7-ethoxycoumarin in rat and hamster acinar cells is decreased in the presence of inhibitors of the cytochrome P-450-dependent monooxygenase system, 7,8-benzoflavone being much more effective than metyrapone. The deethylation product of 7-ethoxycoumarin, 7-hydroxycoumarin, is conjugated with sulfate and glucuronic acid moieties at appreciable rates by acinar cells isolated from both rat and hamster. Pretreatment of rats and hamsters with either 5,6-benzoflavone or phenobarbital has little effect on the rates of conjugation in isolated acinar cell preparations

Wyndham, C; Safe, S. (1978) A comparison of the in vitro metabolism of biphenyl and 4-chlorobiphenyl by rat liver microsomes. Can J Biochem 56(10):993–997.
The comparative metabolism of the hydrocarbons, biphenyl and 4-chlorobiphenyl, was investigated using two different preparations of rat hepatic microsomes. The assay was designed to account for all the metabolic products which included the ether soluble lipophilic metabolites, low molecular weight conjugates, and macromolecular adducts, and to determine the effects of induction with Aroclor 1254 and 1248, two commercial polychlorinated biphenyl (PCB) preparations. 4-chlorobiphenyl was the more metabolically active substrate with the induced and control enzymes. In most metabolic fractions biphenyl was less inducible by the PCB's, with the exception of the 2-biphenylol metabolite which was induced ca. 18-fold. Preincubation of the microsomes with carcinogens did not enhance biphenyl 2-hydroxylation. Instead, a general inhibition of metabolic activity was observed for both biphenyl and 4-chlorobiphenyl substrates. Preincubation with phenobarbitone, a noncarcinogen, did not change the microsome-mediated metabolism of biphenyl or 4-chlorobiphenyl. The substitution of a single halogen atom on the biphenyl nucleus altered both the reactivity and pattern of metabolites for these substrates

3.4. ELIMINATION

Meyer, T; Aarbakke, J; Scheline, RR. (1976) The metabolism of biphenyl. I. Metabolic disposition of 14C-biphenyl in the rat. Acta Pharmacol Toxicol 39(4):412–418.

Meyer, T; Scheline, RR. (1976) The metabolism of biphenyl. II. Phenolic metabolites in the rat. Acta Pharmacol Toxicol 39(4):419–432.

Meyer, T; Larsen, J; Hansen, EV; et al. (1976) The metabolism of biphenyl. III. Phenolic metabolites in the pig. Acta Pharmacol Toxicol 39(4):433–441.

Meyer, T. (1977) The metabolism of biphenyl: IV. Phenolic metabolites in the guinea pig and the rabbit. Acta Pharmacol Toxicol Suppl 40(2) :193–200.

3.5. PHYSIOLOGICALLY BASED TOXICOKINETIC MODELS

No relevant publications were identified.

4. HAZARD IDENTIFICATION

4.1. STUDIES IN HUMANS—EPIDEMIOLOGY, CASE REPORTS, CLINICAL CONTROLS

Chloracne study conducted on two samples of dowtherm a and one sample of dowtherm g with cover letter dated 061093 (1993) Epa/Ots Doc #86-930000286–930000286

Bardodej, Z; Hladik, F; Rejlkova, V; et al. (1980) Hodnota a pouziti exposicnich testu. XIX. Exposicni test pro bifenyl. [The value and use of exposure tests. XIX. Exposure test for biphenyl.]. Cesk Hyg 25(5): 241-251 .
PESTAB. The exposure test for biphenyl and Dowtherm A-Dinyl is based on fluorimetric determination of 4-hydroxybiphenyl in urine. Urine is hydrolyzed by HCl; 4-hydroxybiphenyl is extracted with n-heptane and with 0.1 NaOH, then determined by measuring fluorescence at 407 nm, at excitation 301 nm. On the basis of medical monitoring of workers exposed to the 2 compounds in Czechoslovak polyester plants, atmospheric levels of 1 mg biphenyl or 4 mg Dowtherm A-Dinyl/m3 air were considered admissible; double these values were maximum permissible concentrations. The biphenyl level corresponds to 2.3 mg 4-hydroxybiphenyl/l urine during the last 4 hr of a worker's shift. Recent findings of elevated SGPT activity in workers exposed to 0.46 mg/m3 Dowtherm indicate that these levels are too high. Increased SGPT activity indicates an impact of the pollutant on the liver parenchyma of exposed individuals. It is recommended that new maximum permissible levels be set

Beretta, E; Zerboni, R; Nava, C. (1988) [Allergic contact dermatitis from rubber. Evidence of group sensitization to p-phenylendiamine derivatives]. Med Lav 79(6):482–488. (Italian).
BIOSIS COPYRIGHT: BIOL ABS. RRM HUMAN MILKING MACHINE BENZENE RING P AMINO GROUP PHENYL RADICAL SUBSTITUTION

Butcher, R; Page, R. (1981) Introductory remarks environmental and endogenous hazards to the female reproductive system. Environ Health Perspect 38:35–38.
HEEP COPYRIGHT: BIOL ABS. PESTICIDE OZONE CARBON MON OXIDE METAL TOXICITY ALCOHOL DRUG TOXICITY RADIATION FETAL PATHOLOGY MUTATION HORMONE LEVEL

Carella, G; Bettolo, P. (1994) Reversible hepatotoxic effects of diphenyl: report of a case and a review of the literature. J Occup Med 36(5):575–576.
A case is reported of chronic persistent hepatitis in a 46-year-old woman poisoned with diphenyl, an aromatic hydrocarbon contained in the paper used to pack citrus fruit, with which this woman was in contact for 25 years. The etiology of the disease is discussed, along with its probable link to simultaneous digestive and cutaneous absorption of the product over many years.

Chuang, J; Wise, S; Cao, S; et al. (1992) Chemical characterization of mutagenic fractions of particles from indoor coal combustion: A study of lung cancer in Xuan Wei, China. Environ Sci Technol 26(5):999–1004.
In the rural Xuan Wei County, Yunnan Province (China) lung cancer mortality rates for women are among the highest in China. Most of these women are nonsmokers, and studies have shown that lung cancer in Xuan Wei is associated with domestic use of smoky coal under unvented conditions. The objective of this study is to determine the chemical constituents that may be linked to the high lung cancer rates in Xuan Wei using the bioassay-directed fractionation method. Ten high-volume filter samples (< 10 mum) collected from the home inhabited by a person with lung cancer during cooking periods on four consecutive days were subjected to Soxhlet extraction. This composite sample extract was fractionated on a normal-phase column into seven fractions. The second fraction was the most active in the bioasasay, containing mainly polycyclic aromatic hydrocarbon (PAH) and alkylated PAH. The two polar fractions 6 and 7 were the next most active. The most active PAH fraction was furth

Dorgelo, FO; Verver, G; Wieling, G; et al. (1985) Urinary hydroxydiphenyl excretion of workers occupationally exposed to a mixture of diphenyl and diphenylether (Dowtherm A). Int Arch Occup Environ Health 56(2):129–134.
BIOSIS COPYRIGHT: BIOL ABS. RRM HUMAN NYLON WORKER BIOMONITORING CHEMICAL INDUSTRY HAZARDOUS OCCUPATION HAZARDOUS MATERIALS

Ferrario, JB; Deleon, IR; Tracy, RE. (1985) Evidence for toxic anthropogenic chemicals in human thrombogenic coronary plaques. Arch Environ Contam Toxicol 14(5):529–534.
BIOSIS COPYRIGHT: BIOL ABS. RRM HEART ATTACK ARTERIOSCLEROSIS PESTICIDE POLLUTANT CHOLESTEROL LIPID GAS CHROMATOGRAPHY MASS SPECTROMETRY

Fondu, M. (1992) Food additives intake. Food Addit Contam 9(5):535–539.
BIOSIS COPYRIGHT: BIOL ABS. RRM HUMAN FOOD PRODUCTS FOOD PRESERVATIVES FOOD SAFETY DIET NUTRITION

GINCHEVA, NA. (1971) (Occupational hygiene in attending modern equipment used in forming lavsan fibers.). Gig Tr Prof Zabol 15(9)–36.
HEEP COPYRIGHT: BIOL ABS. Working conditions in the lavsan fiber industry were studied. All machines released a mixutre of vapor, gas and aerosol into the atmosphere of working premises. It was composed of the primary raw material, (terephthalic dimethylated) a side-product of synthesis (methanol) and products of the thermal polymer destruction (acetaldehyde, carbon monoxide and terephthalic acid). The release of the products subsequent to thermal destruction of the polyethyleneterephthalate polymer into the air at work places was determined by the amount of the supplied case and the unit surface area. The use of dinyl for heating 2 types of machines is considered less hygienic than electric heating, since the former releases into the air highly toxic dinyl. The design features of the equipment determine the periods the worker remains within the zone of the noxious chemical substance and the amount of physical stress in attending the machines

Hakkola, J; Pelkonen, O; Pasanen, M; et al. (1998) Xenobiotic-metabolizing cytochrome p450 enzymes in the human feto-placental unit: role in intrauterine toxicity. Crit Rev Toxicol 28(1):35–72.
BIOSIS COPYRIGHT: BIOL ABS. RRM LITERATURE REVIEW HUMAN TOXICOLOGY INTRAUTERINE TOXICITY CYTOCHROME P450 ENZYMES XENOBIOTIC-METABOLIZING FETO-PLACENTAL UNIT ENZYMOLOGY ROLE EMBRYONIC STRUCTURE

Häkkinen, I; Vikkula, E; Hernberg, S. (1971) The clinical picture of diphenyl poisoning. Scand J Clin Lab Invest Suppl 27(116).
HEEP COPYRIGHT: BIOL ABS. ABSTRACT HUMAN PAPER MILL WORKERS LIVER BRAIN FUNGICIDE

Häkkinen, I; Siltanen, E; Hernberg, S; et al. (1973) Diphenyl poisoning in fruit paper production: a new health hazard. Arch Environ Health 26(2):70–74

Hanada, S. (1976) The dietary habits of the Japanese and antifungal treatment of citrus fruits with biphenyl and o-phenylphenol. Eiyo To Shokuryo (Food Nutr) 29(1): 67-68 1976.
PESTAB. It was found that biphenyl, administered to rats, is transformed to o-phenylphenol. o-Phenylphenol (OPP) showed strong antimicrobial activity and had a slightly greater acute oral toxicity, as indicated by an LD50 of 2.7 g/kg. The use of o-phenylphenol as an antiseptic for citrus fruits was considered unsuitable according to the toxicity findings and Japanese dietary habits. OPP showed positive mutagenicity in Salmonella and Escherichia coli as contrasted with biphenyl. Daily painting of an acetone solution containing 5-10 mg produced reddening and ulcer-like symptoms on the backs of rats and the ears of rabbits by the third day. Inhalation of OPP killed some mice by alveolar congestion. OPP penetrated into the peel and pulp of Satsuma orange fruits, and it was not removed by washing with synthetic detergent. The use of o-phenylphenol on citrus fruit in Japan seems inadvisable because of the large quantities of fresh citrus fruit consumed by the Japanese

Hoering, H; Dobberkau, H-J; Seffner, W. (1988) Antithyroid environmental chemicals. Z Gesamte Hyg Grenzgeb 34(3):170–173.
BIOSIS COPYRIGHT: BIOL ABS. RRM HUMAN NITRATES DRINKING WATER DISINFECTANTS IODINE DEFICIENCY GOITER

Ishiwata, H; Nishijima, M; Fukasawa, Y; et al. (1997) Evaluation of the contents of antifungal agents allowed as food additives in foods and the daily intake deduced from the results of the official inspection in Japan in fiscal year 1994. Journal of the Food Hygienic Society of Japan 38(5):296–306.
BIOSIS COPYRIGHT: BIOL ABS. The concentrations of antifungal agents permitted as food additives (diphenyl, imazalil, o-phenylphenol and thiabendazole) in foods sold in Japan were estimated using the results of the official inspection in fiscal year 1994 by 74 local governments. The total number of inspection samples was 6,633 including 289 domestic foods. The detection rates of diphenyl, imazalil, o-phenylphenol and thiabendazole in foods in which the use of these antifungal agents is permitted were 2.7%, 41.5%, 29.1% and 47.0%, respectively. The mean concentrations of these antifungal agents in the whole body of citrus fruits in all tested samples in which their use is permitted were 0.3%, 12.2%, 3.9% and 9.5% of the legal maxima, respectively. Imazalil in the whole body of bananas was 0.2% of the limit, and thiabendazole in the whole banana and banana flesh was 0.2% and 0.5% of each limit, respectively. Some antifungal agents were detected in some processed foods in the category of marmalade and

Kapustina, AN; Primakov, FD. (1983) [2 cases of acute dinil poisoning]. Gig Tr Prof Zabol. 1983, Mar(3):50-1. [Gigiena truda i professional'nye zabolevaniia].

Kauppinen, T; Teschke, K; Savela, A; et al. (1997) International data base of exposure measurements in the pulp, paper and paper product industries. Int Arch Occup Environ Health 70:119–127.
An international data base of exposure measurements in the pulp, paper and paper products industries to be used in exposure assessment for epidemiology studies and hazard control was developed. The structure and contents of the data base, the validity of the measurements made and reports of the occurrence of high levels of exposure exceeding current occupational exposure limits in the industries studied were presented. By August of 1996 there were 31,502 measurements from 13 countries in the data base. The majority of samples were taken from static measuring points. Personal samples from the breathing zone of workers were also common, but biological monitoring was rare. The degree to which the measurements were likely to represent 8 hour time weighted averages was assessed by industrial hygienists or other assessors in each country except three. Altogether 246 different agents were measured. In paper and paperboard manufacturing the commonly measured exposure agents were dust (643 measurements), formaldehyde (50000) (611 measurements), diphenyl (92524) (319 measurements), and ammonia (7664417) (158 measurements). The occupational exposure limit of organic dust was frequently exceeded in soft paper mills. High concentrations of formaldehyde and perchloroethylene may occur in the calandering area and in on-machine coating of paper. Ammonia (7664417) exposure may exceed limits in the stock preparation and on machine coating areas of special paper mills. Agents most often measured in non production departments were hydrogen-sulfide (7783064), dimethylsulfide (75183), methyl-mercaptan (74931), dust, carbon-monoxide (630080), dimethyldisulfide, and chlorine (7782505). Asbestos (1332214) was also frequently encountered. The authors note that their data base summarizes a great deal of previously unpublished exposure data and provides an opportunity to study exposure patterns at the international level

Kosmider, K; Sawinski, J; Soroka, M; et al. (1981) [Evaluation of the circulatory system in workers exposed to caprolactam and diphenyl in 1 of the chemical plants producing polyamine fibers]. Med Pr 32(6): 417–421.
The literature data indicating nonspecific pathologic symptoms of the circulatory system in those occupationally exposed to caprolactam and diphenyl inspired the authors to evaluate the circulatory system in a group of 495 workers of a Chemical Plant producing polyamide fibres. The anamnestic data, family inquiry and subjective changes indicate that any hints of the significant effects of the technological process on circulatory diseases in this professional group are unwarranted. The percentage values of the latent circulatory failure (1-2% of subjects), coronary insufficiency (6.6% of subjects), arterial hypertension (5.7% of subjects) did not show any significant differences, as compared to the control group and normal Polish population. The obtained results of ECG test evaluated according to the Minnesota-Code criterion did not significantly differ from 100 controls composed of those in whom no changes in the circulatory system were found, whereas clear differences were found related to 50 persons with documented heart ischemia

Pacific Northwest Lab. (1979) Appendix to biomedical studies on solvent refined coal (Src-2) liquefaction materials; a status report. Submitted under TSCA Section 8E; EPA Document No. 88-8000297; NTIS No. OTS0200639.

Pacific Northwest Lab. (1979) Biomedical studies on solvent refined coal (Src-2) liquefaction materials: a status report. Submitted under TSCA Section 8E; EPA Document No. 88-7900297; NTIS No. OTS0200639.

PETROV, NV. (1975) The Health of Women Workers in the Man-Made Fibers Industry Based on the Findings of Medical Examinations. Vrachebnoe Delo 10,(Department of Occupational Hygiene and Organization of Public Health)):145–148.
The effects of exposure to carbon-disulfide (75150), caprolactam (105602), and Dinyl (8004135) were studied in 3,624 female workers in the synthetic fiber industry in the Soviet Union. All workers received in depth medical examinations and were divided into three groups. The first group of 2113 workers was comprised of chemical and spinning workers engaged in viscose manufacture and were primarily exposed to carbon-disulfide. The second group of 492 women was composed of chemical and spinning workers engaged in nylon manufacture with primary exposure to caprolactam and Dinyl. The third group of 1,019 women consisted of workers without any chemical exposure. Of the total number of subjects examined, 574 had various health problems with 373 of them in the first group, 85 in the second, and 116 in the third. The frequency of health disorders among all workers increased with age and length of service. Neurological disorders accounted for the majority of health problems in the first and second groups. Most of these disorders were composed of neuroses, vegetovascular dystonia and asthenovegatative syndrome, and diseases of the peripheral nervous system. The second most frequent health disorder among the first and second group of workers were diseases of the urogenital organs, chiefly inflammation of the uterus and appendix. Inflammatory diseases were observed with roughly the same frequency in each of the groups. Respiratory

diseases accounted for the third most frequent medical disorder among workers of the first and third group. Diseases of the digestive organs were observed most often among workers of the third group. An increase in the frequency of diseases of the liver and biliary ducts with length of service was identified in workers of the first group. No correlation between length of service and exposure groups and incidence of circulatory disease was noted. The authors conclude that an etiological link between certain pathological conditions among workers in the synthetic fiber industry and specific hygienic features of the work place does exist. (Russian)

RODIONOV, IS. (1973) Effect of chemical factors in the manufacture of synthetic lavsan fibers on the health status of workers. Gig Tr Prof Zabol 17(2)–4.
HEEP COPYRIGHT: BIOL ABS. Of workers engaged in the manufacture of synthetic lavsan fiber, 850 had single medical examinations and 58 had dynamic examinations. They were exposed to the effect of the dimethyl ether of terephthalic acid (DMT), ethylene glycol, methanol and dinyl. Workers of the spinning department dealing with methanol, dinyl and products of the thermal destruction of resin (polyethylene-terephthalate) and workers in the rectification department dealing with methanol and ethylene glycol had a tendency toward increased arterial tension. Moderate anemia, reticulocytosis, a tendency toward a decrease in the number of thrombocytes, leukocytes, rod-nuclear and segment-nuclear neutrophils, and lymphocytosis were seen on the level of peripheral blood. Changes in liver function consisted of a moderate drop of albumins and modification of glubulin fractions

Seppalainen, AM; Hakkinen, I. (1975) Electrophysiological findings in diphenyl poisoning. J Neurol Neurosurg Psychiat 38(3):248–252.
PESTAB. The fungistatic agent diphenyl (biphenyl) caused fatal poisoning with signs of neurotoxicity in a worker in a Finnish paper mill. This initiated a neurophysiological study of 24 workers (1 woman and 23 men) occupationally exposed to diphenyl. Ten men showed EEG abnormalities which, while non-specific, were compatible with generalized cerebral disturbance. The abnormalities persisted on re-examination 1 and 2 yr later. Nine subjects had EMG abnormalities; 7 also exhibited fibrillations in some muscles. One subject showed a long rhythmic series of fasciculations similar to the spontaneous activity described in infantile spinal muscular atrophy. Nerve conduction velocity, especially that of slower motor fibers, was reduced in several cases. Electroneuromyographic abnormalities also persisted on re-examination. Although diphenyl is considered a comparatively safe chemical, it showed evidence of neurotoxicity when workers were exposed to concentrations in excess of the presently accepted threshold limit of 1 mg/m3. The average concentrations measured in the air at various work places varied from 0.6 to 123.0 mg/m3. Electrophysiological methods should be applied for the early detection of occupational hazards

Sliwinska-Przyjemska, H; Pilawska, H. (1981) [Liver cell function test based on selective laboratory studies]. Med Pr 32(3):187-94. [Medycyna pracy])–94.
Laboratory tests have been carried out in 517 workers of a Chemical Fibres Plant. This was aimed at the detection of the changes resulting from cumulative exposure to caprolactam, dowtherm and physical factors. There have been performed hematological investigations, uninalyses and biochemical tests: total protein level, activity of enzymes: ASPAT, ALAT, PA, ChE, thymol test. The results have been analysed as the mean values for particular divisions and workstands; then they have been compared with standards. In order to evaluate the degree of occupational exposure of particular groups of workers, an index of the liver cell damage has been calculated. It was expressed in % of the results exceeding the standards in relation to all results in a given group of workers. The highest values of the index were those in the group employed at the polymerization division. The authoresses promote the advisability of special care for this group of workers

Swanson, M; Davis, G; Kincaid, L; et al. (1997) A screening method for ranking and scoring chemicals by potential human health and environmental impacts. Environ Toxicol Chem 16(2):372–383.
BIOSIS COPYRIGHT: BIOL ABS. Potential impacts of chemical releases are often evaluated by regulators, industry, and others to set regulatory action priorities, to make business decisions, and to target pollution prevention efforts. A chemical ranking and scoring method entitled "Chemical Hazard Evaluation for Management Strategies" (CHEMS-1) has been developed as a screening tool to provide a relative assessment of chemical hazards to human health and the environment. The purpose of this method is to place chemical release data into perspective by evaluating both the toxic effects of chemicals and the potential exposure to those chemicals. This is done by combining measures of chemical toxicity pertaining to both human health and the environment with chemical release amounts and information on environmental persistence and bioaccumulation. The CHEMS-1 was initially developed to select priority chemicals for assessing safer substitutes for major product and process uses, where chemicals were select

Van Doorn, R; Leijdekkers, C; Bos, RP; et al. (1981) Detection of human exposure to electrophilic compounds by assay of thioether detoxication products in urine. Ann Occup Hyg 24(1):77–92.
HEEP COPYRIGHT: BIOL ABS. The possibilities of thioether or mercapturic acid assay for detection of human exposure to electrophilic agents or their precursors were reviewed. Thioether assay was based on the ability of many alkylating or covalently binding compounds (a class of chemicals that included the genotoxic compounds) to react with glutathione. Often glutathione conjugates formed in this reaction were excreted in urine as (pre)mercapturic acids or other thioethers. Thioethers can be determined spectrophotometrically after alkaline hydrolysis of urine extracts. In practice the most important value of the assay was its signal function. Whenever a significant increase in the excretion of thioethers was observed, it was likely to be the result of exposure to 1 or more suspect compounds. When unknown electrophiles or a mixture of such compounds were involved , no quantitative conclusions were drawn with regard to internal exposure. When thioether values were found, ranging within the limits of the normal distribution, it could not be concluded that no or negligible exposures occurred

Wastensson, G; Hagberg, S; Andersson, E; et al. (2006) Parkinson's disease in diphenyl-exposed workers--a causal association? Parkinsonism Relat Disord 12(1):29–34.
We report a cluster of five cases of Parkinson's disease (PD) among paper mill workers exposed to a fungicide, diphenyl. The cause of PD is still unknown, but epidemiological studies have indicated an elevated risk of developing PD after exposure to pesticides. The five cases of PD were found in a group of 255 diphenyl-exposed workers, and the number of expected cases in the exposed group was estimated to be 0.9, resulting in a relative risk of 5.6 (95% CI 1.8-13). Exposure to diphenyl may have contributed to this PD cluster, but chance is an alternative explanation

Weil, E; Kusterer, L; Brogard, MH. (1965) [Intolerance to an antifungal product used for the impregnation of wrapping paper for citrus fruits]. Arch Mal Prof 26(7):405–408

4.2. LESS-THAN-LIFETIME AND CHRONIC STUDIES AND CANCER BIOASSAYS IN ANIMALS—ORAL AND INHALATION

Chemical listing subject to submission & a 3-month study of therminol vp-1 administered to male & female sprague-dawley rats by inhalation (Final report) W-attach & letter 060889 (1989) Epa/Ots Doc #86-890000353–890000353

Initial submission: Acute toxicity of therminol vp-1 administered by inhalation to sprague-dawley male and female rats with cover letter dated 080592 (1992) Epa/Ots Doc #88-920009870–920009870

Ambrose, A; Booth, A; Deeds, F; et al. (1961) A toxicological study of biphenyl, a citrus fungistat. Food Res 25:328–336

Boutwell, R; Bosch, D. (1959) The tumor-promoting action of phenol and related compounds for mouse skin. Cancer Res 19(4):413–424

BRL (Bionetics Research Labs Inc.). (1968) Evaluation of carcinogenic, teratogenic and mutagenic activities of selected pesticides and industrial chemicals. Vol. I. Carcinogenic study. Available from the National Technical Information Service, Springfield, VA; NTIS PB-223159.

Cannon Labs Inc. (1977) Subacute inhalation toxicity of biphenyl. Submitted under TSCA Section 8D; EPA Document No. 878213531; NTIS No. OTS0206401.
Subchronic toxicity was evaluated in groups of 10 male and 10 female mice (strain not reported) exposed to biphenyl at measured vapor concentrations of 24.8 and 54.75 ppm 7 hrs/day, 5 days/week for 2 weeks. Mortality was observed in one female from the 24.8 ppm dose group. Clinical observations included hyperactivity and closed eyes in both dose groups, while hyperemia was observed in the 54.75 ppm dose group only. Microscopic evaluation of lungs, trachea, liver, kidneys and spleen did not reveal any evidence of test article induced histopathology at either dose level; however, this evaluation was not discussed in depth by the inv
estigators

Cannon Labs Inc. (1977) 90-Day inhalation toxicity study of biphenyl (99+ % purity) in CD, mice. Submitted under TSCA Section 8D; EPA Document No. 878213532; NTIS No. OTS0206401.

Cannon Labs Inc. (1977) Initial submission: 90-day inhalation toxicity study of biphenyl (99 + % purity) in CD1 mice (final report) with cover letter dated 022892. Submitted under TSCA Section 8ECP; EPA Document No. 88-920001856; NTIS No. OTS0539116.

Cannon Labs Inc. (1977) Acute inhalation toxicity of biphenyl with cover letter. Submitted under TSCA Section 8D; EPA Document No. 878213530; NTIS No. OTS0206401.
Acute inhalation toxicity was evaluated in groups of 20 mice (10 male and 10 female, strain not reported) exposed to biphenyl vapor at measured concentrations of 14.0, 38, or 42.0 ppm for 4 hours. Mortality observed in one animal in the 43.0 ppm dose group was not considered to be dose related. Clinical observations included hyperactivity and mild respiratory discomfort during exposure; these effects were not evident at the end of the 14-day recovery period. Gross necropsy of surviving animals at 14 days revealed slight lung congestion

Deichman, WB; Kitzmiller, K; Dierker, M; et al. (1947) Observations on the effects of diphenyl, o- and p-aminodiphenyl, o- and p-nitrodiphenyl and dihydroxyoctachlorodiphenyl upon experimental animals. J Ind Hyg Toxicol 29:1–13

Dow Biochem Res. (1939) Toxicity of diphenyl. Submitted under TSCA Section 8D; EPA Document No. 878213739; NTIS No. OTS0206456.

Dow Chem Co. (1939) Toxicity of diphenyl and diphenyl oxide (sanitized). Submitted under TSCA Section 8D; EPA Document No. 86-890001205S; NTIS No. OTS0520717.
A summary of toxicity tests of diphenyl indicate it is 100% lethal at acute doses of 3 g/kg bw in rats, and repeated doses (20) of 0.1 g/kg was not toxic to the rabbit. A single dermal application of 5% solutions in 95% ethanol and olive oil caused no irritation to rabbit ears and repeated applications (20) to the abdomen caused only a slight reaction. Diphenyl oxide caused 100% lethality to cavies and rats at acute doses of 4.0 g/kg bw. Single dermal application of undiluted diphenyl oxide to rabbit ears produced a slight reaction, while neither 20% nor 5% solutions in olive oil caused irritation. Repeated (20) applications
of the 20% and 5% olive oil solutions produced a slight reaction. Six applications of undiluted material produced a moderate reaction which healed quickly when treatment was discontinued. One abdominal application of undiluted material produced a moderate reaction, while a minimum of 9 applications of the 20% solution and 14 of the 5% solution caused similar reactions

Dow Tox Res Lab. (1974) Acute inhalation toxicity and industrial handling hazards of biphenyl heated to 85 degrees celsius. Submitted under TSCA Section 8D; EPA Document No. 878213725; NTIS No. OTS0206456.
Acute inhalation toxicity was evaluated in 4 female Sprague-Dawley rats exposed to biphenyl at a nominal concentration of 3.02 mg/l for 7 hours. The atmosphere was generated by passing air through a bubbler containing biphenyl maintained at 85 deg. C. Treatment related alterations in appearance, demeanor, food consumption or survival were not observed in any animal

Dow Tox Res Lab. (1983) Acute oral lethality, percutaneous absorption and inhalation toxicity of biphenyl 99. Submitted under TSCA Section 8D; EPA Document No. 878213747; NTIS No. OTS0206456.

Grabecki, J; Haduch, T. (1968) [The influence of Dowtherm A on some hematologic and biochemical parameters in rats]. Int Arch Arbeitsmed 24(4):350-8.)–8

Hanada, S. (1976) The dietary habits of the Japanese and antifungal treatment of citrus fruits with biphenyl and o-phenylphenol. Eiyo To Shokuryo (Food Nutr) 29(1): 67-68 1976.
PESTAB. It was found that biphenyl, administered to rats, is transformed to o-phenylphenol. o-Phenylphenol (OPP) showed strong antimicrobial activity and had a slightly greater acute oral toxicity, as indicated by an LD50 of 2.7 g/kg. The use of o-phenylphenol as an antiseptic for citrus fruits was considered unsuitable according to the toxicity findings and Japanese dietary habits. OPP showed positive mutagenicity in Salmonella and Escherichia coli as contrasted with biphenyl. Daily painting of an acetone solution containing 5-10 mg produced reddening and ulcer-like symptoms on the backs of rats and the ears of rabbits by the third day. Inhalation of OPP killed some mice by alveolar congestion. OPP penetrated into the peel and pulp of Satsuma orange fruits, and it was not removed by washing with synthetic detergent. The use of o-phenylphenol on citrus fruit in Japan seems inadvisable because of the large quantities of fresh citrus fruit consumed by the Japanese

Hanada, S. (1977) Studies on food additives, diphenyl (biphenyl) and O-phenyl phenol from the view point of public health. Part 2. On the toxicities of diphenyl and O-phenyl phenol. Nagoya Shiritsu Daigaku Igakkai Zasshi (J Nagoya City Univ Med Sch) 28(3): 983-995 .
PESTAB. Although not registered as pesticides for agricultural use, biphenyl and o-phenyl phenol are used for preventing molds on citrus fruits in fields, cargo booking stations, storage, transportation and selling market. The present studies were carried out to find their effects on humans. Tests conducted include: (1) inhalation by animals, (2) dermal sensitivity and (3) chromosomal reactions. Inhalation of o-phenyl phenol led to sub-lethal damage to mice and severe and fatal pulmonary damage to rats. O-Phenyl phenol caused severe dermal damage when painted on rabbit's auricles but biphenyl resulted in localized swellings on the skin of rats and rabbit. Rec-assay using a DNA-repair strain of Bacillus subtilis and E. coli indicated mutagenicity by o-phenyl phenol and the same phenomenon was confirmed by a strain TA 1536 of Salmonella typhimurium

Hasegawa, R; Nakaji, Y; Kurokawa, Y; et al. (1989) Acute toxicity tests on 113 environmental chemicals. Sci Rep Res Inst Tohoku Univ Ser C Med 36(1-4):10–16.
BIOSIS COPYRIGHT: BIOL ABS. Acute toxicity tests on 113 environmental chemicals were conducted by the order of the Japanese government agencies. The LD50S or LC50S for 23 household chemicals, 11 medical drugs, 10 drug additives, 20 food additives, 13 industrial chemicals, 14 environmental pollutants, 12 agricultural chemicals and 5 organic solvents are presented together with the major toxic signs and symptoms and macroscopic changes in tissues. These toxicity data will be useful as an information source for regulatory purposes and also for prediction of the potential for acute toxicity of a wide variety of new chemicals

Hazleton Labs. (1956) Chronic oral administration metabolic studies on dogs. Submitted under TSCA Section 8D; EPA Document No. 878213568; NTIS No. OTS0206411.

Innes, JR; Ulland, BM; Valerio, MG; et al. (1969) Bioassay of pesticides and industrial chemicals for tumorigenicity in mice: a preliminary note. J Natl Cancer Inst 42(6):1101–1114

JBRC (Japan Bioassay Research Center). (1996) Two year feeding study of biphenyl in rats and mice. Tokyo, National Institute of Health Sciences (unpublished report). (this was published in 2002 and 2005 by Umeda et al.)

Mellon Inst. (1949) Range finding tests on diphenyl tables of protocols attached with cover letter. Submitted under TSCA Section 8D; EPA Document No. 878213680; NTIS No. OTS0206426.

Mellon Inst. (1961) Range finding tests on diphenyl, refined. Submitted under TSCA Section 8D; EPA Document No. 878213681; NTIS No. OTS0206426.

Monsanto Co. (1986) Initial submission: acute toxicity of therminol vp-1 administered by inhalation to Sprague-Dawley male and female rats with cover letter dated 080592. Submitted under TSCA Section 8ECP; EPA Document No. 88-920009870; NTIS No. OTS0571522.

Newell, G. (1953) A toxicological study of diphenyl in citrus wraps. (Stanford Research Institute Report No. B 326) [cited in Monsanto Co. (1996) Toxicological data on biphenyl]. (Probably identical with: Stanford Research Institute (undated) Final report -- a toxicological study of diphenyl in citrus wraps. Menlo Park, CA [cited in US EPA (1984) Health and environmental effects profile for 1,1'-biphenyl. Cincinnati, OH, US Environmental Protection Agency].).

Pagano, G; Cipollaro, M; Corsale, G; et al. (1988) Comparative toxicity of diphenyl, diphenyl ester, and some of their hydroxy derivatives. Medicine Biologie Environnement 16:291–297

PECCHIAI, L; SAFFIOTTI, U. (1957) [Study of the toxicity of biphenyl, oxydiphenyl and their mixture (Dowtherm).]. Med Lav 48(4):247-54. [La Medicina del lavoro])–54

SRI (Stanford Research Institute). (1953) Toxicological study of diphenyl in citrus wraps with cover letter. Submitted under TSCA Section 8D. EPA Document No. 878213721; NTIS No. OTS0206456 (or could also be OTS84003A according to IRIS record citation, but this number does not appear in a search of Biphenyl in the TSCATS database).

Umeda, Y; Aiso, S; Yamazaki, K; et al. (2005) Carcinogenicity of biphenyl in mice by two years feeding. J Vet Med Sci 67(4):417–424.
Carcinogenicity and chronic toxicity of biphenyl was examined in the male and female BDF1 mice fed a diet containing biphenyl at 667, 2,000 or 6,000 ppm for 2 years. There was no difference in survival rate between any biphenyl-containing diet-fed group of either sex and the respective control. Body weights of the males and females fed 6,000 ppm diet were significantly lower than the respective control. Incidences of hepatocellular carcinomas and hepatocellular adenomas in the females fed diets containing biphenyl were significantly increased in a dose-related manner, and exceeded a range of the historical control data in the Japan Bioassay Research Center. Incidences of basophilic cell foci in the liver were increased in the females fed 2,000 and 6,000 ppm diets. There was no increase in tumor or tumor-related lesion in the males fed diets containing biphenyl. Chronic toxicity of biphenyl was characterized by increased incidences of urothelial desquamation in the renal pelvis in males and females and mineralization in the inner stripe of renal outer medulla in females, as well as changes in serum levels of BUN, ALP and some electrolytes in males and females. In conclusion, the 2-year oral administration of biphenyl-containing diets induced pre-neoplastic and neoplastic lesions in the liver of females and non-neoplastic lesions in the kidney of males and females. Causative factors for the biphenyl-induced hepatocarcinogenicity were discussed in light of our published finding of peroxisome proliferation

Umeda, Y; Arito, H; Kano, H; et al. (2002) Two-year study of carcinogenicity and chronic toxicity of biphenyl in rats. J Occup Health 44(3):176–183.
Carcinogenicity and chronic toxicity of biphenyl were examined in 50 male and 50 female F344 rats exposed to 0, 500, 1,500 or 4,500 ppm biphenyl in the diet for 105 weeks. Bladder tumors were found in the 4,500 ppm males, as evidenced by significantly increased incidence of carcinoma (24/50) and papilloma (10/50) of the transitional cells as well as one rarely observed case both of carcinoma and papilloma of the squamous cells. The survival rate of the 4500 ppm males significantly decreased, due to the bladder tumors and the hematuria accompanied by bladder calculi. The bladder calculi were found in 43 males in the 4,500 ppm group, but in only 8 females. Urinary pH significantly increased in the males, and occult blood was observed both in males and females in the 4,500 ppm group. The pre-neoplastic lesions were hyperplasia of transitional epithelium (simple, nodular and papillary hyperplasia) in the bladder of the 4,500 ppm males. Incidences of calculus formation and transitional cell hyperplasia in the renal pelvis also significantly increased in the 4,500 ppm males and females. On the other hand, the incidences of the transitional cell hyperplasia and the calculus formation in the bladder and the renal pelvis were far lower in females than in males, and no bladder tumors were observed in the females. Causative factors of the bladder tumors and their male predominance were discussed with reference to the findings reported in the literature and the previous study of biphenyl metabolism

Union Carbide. (1982) Acute toxicity and primary irritancy studies peroral, single dose to rats percutaneous, single dose to rabbits inhalation, single exposure to rats skin irritation, rabbits. Submitted under TSCA Section 8D; EPA Document No. 878213653; NTIS No. OTS0206434.

University of Cincinnati. (1946) Final report on the physiological response of experimental animals to the absorption of diphenyl, and several resins, elastomers and plastics with cover letter (sanitized). Submitted under TSCA Section 8D; EPA Document No. 878213563; NTIS No. OTS0206411.

Younger Labs. (1959) Animal inhalation study on biphenyl at 80 degrees f. And 100 degrees f. Submitted under TSCA Section ; EPA Document No. 878213571; NTIS No. OTS0206411.
Acute inhalation toxicity was evaluated in 6 Sprague-Dawley albino rats (sex not reported) exposed to biphenyl at concentrations of 0.8 or 3.0 ppm for 6 hours. The test concentrations were generated by heating petri dishes containing biphenyl to 80 deg. F. (0.8 ppm) or 100 deg. F. (3.0 ppm) in the exposure chamber using light bulbs. No mortality was observed in any animal, and the behavior and appearance of animals during the test was reported to be normal

Younger Labs. (1976) Toxicological investigation of biphenyl. Submitted under TSCA Section 8D; EPA Document No. 878213572; NTIS No. OTS0206411.

Younger Labs Inc. (1973) Initial submission: toxicological investigation of: Mcs 1572 with cover letter dated 081392. Submitted under TSCA Section 8D; EPA Document No. 88-920008114; NTIS No. OTS0546109.

Zablotny, CL; Breslin, WJ; Kociba, R. (1992) Developmental toxicity of ortho-phenylphenol (OPP) in New Zeland White rabbits. Toxicologist 12(1):103.

Orthophenylphenol (OPP) is a broad spectrum antimicrobial used in disinfectants. The purpose of this study was to evaluate the maternal and developmental toxicity of OPP in rabbits following repeated oral exposure. Groups of 16-24 artificially inseminated adult female New Zealand White rabbits were administered OPP in corn oil via oral gavage on days 7-19 of gestation at targeted dose levels of 0, 25, 100 or 250 mg/kg/day. Dams given 250 mg/kg/day had increased mortality (13%), gross pathologic alterations of the gastrointestinal tract and histopathologic alterations of the kidneys. No significant maternal effects were observed at 25 or 100 mg/kg/day of OPP and no adverse embryonal/fetal effects were observed at any dose level tested. Therefore, the no-observed-effect-level (NOEL) for maternal toxicity was 100 mg/kg/day; the embryonal/fetal NOEL was 250 mg/kg/day, the highest dose level tested

4.3. REPRODUCTIVE/DEVELOPMENTAL STUDIES—ORAL AND INHALATION

Chemical listing subject to submission & a developmental toxicity study in rats with therminol vp-1 heat transfer fluid (Final report) With attachments & cover letter dated 060889 (1989) Epa/Ots Doc #86-890000352–890000352

Testicular effects following subacute dermal application of silicone fluids with attachments and cover letter dated 060889 (1989) Epa/Ots Doc #86-890000427–890000427

Biodynamics Inc. (1987) Developmental toxicity study in rats with therminol vp-1 heat transfer fluid with cover letter dated 011388. Submitted under TSCA Section 8D; EPA Document No. 86-880000112; NTIS No. OTS0514002.

Butcher, R; Page, R. (1981) Introductory remarks environmental and endogenous hazards to the female reproductive system. Environ Health Perspect 38:35–38.
HEEP COPYRIGHT: BIOL ABS. PESTICIDE OZONE CARBON MON OXIDE METAL TOXICITY ALCOHOL DRUG TOXICITY RADIATION FETAL PATHOLOGY MUTATION HORMONE LEVEL

Gombar, V; Borgstedt, H; Enslein, K; et al. (1991) A QSAR model of teratogenesis. Quant Struct-Act Relat 10(4):306–332.
BIOSIS COPYRIGHT: BIOL ABS. Four related QSAR models of teratogenesis in experimental animals have been developed one each for heteroaromatic, carboaromatic, alicyclic and acyclic compounds. The numbers of compounds in these models range from 40 (for the alicyclic model) to 144 (for the carboaromatic model). As determined by cross-validation using the leave-one-out, or jackknife, technique, the accuracy of the models in discriminating between teratogens and non-teratogens ranges from 92.4% to 96%. A single overall assessment of experimental teratogenesis was chosen as the biological endpoint; taking into account such factors as dosage, maternal toxicity, and affected organ systems remain to be subjects of further studies

Hakkola, J; Pelkonen, O; Pasanen, M; et al. (1998) Xenobiotic-metabolizing cytochrome p450 enzymes in the human feto-placental unit: role in intrauterine toxicity. Crit Rev Toxicol 28(1):35–72.

Khera, KS; Whalen, C; Trivett, G; et al. (1979) Assessment of the teratogenic potential of biphenyl, ethoxyquin, piperonyl butoxide, diuron, thiabendazole, phosalone, and lindane in rats. Toxicol Appl Pharmacol 48(1):A33.
PESTAB. There are a number of pesticidal agents to which human exposure is highly likely and whose teratological potential remains to be determined. From these the following were investigated at the given doses; biphenyl (99.9%), ethoxyquin (unknown purity), piperonyl butoxide (80%), Karmex (80% diuron) or Mertect (45% thiabendazole) at 0, 125, 250 or 500 mg/kg; and Benesan (50% lindane) at 0, 6.25, 12.5 or 25 mg/kg. These doses were given orally by intubation as single daily administrations to rats from the sixth to the 15th day of pregnancy. The rats were necropsied at term. Fetuses were examined to obtain values on body weight, survival, intrauterine deaths and anomlies (external, visceral and skeletal) by using standard methods. Diuron was found to be associated with an increased incidence of wavy rib anomaly at the 250 mg/kg, and at the maternally toxic dose of 500 mg/kg. Otherwise, in all the remaining test groups, no adverse effects were observed on fetal development.

Khera, KS; Whalen, C; Angers, G; et al. (1979) Assessment of the teratogenic potential of piperonyl butoxide, biphenyl, and phosalone in the rat. Toxicol Appl Pharmacol 47(2):353–358.
PESTAB. Technical grades of piperonyl butoxide and biphenyl, and a formulation of phosalone containing 30% (w/w) phosalone, were administered by esophageal intubation to rats on days 6-15 of gestation. Dams were killed on day 22 of gestation and fetuses were evaluated by routine teratologic methods. Test doses ranging from 62.5 to 500

mg/kg for piperonyl butoxide, 12.5 to 50 mg/kg for the phosalone formation, and 125 to 50 mg/kg for biphenyl, elicited neither teratogenicity nor any adverse maternal effects. Biphenyl, at a dose level of 1000 mg/kg, elicited fetal and maternal toxicity. (Author abstract by permission)

KURZEL, RB; CETRULO, CL. (1985) Chemical teratogenesis and reproductive failure. Obstet Gynecol Surv 40:397-424.

Macina, OT; Sussman, NB; Grant, SG; et al. (2000) Computational evaluation of hazardous air pollutants for developmental toxicity using a structure activity approach. Toxicologist 54(1):298.
Birth defects cause significant infant mortality and morbidity, resulting in great emotional and economic burden in the United States as well as in the rest of the world. In the United States alone, during 1993, developmental abnormalities were the underlying cause of death for 21.3% of infants less than one year of age. There is concern that exposure to air pollutants may effect the integrity of human health within industrialized countries. The United States Environmental Protection Agency's list of Hazardous Air Pollutants were screened against Structure Activity Relationship models derived from a machine learning algorithm for predictions regarding risk of human developmental toxicity. Multiple random sampling was employed in order to derive 10 structurally based models which were utilized to screen individual and representative mixture Hazardous Air Pollutants. The results of the computational screen were pooled in the form of a cumulative index (indicating high, moderate, and low potential) and evaluated according to their level of confidence. Air pollutants such as 2-acetylaminofluorene, 4-aminobiphenyl, biphenyl, 4-nitrobiphenyl, 3,3'-dimethylbenzidine, and 3,3'-dichlorobiphenyl have been identified by the structural models to pose a high risk to the developing human fetus. An additional screen against a mutagenicity data base has identified additional compounds that may be suspect due to their genotoxic risk

Mole, ML; Kavlock, RJ; Beyer, PE; et al. (1991) Effect of hepatocyte source on metabolic profile of biphenyl in an in-vitro developmental toxicity assay. Abstr Pap Am Chem Soc 202(1-2):AGRO 21. (abstract).

Pagano, G; Esposito, A; Giordano, GG; et al. (1983) Genotoxicity and teratogenicity of diphenyl and diphenyl ether: a study of sea urchins, yeast, and Salmonella typhimurium. Teratog Carcinog Mutagen 3(4):377–393.
This study was designed to investigate the possible genotoxic and teratogenic actions of diphenyl (DP), diphenyl ether (DPE), and their eutectic mixture, in a comparative approach including different test systems. Two microbial systems and a metazoan model were used: (1) diploid D7 strain of Saccharomyces cerevisiae; (2) Salmonella typhimurium strains TA100, TA98, TA1535, TA1537, TA1538, TA1532, TA2636; and (3) sea urchins (Paracentrotus lividus and Sphearechinus granularis). Both compounds resulted in severe toxicity in all of test organisms at levels greater than or equal to 10(-5) M (approximately 2 ppm). DP caused genetic effects in yeast with and without activating system, while the two chemicals appeared to be ineffective in Salmonella up to toxic levels. The action of DP and DPE on sea urchins resulted in developmental defects and mitotic abnormalities, following exposure of embryos or by pretreatment of sperm or eggs. In this system DPE appeared to be more effective than DP by about one order of magnitude (minimal active concentrations: 10(-5) M vs 10(-4) M). The eutectic mixture, industrially used as a heat transfer medium, was tested in its virgin and used form, for genotoxicity and embryotoxicity. The latter appeared to be more effective than the virgin eutectic. This increase in the embryo- and genotoxicity of the used eutectic may be related to the appearance of newly formed compounds in the heat transfer process. These compounds have been separated by high-pressure liquid chromatography and detected by fluorimetry

Quinto, I; DE, ME. (1982) Effects of propineb and dowtherm a on sperm morphology in mice.
HEEP COPYRIGHT: BIOL ABS. ABSTRACT FUNGICIDE TOBACCO GRAPE GROWING HEAT EXCHANGER RESIN FIBER INDUSTRY ABNORMALITY

Seiler, JP. (1977) Inhibition of testicular DNA synthesis by chemical mutagens and carcinogens. Preliminary results in the validation of a novel short term test. Mutat Res 46(4):305–310.
PESTAB. Measurement of the inhibition of testicular DNA synthesis by chemical carcinogens and mutagens in male mice has been proposed as a screening test (Friedman-Staub assay). A series of experiments was initiated to validate this test system; results obtained with 100 chemicals tested are presented. A first group of chemicals comprised known mutagens and carcinogens, a second group comprised compounds (especially pesticides) which had previously been tested and had failed to display such activity, and a third group comprised some anilines of unknown properties. At least 86% of the compounds previously known as carcinogens and/or mutagens gave positive results in the test, whereas only 10% of the compounds previously determined to be non-carcinogenic and non-mutagenic significantly depressed DNA synthetic activity. Most of the carcinogens and mutagens detected in this test gave negative results in the Ames test. Positive results in this test were obtained with dichlofluanid, which had been previously reported to be free from carcinogenic activity. The explanation and significance of this finding

remain to be determined. Large amounts of the chemicals tested must be given to the animals to elicit a response. The test will not detect mutagenic or carcinogenic activity of an impurity within an otherwise inactive compound

4.4. OTHER ENDPOINT-SPECIFIC STUDIES

Skin irritation potential of six chemicals: H_2SO_4, HCl, NaOH, phenol, Dowtherm A, and HCBD (1987) Epa/Ots Doc #86-870002208– 870002208

Booth, A; Ambrose, A; Deeds, F. (1956) Reversible nephrotoxic effects of biphenyl. Fed Proc 15:403. (abstract 1313)

Booth, A; Ambrose, A; Deeds, F; et al. (1961) The reversible nephrotoxic effects of biphenyl. Toxicol Appl Pharmacol 3:560–567

Braun, JP; Siest, G; Rico, AG. (1987) Uses of gamma glutamyltransferase in experimental toxicology. In: Rico, A; eds. Advances in veterinary science and comparative medicine. Vol. 31. Experimental and comparative toxicology. San Diego, CA, London, England: Academic Press Inc; pp. 151–172.
BIOSIS COPYRIGHT: BIOL ABS. RRM HUMAN RAT RABBIT DOG MOUSE KIDNEY CARCINOGENESIS

Chu, I; Villeneuve, DC; Cote, M; et al. (1988) Dermal toxicity of a medium-boiling 154-378 c coal liquefaction product in the rat. Part I. J Toxicol Environ Health 23(2):193–206.
Dreist, M; Kolb, J. (1993) Untersuchungen auf hautsensibilisierende Wirkung am Meerschweinchen (Maximierungstest nach Magnusson und Kligman). (Bericht Nr. 22057 vom 19.02.1993) [cited in BUA, 1994].

Hanada, S. (1977) Studies on food additives, diphenyl (biphenyl) and O-phenyl phenol from the view point of public health. Part 2. On the toxicities of diphenyl and O-phenyl phenol. Nagoya Shiritsu Daigaku Igakkai Zasshi (J Nagoya City Univ Med Sch) 28(3): 983-995 .

Kluwe, WM. (1982) Development of resistance to nephrotoxic insult: changes in urine composition and kidney morphology on repeated exposures to mercuric chloride or biphenyl. J Toxicol Environ Health 9(4):619–635

Ohnishi, M; Yajima, H; Takemura, T; et al. (2000) Characterization of hydroxy-biphenyl-O-sulfates in urine and urine crystals induced by biphenyl and KHCOinf 3 administration in rats. J Health Sci 46(4):299–303.
In order to obtain information on the relationship between calculi and urine-crystal constituents, component analyses of the biphenyl sulfate conjugates in urine and urine crystals in rats fed a diet containing biphenyl and KHCOinf 3 were performed by LC-MS/MS and FT-IR. LC-MS/MS analysis revealed the presence of biphenyl metabolites, i.e., three isomers of monohydroxy-biphenyl-O-sulfate (HBPOS) and five isomers of dihydroxy-biphenyl-O-sulfate (DHBPOS), in rat urine. The same results were obtained for the crystals in rat urine. These findings suggested that the metabolism of biphenyl resulting in the formation of sulfate conjugates follows the process: Biphenyl <rt arrow> mono- or dihydroxylation <rt arrow> sulfate conjugation. FT-IR analysis of the urine crystals indicated that the major constituent was the potassium salt of 4-hydroxy-biphenyl-O-sulfate (4-HBPOS), which is known to be the main constituent of urinary bladder calculi. Consequently, in view of the similarity of the major constituent, the potassium salt of 4-HBPOS, in both the urine crystals and calculi, it is thought that the formation of the calculi can be attributed to the lower solubility of the potassium salt of 4-HBPOS, as compared to the other sulfate conjugates

Ohnishi, M; Yajima, H; Yamamoto, S; et al. (2000) Sex dependence of the components and structure of urinary calculi induced by biphenyl administration in rats. Chem Res Toxicol 13(8):727–735.
To obtain definitive information about the mechanisms of urinary calculus formation and the structural characteristics of the calculi induced by biphenyl administration in rats, with a focus on the sex dependency, the constituents of the urinary calculi were analyzed by HPLC, inductively coupled plasma spectroscopy (ICP), micro Fourier transform infrared spectroscopy (mFT-IR), and ion chromatography (IC), and structural analyses were carried out by microscopy, mFT-IR, and the electron probe microanalyzer (EPMA) method. We attempted to account for the appreciably higher incidence of calculi in males than in females. mFT-IR analysis revealed that the biphenyl-induced urinary calculi in male rats are composed mainly of potassium 4-hydroxybiphenyl-o-sulfate (4-HBPOSK), whereas the calculi in female rats are composed mainly of 4-hydroxybiphenyl (4-HBP) and KHSO(4) produced by the hydrolysis of 4-HBPOSK. Observations of photomicrographs and the results of mFT-IR analysis indicated that the calculi in males have a multilayer structure consisting of alternating layers of 4-HBPOSK and

calcium phosphate, whereas the calculi in females have no multilayer structure, but open holes in which needle-shaped crystals are present in some places. In view of the results of these analyses, including the EPMA analysis, it appears that calculus formation in males may involve a series of successive and irreversible reactions, whereas calculus formation in females may result from a series of reversible reactions, including the hydrolysis of 4-HBPOSK. It was inferred that the series of irreversible reactions involved in calculus formation in males is relatively more stable than that in the case of females, and thus, a sex difference in the reaction features may be responsible for the observed difference in the incidence of calculus formation

Ohnishi, M; Yajima, H; Takeuchi, T; et al. (2001) Mechanism of urinary tract crystal formation following biphenyl treatment. Toxicol Appl Pharmacol 174(2):122–129.
Coadministration of biphenyl and KHCO3 in the diet of male rats for 13 weeks produced urine crystals, which, by means of LC-MS/MS analyses, were determined to be composed of the potassium salt of 4-hydroxy-biphenyl-O-sulfate (4-HBPOSK). Biphenyl alone or biphenyl with KCl or NaHCO3 in the diet did not produce urine crystals. It was found that the higher concentration of potassium in the urine and the alkaline pH induced by feeding KHCO3 to rats resulted in the formation of urine crystals of 4-HBPOSK due to 4-HBPOSK solubility being lower in urine than in plasma. Urine crystals of 4-HBPOSK produced hyperplasia of the transitional epithelium of the ureter, ureteral obstruction, and hydronephrosis in the urinary tract

Ohnishi, M; Take, M; Sagawa, M; et al. (1998) Analysis of the components of biphenyl induced urinary bladder calculus in male rats. Japanese Journal of Toxicology and Environmental Health 44(4):256–263.
The components of biphenyl induced urinary bladder calculus in the male rats were studied using HPLC coupled with mass spectrometry/mass spectrometry (LC-MS/MS), IR and inductive coupled plasma (ICP). Two peaks in the calculus components were detected by HPLC and LC-MS/MS. The peaks were identified as 4-hydroxybiphenyl sulfate (4-HBPSC) and 4,4'-dihydroxybiphenyl sulfate (4,4'-DHBPSC). 4-HBPSC was accounted for 54.6% and 4,4'-DHBPSC was accounted for 1.5% by LC-MS/MS. 4-HBPSC was main component by these results and IR. Inorganic elements of urinary bladder calculus were accounted for 25% by ICP.

Rohr, U; Koenig, W; Selenka, F. (1985) [Influence of pesticides on the release of histamine, chemotactic factors and leukotrienes from rat mast cells and human basophils]. Zentralbl Bakteriol Mikrobiol Hyg [B] 181(6):469–486. (German).
BIOSIS COPYRIGHT: BIOL ABS. The influence of pesticides on mediator release from rat peritoneal mast cells and human basophiles was studied. Mediators from mast cells and basophils are important factors in allergic and inflammatory reactions. Release of histamine from rat mast cells and human basophils is demonstrated by stimulation with dieldrin, DDT, heptachlor, heptachlorepoxid and biphenyl. This pesticide-induced histamine secretion is dose-dependent and requires Ca2+. In contrast, incubation with gamma-BHC, HCB and carbaryl produces no significant histamine release. Additive histamine secretion results from simultaneous stimulation of rat mast cells with pesticides and anaphylatoxin C5a. Further, secretion of eosinophil and neutrophil chemotactic factors from rat mast cells is induced during incubation with dieldrin, biphenyl and hepatochlorepoxide. It is also demonstrated that pesticides can stimulate the generation of lipidmediators. Biphenyl, gamma-BHC, heptachlor, heptachlorepoxid, DDT and

Shibata, M-A; Yamada, M; Tanaka, H; et al. (1989) Changes in urine composition, bladder epithelial morphology, and DNA synthesis in male F344 rats in response to ingestion of bladder tumor promoters. Toxicol Appl Pharmacol 99:37–49.
Changes in urine composition, morphology of the bladder epithelium, and DNA synthesis were examined in rat urothelial cells following oral administration of bladder tumor promoters or analogs without promoting potential. Male Fischer-344-rats were administered one of the following compounds in the diet: butylated-hydroxyanisole (25013165) (BHA), butylated-hydroxytoluene (128370) (BHT), tert-butylhydroquinone (1948330), ethoxyquin (91532), L-ascorbic-acid (50817), sodium-L-ascorbate (134032), diphenyl (92524), o-phenylphenol (90437), sodium-o-phenylphenol (132274), sodium-bicarbonate (144558), or sodium-chloride (7647145). Rats were administered the bladder carcinogens N-butyl-N-(4-hydroxybutyl)nitrosamine (3817116) (BBN) or N-ethyl-N-(4-hydroxybutyl)nitrosamine (54897620) (EHBN) in drinking water. The findings of the study indicate a clear link among promotion of bladder carcinogenesis, increased DNA synthesis, and altered surface morphology after administration of exogenous agents. Increased cell division and cell surface changes occurred as a result of fluctuation in sodium ion concentration, increased pH, or direct biochemical or physical trauma. Sodium salts of L-ascorbate, o-phenylphenate, and bicarbonate increased the acidity, sodium content, volume and crystalluria. Parent compounds did not induce these changes. Sodium-chloride ingestion caused natriuresis without increasing urinary pH. Diphenyl administration produced only microcalculi consisting of p-phenylphenol. No changes were noted in urinary acidity or sodium ions following treatment with the antioxidants BHT, BHA, and ethoxyquin. An increase in

acidity was caused by tert-butylhydroquinone. No change in urine composition resulted from treatment with BBN or EHBN except for a decrease in phosphorus concentration. All promoters and carcinogens caused an elevation in DNA synthesis in the urothelium and produced morphologic surface changes. The authors conclude there are considerable variations in the mechanisms involved in the production of tumors by these particular compounds

Shibata, MA; Tanaka, H; Yamada, M; et al. (1989) Proliferative response of renal pelvic epithelium in rats to oral administration of ortho-phenylphenol, sodium ortho-phenylphenate and diphenyl. Cancer Lett 48(1):19–28.
Changes in DNA synthesis levels and morphology as observed by scanning electron microscopy (SEM) and light microscopy in rat renal papilla and pelvis following oral administration of ortho-phenylphenol (OPP), sodium ortho-phenylphenate (OPP-Na) and diphenyl, were investigated in F344 rats. OPP and OPP-Na treatment for 4 weeks was associated with elevated DNA synthesis in both renal papilla and pelvis, in addition to distinct morphological cell surface alterations. Sequential light microscope observation revealed induction of renal papillary necrosis from week 4, followed by regeneration hyperplasia at weeks 16 and 24, but no changes in the renal pelvis in the OPP case. OPP-Na not only similarly affected the renal papilla, but also brought about development of hyperplasia in the renal pelvis. No proliferative response of the kidney was apparent in rats fed diphenyl. The present study indicated that the proliferative responses in the renal pelvic epithelium following OPP-Na are similar to those induced by this chemical in the urinary bladder, and that in both cases they are indicative of promoting or carcinogenic potential

Shiraiwa, K; Takita, M; Tsutsumi, M; et al. (1989) Diphenyl induces urolithiasis but does not possess the ability to promote carcinogenesis by N-ethyl- N-hydroxyethylnitrosamine in kidneys of rats. J Toxicologic Pathol 2:41–48

Sondergaard, D; Blom, L. (1979) Polycystic changes in rat kidney induced by biphenyl fed in different diets. Arch Toxicol Suppl (2):499–502.
Groups of rats were fed biphenyl at various dose levels in a semisynthetic diet and in a commercial chow. The effect levels for induction of polycystic kidney lesions were established by means of urinalysis, organ weight changes, light and electron microscopy, and enzyme histochemistry. The no-effect level, was less than 50 mg/kg bw./day and 300 mg/kg bw./day, when feeding the semisynthetic diet and the commercial chow respectively. This difference in effect level due to the diet is an indication that the diet is of great influence on the results of toxicological experiments

Takita, M. (1983) Urolithiasis induced by oral administration of diphenyl in rats. Journal of the Nara (Medical University) Medical Association 34:565–584

Union Carbide. (1982) Acute toxicity and primary irritancy studies peroral, single dose to rats percutaneous, single dose to rabbits inhalation, single exposure to rats skin irritation, rabbits. Submitted under TSCA Section 8D; EPA Document No. 878213653; NTIS No. OTS0206434.

Yao, H; WANG, X; Xu, X; et al. (2002) [Study on the injury of liver induced by terephthalic acid ethylene glycol and/or dowtherm A in rats].
The joint injury actions and mechanisms of terephthalic acid (TPA), ethylene glycol (EG) and/or dowtherm A (DOW) on liver in rats were investigated. A subchronic toxicity study was designed by a 2(3) factorial method. Some enzymes, biochemical and morphologic indices reflecting the injury of liver were studied. The results showed that serum ALT and serum total bile acid (TBA) of rats in the combined intoxication groups were significantly higher than those in the groups with single toxic agent and control group. The results of factorial analysis showed that the joint action induced by TPA, EG and/or DOW were characterized as additive (TPA + EG), synergistic (EG + DOW), synergistic (TPA + DOW) and additive(TPA + EG + DOW) actions. The deduction was identified by morphologic observations

4.5. MECHANISTIC DATA AND OTHER STUDIES IN SUPPORT OF THE MODE OF ACTION

Ikawa, E; Tagawa, Y; Tsuda, H; et al. (1985) Modification potential of pesticides and environmental chemicals on the induction of preneoplastic liver cell foci in an in-vivo short-term assay system. J Toxicol Sci 10(3) :262.
BIOSIS COPYRIGHT: BIOL ABS. RRM ABSTRACT RAT DIPHENYL CAPTAFOL THIRAM CAPTAN DIELDRIN MALONIC-ACID ALPHA BHC POTASSIUM BROMATE MALONALDEHYDE BISDIETHYLACETATE DICHLOFLUANID URETHANE M PHENYLENEDIAMINE AMARANTH DI-2-ETHYLHEXYLPHTHALATE TUMOR PROMOTER

Ito, N; Fukushima, S; Shirai, T; et al. (1984) Drugs food additives and natural products as promoters in rat urinary bladder carcinogenesis. IARC Sci Publ 56:399–407.
The promoting effects of various chemicals on urinary bladder carcinogenesis in rats initiated with N-butyl-N-(4-hydroxybutyl)nitrosamine (BBN) were studied. Male Fischer 344 rats were given BBN at 0.01% or 0.05% in their drinking-water for four weeks. One of the following chemicals was then administered in the diet for 32 or 34 weeks: acetazolamide, allopurinol, phenobarbital, phenacetin, ortho-phenylphenol, sodium ortho-phenylphenate, diphenyl, sodium L-ascorbate, butylated hydroxyanisole, butylated hydroxytoluene, sodium saccharin, aspartame, sodium cyclamate, stevioside, DL-tryptophan, quercetin, caffeine, nicotine and hippuric acid. Phenacetin, sodium ortho-phenylphenate, sodium L-ascorbate and butylated hydroxyanisole were significant promoters of urinary bladder neoplasia in rats initiated with BBN. Sodium saccharin, diphenyl, butylated hydroxytoluene, allopurinol, and DL-tryptophan caused moderate or slight promotion of neoplastic changes in the experimental animals. No change in tumour yield was observed after administration of the other chemicals.

Jurs, PC; Stouch, TR; Czerwinski, M; et al. (1985) Computer-assisted studies of molecular structure-biological activity relationships. J Chem Inf Comput Sci 25(3):296.
BIOSIS COPYRIGHT: BIOL ABS. RRM ANTIINFLAMMATORY STEROID RETINOIDS DRUG DESIGN AGRICULTURAL CHEMICALS CHEMICAL GENETIC TOXICITY CANCER PREVENTION SISTER CHROMATID EXCHANGE

Kitamura, S; Sanoh, S; Kohta, R; et al. (2003) Metabolic activation of proestrogenic diphenyl and related compounds by rat liver microsomes. J Health Sci 49(4):298–310.
In this study, liver microsome-mediated activation of diphenyl (DP), diphenylmethane (DPM) and 2,2-diphenylpropane (DPP) to estrogens was demonstrated. These three compounds were negative in estrogen reporter assay using estrogen-responsive human breast cancer cell line MCF-7. However, they exhibited estrogenic activity after incubation with liver microsomes of 3-methylcholanthrene-treated rats in the cases of DP and DPM, or of phenobarbital-treated rats in the cases of DP and DPP, in the presence of NADPH. When these compounds were incubated with liver microsomes in the presence of NADPH, monohydroxyl and dihydroxyl derivatives were formed. These hydroxylated metabolites, 4-hydroxydiphenyl, 3-hydroxydiphenyl, 2-hydroxydiphenyl, 4-hydroxydiphenyl-methane, 2-(4-hydroxyphenyl)-2-phenylpropane (4-OH-DPP), 4,4prime-dihydroxydiphenyl, 4,4prime-dihydroxydiphenyl-methane and 2,2-bis(4-hydroxyphenyl)propane (bisphenol A), all exhibited estrogenic activity in MCF-7 cells. Binding assay of these hydroxylated compounds with rat uterus estrogen receptor was also positive. These results suggest that the estrogenic activities of DP, DPM and DPP were due to the formation of hydroxylated metabolites by the liver cytochrome P450 system

Klopman, G; Contreras, R; Rosenkranz, HS; et al. (1985) Structure-genotoxic activity relationships of pesticides comparison of the results from several short-term assays. Mutat Res 147(6):343–356.
BIOSIS COPYRIGHT: BIOL ABS. RRM SALMONELLA-TYPHIMURIUM SACCHAROMYCES-CEREVISIAE MOUSE LYMPHOMA CELL CARBAMATE THIOCARBAMATE ORGANOPHOSPHATE HALO-AROMATIC INSECTICIDE HERBICIDE FUNGICIDE DNA DAMAGE GENE MUTATION HISTIDINE REVERSION

Kokel, D; Xue, D. (2006) A class of benzenoid chemicals suppresses apoptosis in *C. elegans*. Chembiochem 7(12):2010–2015.
Benzene is a human carcinogen that might act through both genotoxic and nongenotoxic mechanisms to promote tumorigenesis. The genotoxic effects of benzene are well established, however, its potential nongenotoxic roles in carcinogenesis are poorly understood. We find that benzene suppresses somatic apoptosis in C. elegans; this suggests a potential nongenotoxic mechanism by which this chemical might promote tumorigenesis. We find that two other benzenoid chemicals, biphenyl and toluene, also inhibit apoptosis in C. elegans. Notably, these chemicals are suspected carcinogens in mammals; this suggests that a subclass of benzenoid chemicals might promote tumorigenesis by suppressing apoptosis. A benzene metabolite, 1,4-benzoquinone, can directly inhibit the activity of caspase-3; this suggests a general molecular mechanism by which benzenoid chemicals might suppress apoptosis. These findings suggest that C. elegans is an excellent alternative animal model for studying the antiapoptotic activity of tumor-promoting chemicals and for identifying in vivo targets of these chemicals

Lygre, H; Moe, G; Solheim, E; et al. (1995) Biologic testing of leachable aromatic compounds from denture base materials. Acta Odontol Scand 53(6):397–401.
Mochida, K; Goto, M; Saito, K. (1983) Effects of diphenyl, o-phenylphenol and 2-(4'-thiazolyl)benzimidazole on growth of cultured mammalian cells. Bull Environ Contam Toxicol 31(4):428–431.
The effects of diphenyl (92524) (DP), o-phenylphenol (90437) (OPP), or 2-(4'-thiazolyl)benzimidazole (148798) (TBZ) on mammalian cells were studied in culture systems. Cultured human oval carcinoma (KB) and African-

green-monkey kidney (AGMK) cells were incubated with DP, OPP, or TBZ for up to 72 hours in a variety of concentrations to determine dose/response relationships. After incubation, the number of viable cells was determined with a cell counter. The growth of KB and AGMK cells was not inhibited by DP, OPP, or TBZ during the first 24 hours. After 72 hours of incubation, sufficient inhibition had occurred to establish dose/response relationships. Dose/response curves were plotted on logarithm probit paper, and the concentrations causing 50 percent inhibition of cell growth (ID/50) were determined. The ID/50 values for KB cells were: DP, 20.5 micrograms per milliliter (microg/ml); OPP, 30.0microg/ml; and TBZ, 64.0microg/ml. The ID/50 values for the AGMK cells were: DP, 17.0microg/ml; OPP, 26.0microg/ml; and TBZ, 59.0microg/ml. The authors note that, although DP is more toxic than OPP or TBZ, there is no significant difference in toxicity of the compounds toward KB and AGMK cells

Nakagawa, Y; Tayama, S; Moore, G; et al. (1993) Cytotoxic effects of biphenyl and hydroxybiphenyls on isolated rat hepatocytes. Biochem Pharmacol 45(10):1959–1965.
The cytotoxic effects of biphenyl (BP) and its hydroxylated derivatives, o-phenylphenol (OPP), m-phenylphenol (MPP), p-phenylphenol (PPP), 2-biphenylyl glycidyl ether (OPP-epoxide), phenyl-hydroquinone (PHQ), o,o'-biphenol (o,o'-BPol) and p,p'-biphenol (p,p'-BPol), were investigated in freshly isolated rat hepatocytes. OPP, MPP and PPP, at concentration of 0.75 mM, resulted in the loss of intracellular ATP, glutathione (GSH) and protein thiols, causing cell death. OPP-epoxide and BP were less toxic than the OPP isomers. MPP or PPP compared with OPP caused serious impairments in oxidative phosphorylation in mitochondria isolated from rat liver. PHQ (0.75 mM) caused a rapid loss of intracellular ATP which preceded the onset of cell death. PHQ was more toxic than o,o'-BPol or p,p'-BPol. PHQ dissolved in Krebs-Henseleit buffer without hepatocytes was rapidly converted to its corresponding quinone, phenyl-benzoquinone. The cytotoxicity produced by PHQ depends on the rate of formation of reactive intermediates. These results indicate that the addition of a hydroxyl group to the aromatic ring of BP enhances BP-induced cytotoxicity and that the mitochondria are a common target of the OPP isomers and other BP derivatives. In addition, the para- or meta-hydroxyl groups rather than the ortho-hydroxyl group increase the toxicity. The cytotoxicity produced by PHQ depends on the rate of formation of reactive intermediate(s) such as phenyl-benzoquinone

Narbonne, JF; Cassand, P; Alzieu, P; et al. (1987) Structure-activity relationships of the n-methylcarbamate series in salmonella typhimurium. Mutat Res 191:21–27.
A possible structure/activity relationship was investigated for 12 chemicals, benzene (71432), phenyl-N-methylcarbamate, phenol (108952), biphenyl (92524), p-biphenylyl-n-methyl-carbamate, 1-hydroxybiphenyl, naphthalene (91203), 1-naphthyl-N-methyl-carbamate (63252), 1-hydroxynaphthalene (90153), phenanthrene (85018), 9-phenanthryl-N-methylcarbamate, and 9-hydroxyphenanthrene (484173), and their mammalian enzyme activated mutagenic activity. The study centered around the reversion of histidine dependent Salmonella-typhimurium (TA-98) and (TA-1535) in the presence of a rat liver 9000-g supernatant fraction. Aromatic hydrocarbons were effective versus (TA-1535) and methylcarbamates versus (TA-98). A weak increase in revertants was noted for compounds with two or three aromatic rings. Increased mutagenic activity was noted on hydroxylation or carbamylation of these aromatic rings. These findings suggest an efficiency of aromatic hydrocarbons in reversion of a base substitution strain. Methylcarbamates appeared efficient in frameshift strains. An increase in mutagenic activity was apparent for compounds with second order specific molecular connectivity indices lower than 0.300 due to physicochemical reasons. This connectivity index indicates a compound with a massed and complicated structure

Nishihara, Y. (1985) Comparative study of the effects of biphenyl and Kanechlor-400 on the respiratory and energy linked activities of rat liver mitochondria. Br J Ind Med 42(2):128–132.
A comparative study of the effects of biphenyl and Kanechlor-400 (KC-400) on the respiratory and energy linked activities of rat liver mitochondria was made, and some differences in effects caused by the chlorination of biphenyl were clarified. The inhibition of state 3 respiration with succinate by biphenyl was less than that observed with alpha-ketoglutarate/malate. By contrast, KC-400 exhibited the opposite trend; state 3 respiration with succinate was more sensitive to inhibition than that observed with alpha-ketoglutarate/malate. Thus the inhibition of state 3 respiration with NAD+-linked substrate was decreased, whereas the inhibition of state 3 respiration with succinate was increased by the chlorination of aromatic rings. Biphenyl also instantaneously stimulated state 4 respiration. The extent of stimulation with succinate by biphenyl was larger than with alpha-ketoglutarate-malate. On the other hand, there was about a 1-2 minute lag period before stimulation of state 4 respiration by KC-400 became obvious. Furthermore, state 4 respiration in the presence of alpha-ketoglutarate/malate was more intensely stimulated by KC-400 than by succinate. Biphenyl and KC-400 dissipated the membrane potential across the mitochondrial membranes. The dissipation of membrane potential by biphenyl was instantaneous whereas that caused by KC-400 was preceded by a lag period (1-2 min). Biphenyl and KC-400 altered the permeability properties of mitochondrial

membranes as evidenced by the release of endogenous K+. The release of K+ due to biphenyl was instantaneous but KC-400 induced K+-release was preceded by a lag period (1-2 min). Thus membrane perturbation by biphenyl was faster than that induced by KC-400. Therefore, it is clear that the chlorination of aromatic rings delays the perturbation in the state of membrane lipids

Poelloth, C; Mangelsdorf, I. (1997) Commentary on the application of (Q)SAR to the toxicological evaluation of existing chemicals. Chemosphere 35(11):2525–2542.
BIOSIS COPYRIGHT: BIOL ABS. For ethical and financial reasons it is impossible to perform thorough toxicological testing for all of the more than 100,000 substances registered in the European Inventory of Existing Substances. It was therefore investigated whether the application of (quantitative) structure-activity relationships (QSAR) with commercially available computer programs could predict the toxicological profile and help identify those substances requiring priority toxicological testing. Whereas predictions with respect to complex endpoints such as carcinogenicity, chronic toxicity and teratogenicity are still disappointing, more reliable predictions should be forthcoming in the immediate future for sensitisation, mutagenicity and genotoxicity endpoints

Purchase, IF; Longstaff, E; Ashby, J; et al. (1978) An evaluation of 6 short-term tests for detecting organic chemical carcinogens. Br J Cancer 37(6):873–903.
A number of tests have been described which are thought to be capable of identifying carcinogens without using the actual induction of cancer as an endpoint. This study compared the performance of 6 such tests on a selection of 120 organic chemicals. The tests studies were: (1) mutation of Salmonella typhimurium; (2) cell transformation; (3) degranulation of endoplasmic reticulum; (4) sebaceous gland suppression; (5) tetrazolium reduction and (6) subcutaneous implant. A further 4 tests were examined briefly, but were not included in the complete evaluation. The chemicals were classified into carcinogens (58) and non-carcinogens (62) on the basis of published experimental data, and into 1 of 4 broad chemical classes. There was considerable variation between tests in their ability to predict carcinogenicity, with the cell-transformation test and the bacterial-mutation test being the most accurate (94% and 93% accurate respectively). These 2 tests were considered to be of general use in screening, since they were clearly more accurate than the others. Statistical consideration of various combinations of these tests showed that the use of cell transformation and bacterial mutation together, provide an advantage over the use of either test alone. The inclusion of the other 4 tests in a screening battery predictably resulted in a great increase in overall inaccuracy and loss of discrimination, even though the detection of carcinogens is improved. All the tests were shown to generate both false positive and false negative results, a situation which may be controlled by the use, where possible, of appropriate chemical-class controls, to identify the test which is optimal for the class of chemical under test. Structural analogy may have a part to play in the rapid detection of environmental carcinogens, and some general guidelines for its use are given

Roy, D. (1990) Cytochrome P-450 catalyzed redox cycling of ortho-phenylphenol. Biochem Int 22(5):849–858.
BIOSIS COPYRIGHT: BIOL ABS. o-Phenylphenol was converted to 2,5-dihydroxy biphenyl (phenylhydroquinone) by microsomal P-450. Depending on the cofactor used, microsomal enzymes catalyzed oxidation and/or reduction of phenylhydroquinone. Phenylhydroquinone was oxidized to phenyl 2,5'-p-quinone by cumene hydroperoxide-supported microsomal P-450. Phenyl 2,5'-p-quinone was reduced to phenylhydroquinone by cytochrome P-450 reductase. This study provides direct evidence of cytochrome P-450 catalyzed redox cycling of o-phenylphenol. It is postulated that redox cycling of o-phenylphenol may play a role in o-phenylphenol-caused bladder cancer

Sassa, S; De, VH; Kappas, A. (1984) Inhibition of uroporphyrinogen decarboxylase activity in polyhalogenated aromatic hydrocarbon poisoning. In: Poland, A; Kimbrough, RD; eds. Banbury report. Vol. 18. Biological mechanisms of dioxin action. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory; pp. 215–224.
BIOSIS COPYRIGHT: BIOL ABS. RRM CHICK EMBRYO LIVER CELL 2 3 7 8 TETRACHLORODIBENZO-P-DIOXIN AROCLOR 1254 DELTA AMINOLEVULINATE SYNTHASE UROPORPHYRIN HEPATOCARBOXYLATE PORPHYRIN CYTOCHROME P-450 BIPHENYL 4'-MONOCHLOROBIPHENYL 3' 4'-DICHLOROBIPHENYL 4 4'-DICHLOROBIPHENYL 2 6 2' 6'-TETRACHLOROBIPHENYL 2 4 3' 4'-TETRACHLOROBIPHENYL 2 3 2' 3' TETRACHLOROBIPHENYL 3 4 3' 4'-TETRACHLOROBIPHENYL 3 4 5 3' 4' 5'-HEXACHLOROBIPHENYL 3 4 5 3' 4' 5'-HEXABROMOBIPHENYL 2 4 5 2' 4' 5'-HEXACHLOROBIPHENYL 2 4 5 2' 4' 5'-HEXABROMOBIPHENYL 2 4 6 2' 4' 6'-HEXACHLOROBIPHENYL 2 3 4 5 2' 3' 4' 5'-OCTACHLOROBIPHENYL 2 3 4 5 6 2' 3' 4' 5' 6'-DECHLOROBIPHENYL

Schultz, T; Sinks, GD; Cronin, MT. (2002) Structure-activity relationships for gene activation oestrogenicity: evaluation of a diverse set of aromatic chemicals. Environ Toxicol 17(1):14–23.

Structure-activity relationships for oestrogenicity were developed based on 120 aromatic chemicals evaluated in the Saccharomyces cerevisiae-based Lac-Z reporter assay. Relative gene activation was compared to 17 beta-estradiol and varied over eight orders of magnitude. Analysis of the data compared to 17 beta-estradiol identified three structural criteria that were related to xenoestrogen activity and potency: (1) the hydrogen-bonding ability of the phenolic ring mimicking the A-ring, (2) a hydrophobic centre similar in size and shape to the B- and C-rings, and (3) a hydrogen-bond donor mimicking the 17 beta-hydroxyl moiety of the D-ring, especially with an oxygen-to-oxygen distance similar to that between the 3- and 17 beta-hydroxyl groups of 17 beta-estradiol. Binding data were segregated into activity clusters including strong, moderate, weak, and detectable gene expression, and those compounds that were inactive. The hydrogen-bonding ability of hydroxy group in the 3-position on 17 beta-estradiol was observed to be essential for gene activation. Compounds with a 4-hydroxyl substituted benzene ring and a hydrophobic moiety of size and shape equivalent to the B-ring of 17 beta-estradiol were generally observed to be weakly active compounds. Moderately active compounds have a 4-hydroxyl substituted benzene ring with a hydrophobic moiety equivalent in size and shape to the B- and C-ring of 17 beta-estradiol, or have a high hydrogen-bond donor capacity owing to the presence of halogens on a nonphenolic ring. Strongly active compounds, similar to 4,4'-diethylethylene bisphenol (DES), possess the same hydrophobic ring structure as described for moderately active compounds and an additional hydroxyl group with an oxygen-to-oxygen distance close to that exhibited by the 3- and 17-hydroxyl groups of 17 beta-estradiol

Seiler, JP. (1977) Inhibition of testicular DNA synthesis by chemical mutagens and carcinogens. Preliminary results in the validation of a novel short term test. Mutat Res 46(4):305–310.

Sirica, A; Pitot, H. (1980) Drug metabolism and effects of carcinogens in cultured hepatic cells. Pharmacol Rev 31:205–228

Sugar, J; Toth, K; Gsuka, O; et al. (1979) Role of pesticides in hepatocarcinogenesis. J Toxicol Environ Health 5(2-3):183–191.
PESTAB. Doses of TCPE and TCDD were administered to outbred Swiss H mice. The doses were given through gastric intubation over a period of 1 yr. The results of the study indicate that people are not subject to the harmful effects of TCPE when the chemical is applied as an herbicide according to the directions. However, the results also support the urgency of reducing exposure of workers producing or using TCPE. Liver tumors were enhanced in male mice exposed to TCPE, but TCDD caused no increase in the incidence of these tumors. No correlation was found between the results of in vivo carcinogenicity studies and induction of aryl hydrocarbon hydroxylase and biphenyl 2-hydroxylase activities

Tamano, S; Asakawa, E; Boomyaphiphat, P; et al. (1993) Lack of promotion of N-butyl-N-(4-hydroxybutyl)nitrosamine-initiated urinary bladder carcinogenesis in mice by rat cancer promoters. Teratog Carcinog Mutagen 13(2) :89–96.
The effects of dietary exposure to sodium L-ascorbate (Na-AsA), butylated hydroxyanisole (BHA), and diphenyl on the development of urinary bladder tumors in a mouse two-stage carcinogenesis model were examined. Male B6C3F1 mice received 0.05% N-butyl-N-(4-hydroxybutyl) nitrosamine (BBN) in the drinking water for 4 weeks and were then treated with 5% Na-AsA, 1% BHA, or 1% diphenyl for 32 weeks. None of these chemicals enhanced the development of either preneoplastic or neoplastic lesions in the urinary bladder. Furthermore, DNA synthesis levels of urinary bladder epithelium in mice treated with each substance alone for 8 weeks were not elevated significantly, although Na-AsA was associated with a significant increase in the urinary pH value and Na+ concentration. The results indicate that Na-AsA, BHA, and diphenyl do not exert an enhancing influence on mouse bladder carcinogenesis, in clear contrast to the case in the rat

Tlas, S; Nebert, D. (1976) Genetic association of increases in naphthalene, acetanilide, and biphenyl hydroxylations with inducible aryl hydrocarbon hydroxylase in mice. Arch Biochem Biophys 175(2):495–506.
HEEP COPYRIGHT: BIOL ABS. The induction of 4 hepatic monooxygenase activities, naphthalene trans-1,2-dihydrodiol formation, acetanilide-4-hydroxylase, biphenyl-4-hydroxylase and biphenyl-2-hydroxylase, by (carcinogenic) polycyclic aromatic compounds is genetically associated with the induction of aryl hydrocarbon (benzo(a)pyrene) hydroxylase activity and cytochrome P1-450 in C57BL/6N and DBA/2N inbred mice and among progeny from the appropriate genetic crosses in involving these 2 progenitor strains. These enzyme activities were studied with respect to preferential inhibition of metyrapone, alpha-naphthoflavone or Tween 80 in vitro; use of the microsomal inducers 3-methylcholanthrene, beta-naphthoflavone, 2,3,7,8-tetrachlorodibenzo-p-dioxin or phenobarbital; apparent Km values; and heat inactivation. Several lines of evidence suggest that aromatic hydrocarbon-induced naphthalene monooxygenase, acetanilide-4-hydroxylase, biphenyl-4-hydroxylase, and biphenyl-2-hydroxylase activities are, like the induced aryl hydrocarbon hydroxylase activity, associated with

cytochrome(s) P1-450, and the basal activities of the first 3 of these enzymes are, like basal aryl hydrocarbon hydroxylase activity, associated with 1 (or more) forms of cytochrome P-450 other than cytochrome(s) P1-450. Basal biphenyl 2-hydroxylase activity in mouse liver appears to be associated solely with cytochrome(s) P1-450. This finding differs from all other basal monooxygenase activities associated with the Ah locus and studied in a similar manner

Umeda, Y; Aiso, S; Arito, H; et al. (2004) Induction of peroxisome proliferation in the liver of biphenyl-fed female mice. J Occup Health 46(6):486–488

Williams, G; Mori, H; McQueen, C. (1989) Structure-activity relationships in the rat hepatocyte DNA-repair test for 300 chemicals. Mutat Res 221:263–286

Yoshida, S; Masubuchi, M; Hiraga, K. (1978) Cytogenetic studies of antimicrobials on cultured cells. Tokyo Toritsu Eisei Kenkyusho Kenkyo Nempo (Annu Rep Tokyo Metrop Res Lab Public Health) 29(2):86–88.
PESTAB. Inhibition of proliferation and cytogenetic effects on Chinese hamster CHO-KI ovary cells by o-phenylphenol (OPP), biphenyl (DIP), thiabendazole (TBZ) and butyl p-hydroxybenzoate (PHB) were studied. DIP showed the strongest inhibition of replication of the cells at concentrations > 50 mug/ml. OPP, PHB and TBZ showed similar degrees of inhibition at concentrations > 100 mug/ml. DIP at 50 mug/ml was a strong inhibitor of colony formation. There was a clear relationship between concentration and effect. OPP gave similar results. TBZ showed inhibition at 100 mug/ml. PHB showed no inhibition up to 100 mug/ml. DIP was the strongest inhibitor of cell proliferation. Effects of these agents on cell chromosomes were not detected up to 48 hr at concentrations of 25-50 mug OPP/ml, 2.5-25 mug DIP/ml, 5-50 mug TBZ/ml and 25-50 mug PHB/ml. It was concluded that none of the chemicals were mutagenic in the cell line tested

Genotoxicity studies:

Abe, S; Sasaki, M. (1977) Chromosome aberrations and sister chromatid exchanges in Chinese hamster cells exposed to various chemicals. J Natl Cancer Inst 58(6):1635–1641

Abilev, S; Liubimova, IK; Migachev, G. (1993) [Effect of structural features of nitro-derivatives of fluorenone and biphenyl on frameshift mutagenesis in tester strains of Salmonella typhimurium]. Genetika 29(10):1640–1645.
Comparative mutagenic activity of 7 derivatives of biphenyl and fluorenone, 4,4'-dinitrobiphenyl-2,2'-dicarboxylic acid; 4,4',6,6'-tetranitrobiphenyl-2,2'-dicarboxylamide; 2-nitrofluorenone-5-carboxylic acid; 2,7-dinitrofluorenone-5-carboxylic acid; 2,7-dinitrofluorenone-5-carboxylamide; 2-nitrofluorenone-5,7-dicarboxylic acid; 2,4-dinitrofluorenone-5,7-dicarboxylic acid was studied. The highest activity was demonstrated for 2,7-DNF-5-KA and 2,7-DNF-5,7-DK which induced frameshift mutations in the tester strains Salmonella typhimurium TA1537, TA97, TA1538, TA98. High mutagenicity of these compounds is correlated with the position of nitro-groups and the effects of carboxylic and carboxyamide groups

Abilev, S; Lyubimova, I; Migachev, G. (1993) Comparative mutagenic activity of 7 derivatives of biphenyl and fluorenone. Genetika 29(10):1640–1645.
BIOSIS COPYRIGHT: BIOL ABS. Comparative mutagenic activity of 7 derivatives of byphenyl and fluorenone, 4,4'-dinitrobyphenyl-2,2'-dicarboxic acid; 4,4',6,6'-tetranitrobyphenyl-2,2'-dicarboxicamid; 2-nitrofluorenon-5-carbosic acid; 2,7-dinitrofluorenon-5-carboxic acid; 2,7-dinitrofluorenon-5-carbonic amid; 2-nitrofluorenon-5,7-dicarboxic acid; 2,4-dinitrofluorenon-5,7-dicarboxic acid was studied. The highest activity was demonstrated for 2,7-DNF-5-KA and 2,7-DNF-5,7-DK which induced frameshift mutations in the tester strains Salmonella typhymurium TA1537, TA97, TA1538, TA98. High mutagenicity of these compounds is correlated with the position of nitrogroups and the effects of carboxic and carboxiamid groups

Alfheim, I; Becher, G; Hongslo, J; et al. (1984) Mutagenicity testing of high performance liquid chromatography fractions from wood stove emission samples using a modified Salmonella assay requiring smaller sample volumes. Environ Mutagen 6(1):91–102.
HEEP COPYRIGHT: BIOL ABS. Organic extracts of emissions from wood combustion were fractionated by high performance liquid chromatography (HPLC) into 25-28 fractions. Each fraction was tested for mutagenic activity in a modified Ames Salmonella/microsome bioassay requiring 1/3 of the test volumes needed for the ususal test. Direct mutagenic activity was noted predominantly in the most polar fractions, whereas indirect mutagenic activity was associated with the fractions containing polycyclic aromatic hydrocarbons (PAH) and with polar fractions probably consisting of aza-arenes and aromatic amines

Anderson, D; Styles, J. (1978) The bacterial mutation test. Six tests for carcinogenicity. Br J Cancer 37(6):924–930

Bickham, JW; Rowe, GT; Palatnikov, G; et al. (1998) Acute and genotoxic effects of baku harbor sediment on russian sturgeon acipenser guildensteidti. Bull Environ Contam Toxicol 61(4):512–518.
BIOSIS COPYRIGHT: BIOL ABS. RRM RESEARCH ARTICLE ACIPENSER-GUILDENSTEIDTI RUSSIAN STURGEON TOXICOLOGY POLLUTION GENETICS SEDIMENTS ENVIRONMENT ECOLOGY GENOTOXIC EFFECTS ACUTE EFFECTS BAKU AZERBAIJAN CASPIAN SEA PALEARCTIC REGION

Bos, RP; Theuws, JL; Jongeneelen, FJ; et al. (1988) Mutagenicity of bi-, tri- and tetra-cyclic aromatic hydrocarbons in the "taped-plate assay" and in the conventional salmonella mutagenicity assay. Mutat Res 204(2):203–206.
Aromatic hydrocarbons in the range of 1-4 nuclear rings were examined for mutagenicity in the so-called "taped-plate assay". This modification of the Ames assay is particularly equipped for the detection of volatile mutagens. Of the many compounds tested only phenanthrene, pyrene, benzo[c]phenanthrene and benzoacenaphthylene were positive in this assay. The present data underline the exceptional behaviour of fluoranthene by being a rather potent bacterial mutagen with a volatile nature (as found in a previous study)

Brams, A; Buchet, J; Crutzen-Fayt, M; et al. (1987) A comparative study, with 40 chemicals, of the efficiency of the salmonella assay and the sos chromotest (Kit procedure). Toxicol Lett 38:123-133,1987 –133

Bronzetti, G; Esposito, A; Pagano, G; et al. (1981) A comparative study on the toxicity and mutagenicity of biphenyl (BP) and diphenyl ether (DPE) in sea urchin, S. typhimurium and S. cerevisiae. Mutat Res 85(4):233

Brouns, R; Poot, M; De Vrind, R; et al. (1979) Measurement of DNA-excision repair in suspensions of freshly isolated rat hepatocytes after exposure to some carcinogenic compounds: its possible use in carcinogenicity screening. Mutat Res 64(6):425–432.
HEEP COPYRIGHT: BIOL ABS. When suspensions of freshly isolated rat hepatocytes were exposed to a number of carcinogenic compounds, it was possible to measure an increased UDS (unscheduled DNA synthesis) by a rapid procedure via liquid-scintillation counting. For a number of carcinogenic compounds and some of their non-carcinogenic structural analogs a good correlation between the carcinogenic property and the ability to induce UDS was demonstrable. Of 12 carcinogenic compounds belonging to several different chemical classes, 10 gave rise to an increased UDS. All 4 non-carcinogenic compounds tested were negative. This method can be of value as a routine screening test, in combination with other short-term test systems, thus improving the predictive value of screening in vitro with respect to carcinogenicity

Chroust, K; Kuglik, P; Relichova, J; et al. (1997) Drosophila melanogaster, *Vicia faba* and *Arabidopsis thaliana* short-term bioassays in genotoxicity evaluation of air and soil samples from sites surrounding two industrial factories in the Czech Republic. Folia Biologica (Prague) 43(2):71–78.
BIOSIS COPYRIGHT: BIOL ABS. The Somatic Mutation and Recombination Test (SMART) in wing cells of Drosophila melanogaster, the Vicia faba cytogenetic te

Chung, K; Adris, P. (2002) Growth inhibition of intestinal bacteria and mutagenicity of aminobiphenyls, biphenyl and benzidine. Abstr Gen Meeting Am Soc Microbiol 102:10.

Chung, KT; Adris, P. (2003) Growth inhibition of intestinal bacteria and mutagenicity of 2-, 3-, 4-aminobiphenyls, benzidine, and biphenyl. Toxicol In Vitro 17(2):145–152.

Claxton, LD. (1983) Characterization of automotive emissions by bacterial mutagenesis bioassay a review. Environ Mutagen 5(4): 609–632.
HEEP COPYRIGHT: BIOL ABS. HUMAN SALMONELLA AIRBORNE POLLUTANTS OXYGEN COMBUSTION PRODUCTS DIESEL GASOLINE MAMMALIAN UPTAKE METABOLISM

Cline, J; McMahon, R. (1977) Detection of chemical mutagens: use of concentration gradient plates in a high capacity screen. Res Commun Chem Pathol Pharmacol 16:523–533

Debnath, A; Debnath, G; Shusterman, A; et al. (1992) A QSAR investigation of the role of hydrophobicity in regulating mutagenicity in the Ames test: 1. Mutagenicity of aromatic and heteroaromatic amines in Salmonella typhimurium TA98 and TA100. Environ Mol Mutagen 19(1):37–52.

Quantitative structure-activity relationships (QSAR) have been derived for the mutagenic activity of 88 aromatic and heteroaromatic amines acting on Salmonella typhimurium TA98 + S9. Mutagenic activity is linearly dependent on hydrophobicity, the energy of the highest occupied molecular orbital, and the energy of the lowest unoccupied molecular orbital of the amine. The dependence of mutagenic activity on hydrophobicity and electronic effects is nearly identical for TA98 and TA100. Mutagenic activity in TA98 is also found to depend on the size of the aromatic ring system. Different QSARs are derived for the mutagenic activity of hydrophilic amines (log P < 1) acting on either TA98 or TA100. The mechanism of amine activation and reaction with DNA is considered in light of these findings

Donnelly, K; Davol, P; Brown, KW; et al. (1987) Mutagenic activity of two soils amended with a wood-preserving waste. Envion Sci Technol 21(1):57–64.
BIOSIS COPYRIGHT: BIOL ABS. RRM SALMONELLA-TYPHIMURIUM ASPERGILLUS-NIDULANS PENTACHLOROPHENOL PYRENE TRIMETHYLNAPHTHALENE FLUORANTHENE ACENAPHTHYLENE CYCLOPENTAPHENANTHRENE SOIL POLLUTION LAND DISPOSAL WASTE DISPOSAL HAZARDOUS WASTE ENVIRONMENTAL SURVEILLANCE

Dow Tox Res Lab. (1976) Cytogenetic effects of diphenyl-99 on rat bone marrow cells. Submitted under TSCA Section 8D; EPA Document No. 878213726; NTIS No. OTS0206456.

Fujita, H; Hiraga, K. (1980) Mutagenicity of paired fungicide mixtures in the Salmonella/microsome test. Tokyo Toritsu Eisei Kenkyusho Kenkyo Nempo (Annu Rep Tokyo Metrop Res Lab Public Health) 31(2):29–32.
PESTAB. The mutagenicity of 6 paired combinations of the fungicides thiabendazole, o-phenylphenol, biphenyl and butyl p-hydroxybenzoate in solution in DMSO was evaluated using the Ames test. Concentrations of 1, 10, 100 and 1000 mug fungicide/plate were used. Homogenate of male Wistar rat liver, induced by phenobarbital, was applied at 150 mul/plate. A mixture of 1000 mug thiabendazole and 30 mug o-phenylphenol showed a 3-fold increase in revertant colonies, corresponding to 0.014 revertants/mumol thiabendazole. o-Phenylphenol was concluded to be a weak comutagen

Fujita, H; Kojima, A; Sasaki, M; et al. (1985) Mutagenicity test of antioxidants and fungicides with *Salmonella typhimurium* TA97a, TA102. Kenkyu Nenpo-Tokyo-Toritsu Eisei Kenkyusho 36:413–417

Garberg, P; Bolcsfoldi, G. (1985) Evaluation of a genotoxicity test measuring DNA strandbreaks in mouse lymphoma cells by alkaline unwinding and hydroxylapatite chromatography. Environ Mutagen 7(Suppl. 3):73

Garberg, P; Akerblom, E-L; Bolcsfoldi, G. (1988) Evaluation of a genotoxicity test measuring DNA-strand breaks in mouse lymphoma cells by alkaline unwinding and hydroxyapatite elution. Mutat Res 203(3):155–176.
BIOSIS COPYRIGHT: BIOL ABS. RRM TOXICITY CARCINOGENICITY MUTATION CARBON TETRACHLORIDE PREDNISOLONE ANTHRANILIC ACID BENZOQUINONE P CHLOROANILINE DIETHYLMALEATE GLUCOSE PROCARBAZINE HYDROCHLORIDE

Garrett, NE; Stack, HF; Waters, MD. (1986) Evaluation of the genetic activity profiles of 65 pesticides. Mutat Res 168:301–325

Glatt, H; Anklam, E; Robertson, LW. (1992) Biphenyl and fluorinated derivatives: liver enzyme-mediated mutagenicity detected in Salmonella typhimurium and Chinese hamster V79 cells. Mutat Res 281(3):151–156.
Hepatocarcinogenic polychlorinated and polybrominated biphenyls usually show negative results in in vitro mutagenicity assays. Problems in their testing result from their low water solubility and their slow rate of metabolism. We therefore investigated better soluble model compounds, namely biphenyl and its 3 possible monofluorinated derivatives. In the direct test, these compounds proved to be nonmutagenic in Salmonella typhimurium TA98 and TA100 (reversion to histidine prototrophy) and in Chinese hamster V79 cells (acquisition of resistance to 6-thioguanine). However, when the exposure was carried out in the presence of NADPH-fortified postmitochondrial fraction of liver homogenate from Aroclor 1254-treated rats, all 4 compounds showed mutagenic activity in V79 cells. 3-Fluorobiphenyl produced strong mutagenic effects in S. typhimurium TA100 as well, whereas the other biphenyls were inactive. In strain TA98, 3- and 4-fluorobiphenyl showed mutagenic activity. This mutagenicity was enhanced in the presence of 1,1,1-trichloropropene 2,3-oxide, an inhibitor of microsomal epoxide hydrolase, thus suggesting that epoxides may be active metabolites

Hanada, S. (1976) The dietary habits of the Japanese and antifungal treatment of citrus fruits with biphenyl and o-phenylphenol. Eiyo To Shokuryo (Food Nutr) 29(1): 67-68 1976.

Hanada, S. (1977) Studies on food additives, diphenyl (biphenyl) and O-phenyl phenol from the view point of public health. Part 2. On the toxicities of diphenyl and O-phenyl phenol. Nagoya Shiritsu Daigaku Igakkai Zasshi (J Nagoya City Univ Med Sch) 28(3): 983-995 .

Haugen, D; Stamoudis, VC. (1986) Isolation and identification of mutagenic polycyclic aromatic hydrocarbons from a coal gasifier condensate. Environmental Research 41:400–419.
Bacterial mutagenesis tests in combination with multidimensional high performance liquid chromatography methods were used to isolate and identify a series of mutagenic products from the neutral fraction of a carcinogenic tar generated by a coal gasification process. Mutagenic activities were measured using Salmonella-typhimurium strains (TA-98) and (TA-100). Due to the presence of alkyl and methylene bridged products in the fraction tested, the mutagens present in reversed phase and normal phase high pressure liquid chromatography systems were identified by means of capillary column gas chromatographic fractionation and subsequent resolution by gas chromatography combined with mass spectrometry. The prevailing mutagenic products consisted of a series of unsubstituted polynuclear aromatic compounds with four to six rings, together with their alkylated homologs and methylene bridged products. The majority of the unsubstituted products were carcinogenic compounds of the same type as those identified in other coal and cigarette tars, such as chrysenes, benz(a)anthracenes, biphenyls, fluorenes, and benzpyrenes. The authors conclude that the method used is well suited for the analysis of mixtures of aromatic products and their alkyl homologs and that the polynuclear compounds generated during coal gasification are not quantitatively different from those generated during other combustion processes

Haworth, S; Lawlor, T; Mortelmans, K; et al. (1983) Salmonella mutagenicity test results for 250 chemicals. Environ Mutagen 5(Suppl. 1):1–142

Hellmer, L; Bolcsfoldi, G. (1992) An evaluation on the Escherichia coli K-12 uvrB/recA DNA repair host-mediated assay: I. In vitro sensitivity of the bacteria to 61 compounds. Mutat Res 272(2):145–160.
BIOSIS COPYRIGHT: BIOL ABS. A differential DNA repair test was evaluated in vitro, using derivatives of Escherichia coli K-12 343/113 with the genotype uvrB-/

Houk, VS; Schlakowsky, S; Claxton, LD. (1989) Development and validation of the spiral salmonella assay: an automated approach to bacterial mutagenicity testing. Mutat Res 223(1):49–64.
BIOSIS COPYRIGHT: BIOL ABS. RRM CHEMICAL TOXICITY CARCINOGENICITY TESTING

Hsia, M; Kreamer, B; Dolara, P. (1983) Quantitation of chemically induced DNA damage and repair in isolated rat hepatocytes by a filter elution method. Dev Toxicol Environ Sci 11(375):378

Hsia, M; Kreamer, B; Dolara, P. (1983) A rapid and simple method to quantitate chemically induced unscheduled DNA synthesis in freshly isolated rat hepatocytes facilitated by DNA retention of membrane filters. Mutat Res 122(2):177–186.
HEEP COPYRIGHT: BIOL ABS. The filter elution method used for the detection of DNA strand breaks was modified to quantitate chemically induced DNA repair which is measured as unscheduled DNA synthesis (UDS) in suspension of freshly isolated rat hepatocytes. This method is based on DNA purification by retention on polyvinyl chloride filters, and is capable of handling a large number of samples simultaneously. By using the present assay system, positive dose-dependent UDS data was obtained on the following carcinogens: aflatoxin B1, 2-acetylaminofluorene, 4-aminobiphenyl, 2-aminofluorene, methyl methanesulfonate, N-methyl-N'-nitro-N-nitrosoguanidine and 4-nitroquinoline-1-oxide. Non-carcinogenic biphenyl, fluorene and sodium ascorbate did not elicit any detectable levels of UDS at all concentrations tested. UDS as measured by the present filter retention method may serve as an efficient and reliable means of screening chemical mutagens/carcinogens

Inoue, S; Yamamoto, K; Kawanishi, S. (1990) DNA damage induced by metabolites of o-phenylphenol in the presence of copper(II) ion. Chem Res Toxicol 3(2):144–149.
Reactivities of o-phenylphenol and its metabolites (2,5-dihydroxybiphenyl, 2-phenyl-1,4-benzoquinone) with DNA were investigated by a DNA sequencing technique, and the reaction mechanism was studied by UV-visible and ESR spectroscopies. In the presence of Cu(II), 2,5-dihydroxybiphenyl caused strong DNA damage even without piperidine treatment. Catalase, methionine, and methional inhibited the DNA damage completely, whereas mannitol, sodium formate, ethanol, tert-butyl alcohol, and superoxide dismutase did not. 2,5-Dihydroxybiphenyl plus Cu(II) frequently induced a piperidine-labile site at thymine and guanine residues. The addition of Fe(III), Mn(II), Co(II), Ni(II), Zn(II), Cd(II), or Pb(II) did not induce DNA damage with 2,5-dihydroxybiphenyl. When H2O2 was added, 2-phenyl-1,4-benzoquinone also induced DNA damage in the presence of Cu(II). Cu(II) accelerated the autoxidation

of 2,5-dihydroxybiphenyl to quinone. An ESR study revealed that the semiquinone radical is an intermediate of the autoxidation. Catalase had no inhibitory effect on the acceleration by Cu(II). Superoxide dismutase promoted both the autoxidation of 2,5-dihydroxybiphenyl and the initial rate of semiquinone radical production. ESR spin trapping experiments showed that the addition of Fe(III) produced hydroxyl radical during the autoxidation of 2,5-dihydroxybiphenyl, whereas the addition of Cu(II) hardly did so. The results suggest that DNA damage by 2,5-dihydroxybiphenyl plus Cu(II) is due to active species other than hydroxyl free radical

Ishidate, M, Jr.; Odashima, S. (1977) Chromosome tests with 134 compounds on Chinese hamster cells in vitro - a screening for chemical carcinogens. Mutat Res 48(3-4):337–354

Ishidate, M, Jr.; Sofuni, T; Yoshikawa, K; et al. (1984) Primary mutagenicity screening of food additives currently used in Japan. Food Chem Toxicol 22(8):623–636.
Salmonella/microsome tests (Ames tests) and chromosomal aberration tests in vitro using a Chinese hamster fibroblast cell line were carried out on 190 synthetic food additives and 52 food additives derived from natural sources, all of which are currently used in Japan. Fourteen out of 200 tested in the Ames assay showed positive effects and 54 out of 242 were positive in the chromosome test. Three additives (erythorbic acid, chlorine dioxide and beet red) were positive only in the Ames test, although their mutagenic potentials were relatively weak, while 43 additives were positive only in the chromosome test. Eleven additives (calcium hypochlorite, cinnamic aldehyde, L-cysteine monohydrochloride, Food Green No. 3 (Fast Green FCF), hydrogen peroxide, potassium bromate, sodium chlorite, sodium hypochlorite, sodium nitrite, cacao pigment and caramel) were positive in both the Ames test and the chromosome test. The usefulness of such primary screening tests combining two different genetic end-points, gene mutation and chromosomal aberration, and some correlation between mutagenicity and carcinogenicity of food additives are discussed

Kamiya, A; Ose, Y. (1987) Mutagenic activity and PAH analysis in municipal incinerators. Sci Total Environ 61:37–50.
BIOSIS COPYRIGHT: BIOL ABS. RRM POLYCYCLIC AROMATIC HYDROCARBONS VOLATILE EMISSION GASES ASH INCOMPLETE COMBUSTION LUNG CANCER

Kawachi, T; Yahagi, T; Kada, T; et al. (1980) Cooperative programme on short-term assays for carcinogenicity in Japan. IARC Sci Publ (27):323–330

Klopman, G; Contreras, R; Rosenkranz, HS; et al. (1985) Structure-genotoxic activity relationships of pesticides comparison of the results from several short-term assays. Mutat Res 147(6):343–356.

Kojima, A; Hiraga, K. (1978) Mutagenicity of citrus fungicides in the microbial system. Tokyo Toritsu Eisei Kenkyusho Nempo 29:83–85

Krassov, SV; Lukmanova, NE; Neiaskina, EV. (1992) [An analysis of the mutagenic activity of the chemical substances used in capron manufacture]. Gig Sanit 3:26–27

Kringstad, K; DE, SF; Stromberg, L. (1984) Evaluation of lipophilic properties of mutagens present in the spent chlorination liquor from pulp bleaching. Environ Sci Technol 18(3):200–203.
HEEP COPYRIGHT: BIOL ABS. By use of reversed-phase high-performance liquid chromatogrpahy, it was found that a minor part of the mutagenic activity of the spent chlorination liquor from the bleaching of softwood kraft pulp originates from compounds with a high degree of lipophilicity. The compounds appeared to be stable under conditions similar to those prevailing in receiving waters. The nature of the compounds was not known

Later, D; Pelroy, R; Stewart, D; et al. (1984) Microbial mutagenicity of isomeric 2-ring, 3-ring and 4-ring amino polycyclic aromatic hydrocarbons. Environ Mutagen 6(4):497–516.
HEEP COPYRIGHT: BIOL ABS. The isomers of various 2-, 3- and 4-ring amino polycyclic aromatic hydrocarbons were tested for mutagenic activity using a microbial plate incorporation test with 4 Salmonella typhimurium strains (TA98, TA100, TA1535 and TA1537). All compounds were assayed with an S9 metabolic activating enzyme system. The 2-ring compounds were tested only with TA98. All were weakly mutagenic (1-10 revolution/mug) except 2-aminobiphenyl, which was not mutagenic under these test conditions. All except 2 of the 13 aminophenanthrenes) were active frame shift mutagens: only the aminophenanthrenes were active base-pair mutagens. The potency of this group of isomeric compounds ranged from moderately (20 rev/mug) to strongly (> 5000 rev/mug) mutagenic. As a group, the pericondensed 4-ring amino compounds were the most mutagenic of the

3 groups tested. All of the aminofluoranthene and aminopyrene isomers showed significant mutagenic activity with TA98, TA100 and TA1537. In general, the mutagenic potency of the amino polycyclic aromatic compounds tested was highly dependent on the structural position of the amino group

Monsanto Co. (1990) Ames/salmonella mutagenicity assay of therminol vpi (final report) with cover sheet and letter dated 021690. Submitted under TSCA Section 8D; EPA Document No. 86-900000101; NTIS No. OTS0522355.

Monsanto Co. (1990) Micronucleus assay with therminol vp-1 with cover letter. Submitted under TSCA Section 8D; EPA Document No. 86-910000014; NTIS No. OTS0530068.

Monsanto Department of Health. (1987) The evaluation of the potential of therminol r vp-1 to induce unscheduled DNA synthesis in primary rat hepatocyte cultures (final report) with cover letter dated 042287. Submitted under TSCA Section 8D; EPA Document No. 86870000307; NTIS No. OTS0513056.

Narbonne, JF; Cassand, P; Alzieu, P; et al. (1987) Structure-activity relationships of the n-methylcarbamate series in salmonella typhimurium. Mutat Res 191:21–27.

Nishioka, H; Ogasawara, H. (1978) Mutagenicity testing for di phenyl derivatives in bacterial systems. Mutat Res 54:248–249.
HEEP COPYRIGHT: BIOL ABS. ABSTRACT ESCHERICHIA-COLI SALMONELLA-TYPHIMURIUM DNA REPAIR CARCINOGENICITY

Nohara, M; Hirayama, T; Fujioka, Y; et al. (1985) Relationship between mutagenic potency in *Salmonella typhimurium* and chemical structure of amino and nitro substituted biphenyls. Mutat Res 149(1):9–15.
Positional isomers of amino substituted biphenyls and nitro substituted biphenyls were assayed for mutagenicity in Salmonella-typhimurium. Mutagenicity tests were performed by the Ames method. The assays were carried out in-vitro on four histidine requiring strains of Salmonella-typhimurium: TA-98, TA-100, TA-98NR, and TA-98/1,8-DNP6. Each tester strain was routinely checked, with and without metabolic activation, for optimal response to known mutagenic chemicals: 5 micrograms (microg) per plate benzo(a)pyrene (50328) (BaP), 5microg per plate 2-acetylaminofluorene (53963) (AAF), or 0.5microg per plate 4-nitroquinoline-N-oxide (56575) (NQO). The assay was performed in the absence and presence of S9 mix from mammalian tissue to simulate mammalian metabolism. Structural requirements favoring mutagenic activity were the presence of substituents at the 4 position and their absence at the 2' position. Among the aminonitrobiphenyls, three of nine tested were extremely mutagenic. Introduction of an amino group to the 3' position or 4' position of 4-nitrobiphenyl (92933) or a nitro group to the 3' position or 4' position of 4-aminobiphenyl (92671) enhanced mutagenicity. Of the nine nitrobiphenyls tested, four were mutagenic in strains TA-98 and TA-100 in the absence of a microsomal metabolic activation system. Strain TA-98NR was not reverted by the direct acting mutagens, whereas strain TA-98/1,8-DNP6 was as revertible as strain TA-98. The authors conclude that the structural requirements favoring mutagenic activity of amino substituted or nitro substituted biphenyls in Salmonella-typhimurium are the presence of substituents at the 4 position and their absence at the 2 position

Nylund, L; Heikkila, P; Hameila, M; et al. (1992) Genotoxic effects and chemical compositions of four creosotes. Mutat Res 265(2):223–236.
BIOSIS COPYRIGHT: BIOL ABS. Four creosotes used in Finland for impregnating wood were tested in the Ames Salmonella test, the SCE test and the SOS chromotest. Compounds volatile at 37ê C were assayed using the taped plate testing protocol. The creosotes were fractionated according to their natural boiling ranges and the fractions were tested in the Ames Salmonella assay. Chemical compositions of creosotes and fractions were determined by high resolution gas chromatography/mass spectrophotometry techniques and by reversed phase high performance liquid chromatography. Mutagenic activities were shown to reside in fractions having the highest boiling point ranges (> 290ê C). The concentrations of mutagenic polycyclic aromatic hydrocarbons in creosotes and in some of their corresponding distillation fractions, when compared with mutagenic activities, indicated synergistic or antagonistic interactions

Pagano, G; Esposito, A; Giordano, GG; et al. (1983) Genotoxicity and teratogenicity of diphenyl and diphenyl ether: a study of sea urchins, yeast, and Salmonella typhimurium. Teratog Carcinog Mutagen 3(4):377–393.
This study was designed to investigate the possible genotoxic and teratogenic actions of diphenyl (DP), diphenyl ether (DPE), and their eutectic mixture, in a comparative approach including different test systems. Two microbial systems and a metazoan model were used: (1) diploid D7 strain of Saccharomyces cerevisiae; (2) Salmonella

typhimurium strains TA100, TA98, TA1535, TA1537, TA1538, TA1532, TA2636; and (3) sea urchins (Paracentrotus lividus and Sphearechinus granularis). Both compounds resulted in severe toxicity in all of test organisms at levels greater than or equal to 10(-5) M (approximately 2 ppm). DP caused genetic effects in yeast with and without activating system, while the two chemicals appeared to be ineffective in Salmonella up to toxic levels. The action of DP and DPE on sea urchins resulted in developmental defects and mitotic abnormalities, following exposure of embryos or by pretreatment of sperm or eggs. In this system DPE appeared to be more effective than DP by about one order of magnitude (minimal active concentrations: 10(-5) M vs 10(-4) M). The eutectic mixture, industrially used as a heat transfer medium, was tested in its virgin and used form, for genotoxicity and embryotoxicity. The latter appeared to be more effective than the virgin eutectic. This increase in the embryo- and genotoxicity of the used eutectic may be related to the appearance of newly formed compounds in the heat transfer process. These compounds have been separated by high-pressure liquid chromatography and detected by fluorimetry

Pathak, DN; Roy, D. (1993) In vivo genotoxicity of sodium ortho-phenylphenol: phenylbenzoquinone is one of the DNA-binding metabolite(s) of sodium ortho-phenylphenol. Mutat Res 286(2):309–319.
We have previously demonstrated microsomal cytochromes P450-dependent redox cycling of o-phenylphenol and in vitro genotoxicity of o-phenylphenol. In the present work, we have investigated in vivo covalent modification in skin DNA by Na-o-phenylphenol using the 32P-postlabeling method in an attempt to understand the biochemical mechanism of promotion of chemical-induced skin carcinogenesis by Na-o-phenylphenol. Topical application of Na-o-phenylphenol or phenylhydroquinone, a hydroxylated metabolite of o-phenylphenol, to female CD-1 mice skin produced 4 distinct major and several minor adducts in skin DNA. The total covalent bindings in skin DNA produced by treatment of mice with 10 mg and 20 mg Na-o-phenylphenol (doses shown to be effective for tumor promotion) were 0.31 fmoles/microgram DNA and 0.62 fmoles/microgram DNA, respectively. The adducts were not observed in untreated animal skin DNA. Pretreatment of mice with alpha-naphthylisothiocyanate, an inhibitor of cytochromes P450, or indomethacin, an inhibitor of prostaglandin synthase, resulted in lower levels of DNA adducts produced by Na-OPP. The in vitro incubation of DNA with o-phenylphenol or phenylhydroquinone in the presence of cytochromes P450 activation or prostaglandin synthase activation system produced 4 major adducts. The adduct pattern observed in the presence of in vitro enzymatic activation systems appears to be similar in chromatographic mobility to the in vivo adduct pattern. The chemical reaction of DNA or deoxyguanosine monophosphate with pure phenylbenzoquinone, an electrophilic metabolite of o-phenylphenol, also produced 4 major and several minor adducts. The 4 major adducts obtained in chemical reaction of phenylbenzoquinone with deoxyguanosine monophosphate are identical in chromatographic mobility to those of in vivo or in vitro DNA adducts. The results of this study demonstrated that o-phenylphenol or phenylhydroquinone, a hydroxylated metabolite of o-phenylphenol, is able to covalently bind to DNA. DNA binding can be inhibited by the inhibitor of cytochromes, P450 alpha-naphthylisothiocyanate or prostaglandin synthase, indomethacin. One of the DNA-binding metabolite(s) of o-phenylphenol both in vivo and in vitro may be phenylbenzoquinone. We conclude that Na-OPP is genotoxic. Genotoxicity caused by Na-o-phenylphenol treatment in CD-1 mice may play a role in the promotion of dimethylbenz[a]anthracene-induced skin neoplasm

Probst, G; McMahon, R; Hill, L; et al. (1981) Chemically-induced unscheduled DNA synthesis in primary rat hepatocyte cultures: a comparison with bacterial mutagenicity using 218 compounds. Environ Mutagen 3:11–32

Purchase, IF; Longstaff, E; Ashby, J; et al. (1978) An evaluation of 6 short-term tests for detecting organic chemical carcinogens. Br J Cancer 37(6):873–903.

Sasaki, YF; Saga, A; Akasaka, M; et al. (1997) In vivo genotoxicity of ortho-phenylphenol, biphenyl, and thiabendazole detected in multiple mouse organs by the alkaline single cell gel electrophoresis assay. Mutat Res 395(2-3):189–198.
In Japan, ortho-phenylphenol (OPP), biphenyl (BP), and thiabendazole (2-(4'-thiazolyl)benzimidazole, TBZ) are commonly used as a postharvest treatment to preserve imported citrus fruits during transport and storage. We used a modification of the alkaline single cell gel electrophoresis (SCG) (Comet) assay to test the in vivo genotoxicity of those agents in mouse stomach, liver, kidney, bladder, lung, brain, and bone marrow. CD-1 male mice were sacrificed 3, 8, and 24 h after oral administration of the test compounds. OPP (2000 mg/kg) induced DNA damage in the stomach, liver, kidney, bladder, and lung, BP (2000 mg/kg) and TBZ (200 mg/kg) induced DNA damage in all the organs studied. For OPP, increased DNA damage peaked at 3-8 h and tended to decrease at 24 h. For BP, on the contrary, increased DNA migration peaked at 24 h. That delay may have been due to the fact that OPP is metabolized by cytochrome 450 and prostaglandin H synthase to phenylbenzoquinone (PBQ), a DNA binding metabolite, and BP is metabolized to PBQ via OPP and m-phenylphenol. The positive response to TBZ, an aneugen, supports the in vivo DNA-damaging action of TBZ

Simmon, V; Riccio, E; Robinson, D; et al. (1979) In vitro microbiological mutagenicity and unscheduled dna synthesis studies of fifteen pesticides. Final report-phase III.

Snyder, R; Matheson, D. (1985) Nick translation-a new assay for monitoring DNA damage and repair in cultured human fibroblasts. Environ Mutagen 7:267–279

Sofuni, T; Hayashi, M; Matsuoka, A; et al. (1985) Mutagenicity tests on organic chemical contaminants in city water and related compounds ii. Chromosome aberration tests in cultured mammalian cells. Bull Natl Inst Hyg Sci (Tokyo) 103:64–75.
BIOSIS COPYRIGHT: BIOL ABS. RRM CHL CHINESE HAMSTER CELL CULTURE ACRYLONITRILE ACRYLAMIDE ANTHRACENE PYRENE ACETOPHENONE BIPHENYL 1 2 DICHLOROETHANE BENZALDEHYDE METABOLIC ACTIVATION

SRI International. (1989) Evaluation of the potential of therminol vp-1 to induce unscheduled DNA synthesis in primary rat hepatocyte cultures (final report) with attachments and cover letter dated 060889. Submitted under TSCA Section 8D; EPA Document No. 86-890000350; NTIS No. OTS0518147.

Tani, S; Yonezawa, Y; Morisawa, S; et al. (2007) Development of a new E. coli strain to detect oxidative mutation and its application to the fungicide o-phenylphenol and its metabolites. Mutat Res 628:123-128.

Toste, A; Sklarew, D; Pelroy, R. (1982) Partition chromatography-high-performance liquid chromatography facilitates the organic analysis and biotesting of synfuels. J Chromatogr 249(2):267–282.
HEEP COPYRIGHT: BIOL ABS. Partition chromatography (Sephadex LH-20 or C18-partition) followed by high-performance liquid chromatography facilitated the organic and mutagenic characterization of synfuel samples. The mutagens in oil shale retort waters were polar, whereas those in a shale oil ranged from moderately polar to polar. The mutagens in an solvent refined coal-II (SRC-II) distillate blend were primarily moderately polar. The mutagens in an SRC-I process solvent were both less polar and less heterogeneous than those of an SRC-I solid product. Known mutagens (primary aromatic amines and aza-polynuclear aromatic hydrocarbons) were identified in the SRC-I and SRC-II samples but not in the shale oil and retort waters. (This study may be applicable to environmental carcinogenesis.)

Vasilieva, S; Tanirbergenov, B; Abilev, S; et al. (1990) A comparative study of mutagenic and SOS-inducing activity of biphenyls, phenanthrenequinones and fluorenones. Mutat Res 244:321–329.
The mutagenic potency and SOS inducing activity of 23 polycyclic aromatic compounds, including biphenyls, phenanthrenequinones, and fluorenones, were examined. Fourteen of the 23 chemicals induced His(+) revertants in Salmonella-typhimurium (TA-1538) hisD305 (-1 frameshift); none induced His(+) reversions in (TA-1535) (base pair substitution). The mutagenicity of chemicals in (TA-98) was lower than in (TA-1538). SOS inducing activity was examined in terms of SOS inducing potency in Escherichia-coli (PQ-37) using an automated instrument controlled by a computer program for the SOS Chromotest. The presence of a nitro group and its location in the chemical structure had a dramatic effect on mutagenicity and the SOS response. While there was a close correlation between mutagenicity and SOS inducing activity of fluorenones and phenanthrenequinones, none of the biphenyls induced the SOS response and this property did not depend on mutagenic activity. The SOS Chromotest was particularly valid in detecting chemicals which gave rise to base pair substitutions through SOS induction; it could not, however, replace the Ames test for the primary screening of chemicals with unknown structure

Wangenheim, J; Bolcsfoldi, G. (1986) Mouse lymphoma tk+/- assay of 30 compounds. Environ Mutagen 8(Suppl. 6):90

Wangenheim, J; Bolcsfoldi, G. (1988) Mouse lymphoma L5178Y thymidine kinase locus assay of 50 compounds. Mutagenesis 3(3):193–205

Waters, MD; Sandhu, SS; Simmon, V; et al. (1982) Study of pesticide genotoxicity. Basic Life Sci 21:275–326

Westinghouse Electric Corp. (1977) Potential carcinogenicity testing of PCB replacements using the Ames test with cover letter. Submitted under TSCA Section 8D; EPA Document No. 878214672; NTIS No. OTS0206616.

Williams, D; Nestmann, E; Lebel, G; et al. (1982) Determination of mutagenic potential and organic contaminants of Great Lakes (Canada, USA) drinking water. Chemosphere 11(3):263–276.

HEEP COPYRIGHT: BIOL ABS. Extracts of organic compounds were obtained, using XAD-2 macroreticular resin, from drinking water supplies in 12 Great Lakes municipalities. The extracts were tested for mutagenic potential using the Salmonella/mammalian-microsome assay and analyzed for organochlorine pesticides, polyaromatic hydrocarbons, organophosphorous pesticides and trialkyl-arylphosphates. Grab samples of drinking water were also analyzed for volatile organic compounds. Dose-related increases in mutagenicity were found in extracts from 11 of the drinking water supplies. (This study could implicate human health hazards.)

Williams, G. (1978) Further improvements in the hepatocyte primary culture DNA repair test for carcinogens: detection of carcinogenic biphenyl derivatives. Cancer Lett 4(2):69–76.
HEEP COPYRIGHT: BIOL ABS. DNA repair in hepatocyte primary cultures was induced by simultaneous treatment with the carcinogen and (3H)thymidine for 18 h beginning immediately after attachment of cells. Unscheduled DNA synthesis elicited by carcinogens was determined by counting grains with an automatic grain counter. In 5 biphenyl derivatives, a correlation was found between carcinogenicity and the ability to induce DNA repair. The method offers promise as a means of screening chemical carcinogens

Williams, G. (1980) DNA repair and mutagenesis in liver cultures as indicators in chemical carcinogen screening, in: mammalian cell transformation by chemical carcinogens. Adv Mod Environ Toxicol 1:273–296

Williams, G; Mori, H; McQueen, C. (1989) Structure-activity relationships in the rat hepatocyte DNA-repair test for 300 chemicals. Mutat Res 221:263–286

Zimmermann, F; von Borstel, R; von Halle, E; et al. (1984) Testing of chemicals for genetic activity with Saccharomyces cerevisiae: a report of the U.S. Environmental Protection Agency Gene-Tox Program. Mutat Res 133:199–244

4.6. SYNTHESIS OF MAJOR NONCANCER EFFECTS

In addition to applicable studies highlighted in Sections 4.1–4.5:

Gombar, V; Borgstedt, H; Enslein, K; et al. (1991) A QSAR model of teratogenesis. Quant Struct-Act Relat 10(4):306–332.
BIOSIS COPYRIGHT: BIOL ABS. Four related QSAR models of teratogenesis in experimental animals have been developed one each for heteroaromatic, carboaromatic, alicyclic and acyclic compounds. The numbers of compounds in these models range from 40 (for the alicyclic model) to 144 (for the carboaromatic model). As determined by cross-validation using the leave-one-out, or jackknife, technique, the accuracy of the models in discriminating between teratogens and non-teratogens ranges from 92.4% to 96%. A single overall assessment of experimental teratogenesis was chosen as the biological endpoint; taking into account such factors as dosage, maternal toxicity, and affected organ systems remain to be subjects of further studies

Macina, OT; Sussman, NB; Grant, SG; et al. (2000) Computational evaluation of hazardous air pollutants for developmental toxicity using a structure activity approach. Toxicologist 54(1):298.
Birth defects cause significant infant mortality and morbidity, resulting in great emotional and economic burden in the United States as well as in the rest of the world. In the United States alone, during 1993, developmental abnormalities were the underlying cause of death for 21.3% of infants less than one year of age. There is concern that exposure to air pollutants may effect the integrity of human health within industrialized countries. The United States Environmental Protection Agency's list of Hazardous Air Pollutants were screened against Structure Activity Relationship models derived from a machine learning algorithm for predictions regarding risk of human developmental toxicity. Multiple random sampling was employed in order to derive 10 structurally based models which were utilized to screen individual and representative mixture Hazardous Air Pollutants. The results of the computational screen were pooled in the form of a cumulative index (indicating high, moderate, and low potential) and evaluated according to their level of confidence. Air pollutants such as 2-acetylaminofluorene, 4-aminobiphenyl, biphenyl, 4-nitrobiphenyl, 3,3'-dimethylbenzidine, and 3,3'-dichlorobiphenyl have been identified by the structural models to pose a high risk to the developing human fetus. An additional screen against a mutagenicity data base has identified additional compounds that may be suspect due to their genotoxic risk

Ohnishi, M; Yajima, H; Takemura, T; et al. (2000) Characterization of hydroxy-biphenyl-O-sulfates in urine and urine crystals induced by biphenyl and KHCOinf 3 administration in rats. J Health Sci 46(4):299–303.

Ohnishi, M; Yajima, H; Takeuchi, T; et al. (2001) Mechanism of urinary tract crystal formation following biphenyl treatment. Toxicol Appl Pharmacol 174(2):122–129.

Venman, BC; Flaga, C. (1985) Development of an acceptable factor to estimate chronic end points from acute toxicity data. Toxicol Ind Health 1(4):261–270.
BIOSIS COPYRIGHT: BIOL ABS. RRM HUMAN ANIMAL RAT LD-50 WATER POLLUTION CARCINOGEN REGULATION

4.7. EVALUATION OF CARCINOGENICITY

In addition to applicable studies highlighted in Sections 4.1–4.5:

Ames, BN; Gold, LS. (1998) The prevention of cancer. Drug Metab Rev 30(2):201–223.
BIOSIS COPYRIGHT: BIOL ABS. RRM LITERATURE REVIEW HUMAN ONCOLOGY CARCINOGENS CANCER DIET PESTICIDES RISK ASSESSMENT NEOPLASTIC DISEASE

Ames, BN; Gold, LS. (1998) The causes and prevention of cancer: the role of environment. Biotherapy (Dordrecht) 11(2-3):205-220.
BIOSIS COPYRIGHT: BIOL ABS. The idea that synthetic chemicals such as DDT are major contributors to human cancer has been inspired, in part, by Rachel Carson's passionate book, Silent Spring. This chapter discusses evidence showing why this is not true. We also review research on the causes of cancer, and show why much cancer is preventable. Epidemiological evidence indicates several factors likely to have a major effect on reducing rates of cancer: reduction of smoking, increased consumption of fruits and vegetables, and control of infections. Other factors are avoidance of intense sun exposure, increases in physical activity, and reduction of alcohol consumption and possibly red meat. Already, risks of many forms of cancer can be reduced and the potential for further reductions is great. If lung cancer (which is primarily due to smoking) is excluded, cancer death rates are decreasing in the United States for all other cancers combined. Pollution appears to account for less than 1% of human cance

Ayrton, A; McFarlane, M; Walker, R; et al. (1990) The induction of P450 I proteins by aromatic amines may be related to their carcinogenic potential. Carcinogenesis 11(5):803–809.
The hypothesis has been put forward that genotoxic aromatic amines which induce the P450 I family of haemoproteins, the major enzyme involved in their bioactivation, are more likely to be carcinogenic when compared to those chemicals that fail to do so. Induction of the hepatic P450 I family of proteins by carcinogenic aromatic amines and their non-carcinogenic isomers and analogues was investigated in the rat and correlated to their carcinogenic potential. The activity of the P450 I A1 protein was monitored by the O-deethylation of ethoxyresorufin and of the P450 I A2 by the activation of the premutagen Glu-P-1 to mutagenic intermediates in the Ames test. Results were always confirmed immunologically in Western blots employing antibodies to rat P450 I A1 which recognize both proteins of the P450 I family. With all groups of chemicals used in the present study, the members displaying carcinogenicity were always the more potent inducers, while the non-carcinogenic isomers or analogues displayed little or no induction. It appears that a relationship exists between the carcinogenicity of aromatic amines and their ability to induce hepatic P450 I activity

Brown, T. (1992) Methods to evaluate adverse consequences of genetic changes caused by pesticides. In: Tardiff, R; Scientific Group on Methodologies for the Safety Evaluation of Chemicals; International Council of Scientific Unions; eds. Methods to assess adverse effects of pesticides on non-target organisms. New York, NY, Chichester, England: John Wiley and Sons; pp. 221–242.
BIOSIS COPYRIGHT: BIOL ABS. RRM INSECT RESISTANCE INSECTICIDE SUSCEPTIBILITY MUTAGEN EVOLUTION

Cohen, SM; Ellwein, LB. (1991) Genetic errors cell proliferation and carcinogenesis. Cancer Res 51(24):6493–6505.
BIOSIS COPYRIGHT: BIOL ABS. RRM REVIEW HUMAN RAT LIVER DNA REPLICATION CHANGES CHEMICAL EXPOSURE

Cohen, SM. (1995) Cell proliferation in the bladder and implications for cancer risk assessment. Toxicology 102(1-2):149–159.
BIOSIS COPYRIGHT: BIOL ABS. Chemicals can increase carcinogenic risk by either directly damaging DNA or increasing cell replication or they can do both. These effects have different implications for a biologically-based extrapolation from rodent bioassays to humans. 2-Acetylaminofluorene (2-AAF) administered at low doses to mice for a lifetime has a different dose-response for the liver (approximately linear) compared to the urinary bladder (apparent no effect dose of 45 ppm with a sigmoidal dose response at 60-150 ppm), which can be explained if carcinogen metabolism, DNA adduct formation and cell proliferation effects are considered. In contrast to 2-AAF and other genotoxic chemicals, chemicals which form calculi in the urine do not generally damage DNA directly but increase cell proliferation dramatically by eroding the bladder surface, leading to regenerative hyperplasia. This occurs only at doses at which calculi form; lower doses do not produce calculi and, therefore, do not increase cell pr

Cohen, SM. (1995) Human relevance of animal carcinogenicity studies. Regul Toxicol Pharmacol 21(1):75–80.
Extrapolation of results from rodent bioassays involving high-dose exposures to possible carcinogenic risk in humans exposed to low doses is based on the assumptions of species relevance and high- to low-dose extrapolation. For genotoxic chemicals, such as 2-acetylaminofluorene and N-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide, these assumptions appear to be appropriate, although the dose response can be greatly modified by cell proliferation effects of these chemicals at high doses. In contrast, nongenotoxic chemicals, such as chemicals causing urinary calculi or sodium saccharin and related sodium and potassium salts, frequently are carcinogenic only at high doses and/or only in specific species. Consequently, for extrapolation of results for nongenotoxic chemicals these assumptions may not be appropriate

Cohen, SM. (1998) Cell proliferation and carcinogenesis. Drug Metab Rev 30(2):339–357.
BIOSIS COPYRIGHT: BIOL ABS. RRM JOURNAL ARTICLE MOUSE TUMOR BIOLOGY CELL BIOLOGY CARCINOGENS GENOTOXIC SODIUM SACCHARIN CELL PROLIFERATION CARCINOGENESIS

Harvey, R; Halonen, M. (1968) Interaction between carcinogenic hydrocarbons and nucleosides. Cancer Res 28:2183–2186

Kawachi, T; Yahagi, T; Kada, T; et al. (1980) Cooperative programme on short-term assays for carcinogenicity in Japan. IARC Sci Publ (27):323–330.

Miertus, S; Frecer, V; Majekova, M. (1991) Environmental effects in the molecular mechanisms of action of bioactive compounds. In: Beveridge, D; Lavery, R; eds. Theorectical biochemistry and molecular biophysics. Vol. 2. Proteins. Schenectady, NY: Adenine Press; pp. 131–152.
BIOSIS COPYRIGHT: BIOL ABS. RRM DNA PROTEIN CARCINOGENS SOLVENT EFFECTS TRANSPORT PROPERTIES

Newell, G. (1981) General mechanisms of carcinogenesis. In: Newell, G; Ellison, M; eds. Progress in cancer research and therapy. Vol. 17. Nutrition and cancer: etiology and treatment. New York, NY: Raven Press; pp. 49–58.
HEEP COPYRIGHT: BIOL ABS. HUMAN VIRUS ANIMAL GENETICS RADIATION CHEMICALS

Odashima, S. (1980) Cooperative program on long-term assays for carcinogenicity in Japan. IARC Sci Publ 27:315–322

Parke, DV. (1977) The activation and induction of biphenyl hydroxylation and chemical carcinogenesis. In: Ullrich, V; Roots, I; Hildebrandt, A; Estabrook, R; Conney, A; eds. Microsomes and drug oxidations. New York, NY: Pergamon Press; pp. 721–729.
PESTAB. Observations are presented which suggest that the activation of biphenyl hydroxylase represents a highly specific change in the physico-chemical state of the endoplasmic reticulum, produced by interaction with carcinogenic chemicals or their metabolites and resulting in a change in the nature of cytochrome P450 which, although apparently reversible, is not repeatable. Further evidence suggests that the activation of biphenyl 2-hydroxylase following the administration of carcinogens in vivo or the incubation of microsomal preparations with carcinogens plus NADPH in vitro leads to the metabolic activation of the carcinogen and formation of a highly reactive metabolite which, in addition to alkylating the nuclear DNA, also damages the endoplasmic reticu

Purchase, IF; Longstaff, E; Ashby, J; et al. (1978) An evaluation of 6 short-term tests for detecting organic chemical carcinogens. Br J Cancer 37(6):873–903.

A number of tests have been described which are thought to be capable of identifying carcinogens without using the actual induction of cancer as an endpoint. This study compared the performance of 6 such tests on a selection of 120 organic chemicals. The tests studies were: (1) mutation of Salmonella typhimurium; (2) cell transformation; (3) degranulation of endoplasmic reticulum; (4) sebaceous gland suppression; (5) tetrazolium reduction and (6) subcutaneous implant. A further 4 tests were examined briefly, but were not included in the complete evaluation. The chemicals were classified into carcinogens (58) and non-carcinogens (62) on the basis of published experimental data, and into 1 of 4 broad chemical classes. There was considerable variation between tests in their ability to predict carcinogenicity, with the cell-transformation test and the bacterial-mutation test being the most accurate (94% and 93% accurate respectively). These 2 tests were considered to be of general use in screening, since they were clearly more accurate than the others. Statistical consideration of various combinations of these tests showed that the use of cell transformation and bacterial mutation together, provide an advantage over the use of either test alone. The inclusion of the other 4 tests in a screening battery predictably resulted in a great increase in overall inaccuracy and loss of discrimination, even though the detection of carcinogens is improved. All the tests were shown to generate both false positive and false negative results, a situation which may be controlled by the use, where possible, of appropriate chemical-class controls, to identify the test which is optimal for the class of chemical under test. Structural analogy may have a part to play in the rapid detection of environmental carcinogens, and some general guidelines for its use are given

Roy, D. (1990) Cytochrome P-450 catalyzed redox cycling of ortho-phenylphenol. Biochem Int 22(5):849–858.
BIOSIS COPYRIGHT: BIOL ABS. o-Phenylphenol was converted to 2,5-dihydroxy biphenyl (phenylhydroquinone) by microsomal P-450. Depending on the cofactor used, microsomal enzymes catalyzed oxidation and/or reduction of phenylhydroquinone. Phenylhydroquinone was oxidized to phenyl 2,5'-p-quinone by cumene hydroperoxide-supported microsomal P-450. Phenyl 2,5'-p-quinone was reduced to phenylhydroquinone by cytochrome P-450 reductase. This study provides direct evidence of cytochrome P-450 catalyzed redox cycling of o-phenylphenol. It is postulated that redox cycling of o-phenylphenol may play a role in o-phenylphenol-caused bladder cancer

Sugar, J; Toth, K; Gsuka, O; et al. (1979) Role of pesticides in hepatocarcinogenesis. J Toxicol Environ Health 5(2-3):183–191.
PESTAB. Doses of TCPE and TCDD were administered to outbred Swiss H mice. The doses were given through gastric intubation over a period of 1 yr. The results of the study indicate that people are not subject to the harmful effects of TCPE when the chemical is applied as an herbicide according to the directions. However, the results also support the urgency of reducing exposure of workers producing or using TCPE. Liver tumors were enhanced in male mice exposed to TCPE, but TCDD caused no increase in the incidence of these tumors. No correlation was found between the results of in vivo carcinogenicity studies and induction of aryl hydrocarbon hydroxylase and biphenyl 2-hydroxylase activities

Tong, S; Ioannides, C; Parke, DV. (1977) Possible pitfalls of the biphenyl test for chemical carcinogens. Biochem Soc Trans 5(5):1372–1374.
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Yoshida, S; Masubuchi, M; Hiraga, K. (1978) Cytogenetic studies of antimicrobials on cultured cells. Tokyo Toritsu Eisei Kenkyusho Kenkyo Nempo (Annu Rep Tokyo Metrop Res Lab Public Health) 29(2):86–88.

4.8. SUSCEPTIBLE POPULATIONS AND LIFE STAGES

Baty, JD. (1979) Species, strain, and sex differences in metabolism. In: Hathaway, D; eds. Foreign compound metabolism in mammals. A specialist periodical report. London: Chemical Society; pp. 159–189.
PESTAB. Many species, strain and sex differences in the metabolism of foreign compounds have been documented. This brief review of some species differences includes comparisons of catabolic reactions, conjugation, biliary excretion and enzyme activity. The pharmacogenetics of sex and strain differences are also outlined. DDT metabolism was different in CF-1 mice and the Syrian hamster. The major urinary metabolites in both species were conjugates of bis(p-chlorophenyl)acetic acid. The mouse urine also contained small amounts of DDE. Minor qualitative differences and substantial quantitative differences were noted in the hydroxylation patterns of biphenyl in the rat, rabbit and guinea pig. The main metabolite in these three species was 4-hydroxybiphenyl. In studies on 16 strains of mice, piperonyl butoxide lengthened hexobarbitone sleeping times, but had no effect on zoxazolamine

paralysis times. Pretreatment of the mice with either phenobarbital or piperonyl butoxide had no effect on warfarin survival. A genetic influence in plasma protein binding has been found for the binding of racemic warfarin

Butcher, R; Page, R. (1981) Introductory remarks environmental and endogenous hazards to the female reproductive system. Environ Health Perspect 38:35–38.

Benford, D; Bridges, J. (1983) Tissue and sex differences in the activation of aromatic hydrocarbon hydroxylases in rats. Biochem Pharmacol 32:309–313.

Dencker, L; Danielsson, BR. (1987) Transfer of drugs to the embryo and fetus after placentation. In: Nau, H; Scott, WJ; eds. Pharmacokinetics in teratogenesis. Vol. 1. Interspecies comparison and maternal-fetal drug transfer. Boca Raton, FL: CRC Press, Inc; pp. 55–70.
BIOSIS COPYRIGHT: BIOL ABS. RRM HUMAN TOXICITY METALS ANESTHETIC GASES OCCUPATIONAL EXPOSURE

Hakkola, J; Pelkonen, O; Pasanen, M; et al. (1998) Xenobiotic-metabolizing cytochrome p450 enzymes in the human feto-placental unit role in intrauterine toxicity. Crit Rev Toxicol 28(1):35–72.

KURZEL, RB; CETRULO, CL. (1985) Chemical teratogenesis and reproductive failure. Obstet Gynecol Surv 40:397-424,1985 –424

Lum, PY; Walker, S; Ioannides, C. (1985) Foetal and neonatal development of cytochrome P-450 and cytochrome P-448 catalysed mixed function oxidases in the rat: induction by 3-methylcholanthrene. Toxicology 35:307–317.
The effect of age on the development of the polycyclic aromatic hydrocarbon induced cytochrome-P-448 and the phenobarbital induced cytochrome-P-450 was studied in Wistar-rats. Fetal and neonatal development of these cytochromes were investigated in rat livers from animals given a single intraperitoneal (ip) injection of 20 milligrams per kilogram (mg/kg) 3-methylcholanthrene (56495). Cytochrome-P-450 activity was monitored by following the N-demethylation of benzphetamine, and O-deethylation of ethoxyresorufin reflected cytochrome-P-448 activity. Developmental patterns of cytochrome-P-450 and cytochrome-P-448 activities differed markedly. As the animals grew, cytochrome-P-450 activity rose while that of cytochrome-P-448 was suppressed. Cytochrome-P-448 was the predominant form in the fetal and neonatal livers but was gradually replaced by cytochrome-P-450 in adult animals. The ip injection of 3-methylcholanthrene enhanced the O-deethylation of ethoxyresorufin and the 2-hydroxylation of biphenyl at all ages post partum. Extent of induction increased with age and no plateau was achieved even at 14 weeks following birth. Modest increases in total cytochrome-P-450 concentrations were observed at all ages but were statistically significant only in the older animals. The authors conclude that the inducibilities of cytochrome-P-450 and cytochrome-P-448 appear to be age dependent and that markedly different developmental patterns occur for cytochrome-P-450 and cytochrome-P-448

McPherson, F; Bridges, J; Parke, DV. (1976) The effects of benzopyrene and safrole on biphenyl 2-hydroxylase and other drug-metabolizing enzymes. Biochem J 154(3):773–780.

Pelkonen, O. (1977) Transplacental transfer of foreign compounds and their metabolism by the foetus. Prog Drug Metab 2(119):161.
PESTAB. Aspects of the placental transfer of foreign compounds and their metabolism by the fetus are reviewed in terms of the drugs and other xenobiotics likely to be encountered and the mechanism by which they are handled in various species. The human fetus is exposed, via the maternal organism, to many foreign substances; correlation of this fact with observed fetal damage is extremely difficult. Harmful effects may be caused directly by the xenobiotic compound or by a more active metabolite. Pesticides are among the environmental pollutants that are being examined for harmful effects to the fetus. The ability of the human fetus to oxidize foreign compounds mainly resides in the liver and adrenal glands, which possess cytochrome P-450-linked electron-transport chains. Some conjugation reactions are well developed in the fetus during the first half of pregnancy, whereas glucuronic acid conjugation seems to be somewhat deficient. Drug metabolism develops much later in fetuses of common laboratory animals than in human fetuses, predominantly after birth. The ability of the human fetus to oxidize foreign compounds seems to closely parallel to active steroid-hydroxylation characteristic of the human fetus. Possible consequences of the fetal drug metabolizing capacity are accumulation of water-soluble metabolites, formation of toxic intermediates, and interactions between steroids and antibiotics

Pelkonen, O; Moilanen, M-L. (1979) The specificity and multiplicity of human placental xenobiotic-metabolizing monooxygenase system studied by potential substrates, inhibitors and gel electrophoresis. Med Biol (Helsinki) 57(5):306–312.
HEEP COPYRIGHT: BIOL ABS. The specificity of the placental monooxygenase system to metabolize foreign compounds was studied by using different potential substrates and inhibitors and by performing electrophoresis of placental microsomes. Placental preparations from smokers catalyzed benzo(a)pyrene hydroxylation, 7-ethoxycoumarin O-deethylation and 2,5-diphenyloxazole hydroxylation, but not biphenyl hydroxylation at 2-, 3- or 4-C, aldrin epoxidation to dieldrin or coumarin hydroxylation or aminopyrine N-demethylation. Enzyme activities were inhibited by alpha-naphthoflavone, but to a much lesser extent by SKF 525-A (proadifen hydrochloride) or metyrapone. Correlations between the metabolism of benzo(a)pyrene, 7-ethoxycoumarin and 2,5-diphenyloxazole were highly significant. There was a clear difference in Michaelis-Menten constant of 7-ethoxycoumarin O-deethylatin between placentas from smokers and nonsmokers. Gel electrophoresis revealed that protein bands of placental microsomes in the region of cytochrome P-450 enzymes were less prominent than those of rat liver microsomes, a finding that accorded with the relative amounts of cytochrome P-450. There were no consistent differences in the electrophoretic pattern between placentas of viable benzo(a)pyrene hydroxylase activities. Results show that the human placental monooxygenase system is restricted in substrate specificity, that there may be a qualitative difference between smokers and nonsmokers and that the increase in several enzyme activities by cigarette smoking cannot be detected by the standard gel electrophoresis

Tredger, J; Chhabra, R; Fouts, J. (1976) Postnatal development of mixed-function oxidation as measured in microsomes from the small intestine and liver of rabbits. Drug Metab Dispos 4(1):17–24.
HEEP COPYRIGHT: BIOL ABS. The postnatal development of aminopyrine N-demethylase, aniline 4-hydroxylase, benzpyrene hydroxylase, biphenyl 4-hydroxylase, 7-ethoxycoumarin O-deethylase activities, NADPH-cytochrome c reductase and cytochrome P-450 was compared in microsomes from the liver and small intestine of New Zealand white rabbits. Apart from hepatic aniline hydroxylase activity, all of the xenobiotic-metabolizing enzyme activities examined had a similar pattern of development in the liver and the small intestine. In both tissues the ability to metabolize, xenobiotics was generally undetectable at 2 days of age and remained relatively low for the 1st 20 days of life. Thereafter, a rapid 2- to 5-fold increase in all the enzyme activities studied was noted, and adult values were reached or exceeded by 30 days of age. Subsequent development of xenobiotic-metabolizing enzyme activities in the small intestine, but not in the liver, exhibited a transient fall at 50 days of age before adult activities were attained after 75 days of age. The developmental pattern of cytochrome P-450 in the small intestine closely resembled that of the xenobiotic-metabolizing enzyme activities, but in the liver this correlation was less extact.