Literature Search Product for the Toxicological Review

of

Toxaphene

(CAS No. 8001-35-2)

In Support of Summary Information on the Integrated Risk Information System (IRIS)

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Literature Search Strategy

The Statement of Work provided by EPA called for a literature search not limited by time. An initial comprehensive search was conducted in PubMed using the terms (weathered toxaphene OR toxaphene OR 800-35-2) AND combinations of search terms based on the USEPA outline for a Toxicological Review to identify those references that would be relevant to the outlined sections. For Chapter 3, the search terms included absorption, distribution, fate, kinetics, metabolism, elimination, and biliary. For Chapter 4, the search terms included epidemiology, clinical, case, occupational, cohort, community, toxicity, reproductive, developmental, teratogenic, teratogenicity, neurotoxicity, immune, immunotoxicity, immunology, kidney, renal, nephrotoxicity, bladder, blood, hematopoietic, liver, hepatic, tumor promotion, mode of action, mechanism, mutagenicity and genotoxicity. The use of these search strings resulted in the identification of approximately 600 unique abstracts.

A Toxline search was also conducted using the same search strategy as used for PubMed. The combined hits from PubMed and Toxline were combined in a RefMan database, checked for duplicates, and subsequently all material showing the CASRN for toxaphene, or the word toxaphene alone as a keyword, were labeled “Relevant”.

Additional searches of Biosis, RTECS, Current Contents, FEDRIP, NTIS and Embase (in Dialog) were conducted using the same search strings as those used in PubMed. These searches yielded a limited number of useful hits that were added to the database.

The reference sections of ATSDR (1996) and Simon and Manning (2006) were compared to the database and any previously not identified references were added. Included in this LSP are studies on both weathered toxaphene and toxaphene. The TSCATS database of SRC was also searched, and any relevant reports not previously identified were added to the database.

The following Literature Search Product presents 339 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. References that apply to more than one section are listed only once in the most appropriate section and have an added reference to the other sections as they might apply. For Chapter 3, references that refer to more than two of the categories Uptake, Distribution, Metabolism, Excretion, or PBPK, were placed in an initial general section.

All references that the individual members of the research team consider primary references that are central to this IRIS Toxicological Review are highlighted in COLOR. Because of the limited number of studies with the keyword “weathered toxaphene” the relevant citations were expanded to include those that had the keyword “toxaphene”. References not highlighted represent various categories: those that contain the CASRN without evident relevance to toxicology 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.

Toxicological Review of
Weathered Toxaphene, CASRN 8001-35-2

1. INTRODUCTION

2. CHEMICAL AND PHYSICAL INFORMATION

Andrews, P; Vetter, W. (1995) A systematic nonmenclature system for toxaphene cogeners part I: Chlorinated bornanes. Chemosphere 31(8):3879-3886.
A systematic code for a comprehensive numbering of toxaphene congeners on the basis of IUPAC rules has been developed. All chlorinated bornanes were characterized with a descriptor consisting of up to six letters and numbers. Each descriptor presents both enantiomers in the case of chiral compounds. Furthermore, chlorinated bornane congeners with a known structure are presented with both IUPAC nomenclature and the new systematic code. A computer program listing all the congener numbers is available from the authors.

RTECS. (2006) Toxaphene. RTECS Number: XW5250000.

Casida, J; Holmstead, R; Khalifa, S; et al. (1974) Toxaphene insecticide: A complex biodegradable mixture. Science 183(124):520-521.
Adsorption and gas-liquid chromatography separate toxaphene into at least 175 polychlorinated 10-carbon compounds including Cl(6), Cl(7), Cl(8), Cl(9), and Cl(10) derivatives. One toxic component is 2,2,5-endo,6-exo,8,9,10-heptachlorobornane. Rats metabolically dechlorinate toxaphene, removing about half of the chlorine from the technical insecticide and from each of seven subfractions of varying composition and toxicity. Also may be used in Section(s): 4.2

IUPAC. (1979) Iupac reports on pesticides 7 toxaphene (camphechlor) a special report. Pure and Applied Chemistry 511583-1601.

NLM (National Library of Medicine). (2005) Toxaphene. HSDB (Hazardous Substances Data Bank). National Institutes of Health, U.S. Department of Health and Human Services, Bethesda, MD. Available from: <http://toxnet.nlm.nih.gov>.

REVIEW DOCUMENTS

ATSDR. (1996) Toxicological profile for toxaphene (update).
This updated report on toxaphene (8001352) discussed the health effects of inhalation, oral and dermal exposure to the chemical; toxicokinetics; chemical and physical information; production, use and disposal; the potential for human exposure; analytical methods for detection and quantification; and regulations and advisories pertinent to safe handling. Current human exposure occurs through ingestion of contaminated foodstuffs and possibly through inhalation of ambient air. OSHA indicates that the current 8 hour time weighted average permissible exposure level for toxaphene is 0.5mg/m3 in workplace air. Toxaphene was formerly used as a nonsystemic stomach and contact insecticide. The distribution and sale of remaining stocks of toxaphene formulations were permitted until December 31 of 1986. Toxaphene is persistent in the environment, and has been found at waste sties. Exposure to toxaphene may damage the

lungs, nervous system, liver, and kidneys. Animal studies have indicated that toxaphene may be a carcinogen.

Buranatrevedh, S. (2004) Cancer risk assessment of toxaphene. Ind Health 42(3):321-327.
The primary purpose is to do cancer risk assessment of toxaphene by using four steps of risk assessment proposed by the United States National Academy of Sciences/National Research Council (NAS/NRC). Four steps of risk assessment including hazard identification, dose-response relationship, exposure assessment, and risk characterization were used to evaluate cancer risk of toxaphene. Toxaphene was the most heavily used insecticide in many parts of the world before it was banned in 1982. It increased incidence of neoplasms of liver and uterus in mice and increased incidence of neoplasms of endocrine organs, thyroid, pituitary, adrenal, mammary glands, and reproductive systems in rats. From mice's and rats' study, slope factor for toxaphene is 0.8557 (mg/ kg/day)(-1). Lifetime average daily dose (LADD) of toxaphene from ambient air, surface water, soil, and fish were 1.08 x 10(-6), 5.71 x 10(-6), 3.43 x 10(-7), and 7.96 x 10(-5) mg/kg/day, respectively. Cancer risk of toxaphene for average exposure is 7.42 x 10(-5). From this study, toxaphene might have carcinogenic risk among humans. Also may be used in Section(s): 4.2

Casida, J; Saleh, M. (1978) Toxaphene composition and toxicology.
The composition and metabolism of toxaphene have been examined to aid in understanding the conditions under which this insecticide can be most effectively and safely used. Each of 8 toxaphene samples manufactured by Hercules Chemical Co. from 1949 to 1975 shows the same 29 major peaks and in almost identical ratios. About 85% of the total peak area is accounted for by these 29 peaks which individually vary from 1 to 8% of the total. The 8 toxaphene samples were easily differentiated from 12 samples of chlorinated terpenes from other manufacturers in the United States and abroad. There is surprisingly little variation in the acute toxicity of any sample. Five major toxaphene components (2,2,5-endo, 6-exo,8,9,10- heptachlorobornane (I) and its 3-exo-chloro-, 8-chloro, 9-chloro and 10-chloro- derivatives) collectively account for up to 23% of the technical grade toxaphene and up to 31% of those of chlorinated 2-exo,10-dichlorobornane. Chlorination of 2-exo,10- dichlorobornane provides a convenient source of I and other chlorinated bornanes. The toxicity to mice, houseflies and goldfish of the octachlorobornanes formed by introducing chlorine substituents into I, relative to I itself, generally decreases in the order: 9-chloro > 8-chloro > no added chlorine (I) > 3-exo-chloro, 5-exo-chloro or 10-chloro. Fat from chickens and mammals treated orally with toxaphene contains products similar in GLC characteristics to toxaphene itself whereas liver and feces contain toxaphene-derived products of greatly altered GLC properties. Toxaphene preparations and related chlorinated terpenes are mutagens in the histidine-requiring Salmonella typhimurium assay. The most potent mutagenic components, which are not identified, reside in the polar fractions on crystallization or column chromatography.

Casida, J; Saleh, M. (2002) Toxaphene composition and toxicology. EPA/600/1-78/060.
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were easily differentiated from 12 samples of chlorinated terpenes from other manufacturers in the United States and abroad. There is surprisingly little variation in the acute toxicity of any sample. Fat from chickens and mammals treated orally with Toxaphene contains products similar in GLC characteristics to Toxaphene itself whereas liver and feces contain Toxaphene-derived products of greatly altered GLC properties. Toxaphene preparations and related chlorinated terpenes are mutagens in the histidine-requiring Salmonella typhimurium assay. The most potent mutagenic components, which are not identified, reside in the polar fractions on crystallization or column chromatography.

Daston, G; Gooch, J; Breslin, W; et al. (1997) Environmental estrogens and reproductive health: A discussion of the human and environmental data. Reprod Toxicol 11(4):465-481. Estrogenic activity of certain xenobiotics is an established mechanism of toxicity that can impair reproductive function in adults of either sex, lead to irreversible abnormalities when administered during development, or cause cancer. The concern has been raised that exposure to ambient levels of estrogenic xenobiotics may be having widespread adverse effects on reproductive health of humans and wildlife. The purpose of this review is to evaluate (a) the nature of the evidence supporting this concern, and (b) the adequacy of toxicity screening to detect, and risk assessment procedures to establish safe levels for, agents acting by this mechanism. Observations such as adverse developmental effects after maternal exposure to therapeutic levels of the potent estrogen diethylstilbestrol or male fertility problems after exposure to high levels of the weak estrogen chlordecone clearly demonstrate that estrogenicity is active as a toxic mechanism in humans. High level exposur. Also may be used in Section(s): 4.5

de Geus, H; Besselink, H; Brouwer, A; et al. (1999) Environmental occurrence, analysis, and toxicology of toxaphene compounds. Environ Health Perspect 107 Suppl 1115-144. Toxaphene production, in quantities similar to those of polychlorinated biphenyls, has resulted in high toxaphene levels in fish from the Great Lakes and in Arctic marine mammals (up to 10 and 16 microg g-1 lipid). Because of the large variabiliity in total toxaphene data, few reliable conclusions can be drawn about trends or geographic differences in toxaphene concentrations. New developments in mass spectrometric detection using either negative chemical ionization or electron impact modes as well as in multidimensional gas chromatography recently have led researchers to suggest congener-specific approaches. Recently, several nomenclature systems have been developed for toxaphene compounds. Although all systems have specific advantages and limitations, it is suggested that an international body such as the International Union of Pure and Applied Chemistry make an attempt to obtain uniformity in the literature. Toxicologic information on individual chlorobornanes is scarce, but some reports have recently appeared. Neurotoxic effects of toxaphene exposure such as those on behavior and learning have been reported. Technical toxaphene and some individual congeners were found to be weakly estrogenic in in vitro test systems; no evidence for endocrine effects in vivo has been reported. In vitro studies show technical toxaphene and toxaphene congeners to be mutagenic. However, in vivo studies have not shown genotoxicity; therefore, a nongenotoxic mechanism is proposed. Nevertheless, toxaphene is believed to present a potential carcinogenic risk to humans. Until now, only Germany has established a legal tolerance level for toxaphene--0.1 mg kg-1 wet weight for fish. Also may be used in Section(s): 4.5

Dich, J; Zahm, S; Hanberg, A; et al. (1997) Pesticides and cancer. Cancer Causes Control 8(3):420-443.
Epidemiologic evidence on the relationship between chemical pesticides and cancer is reviewed. In animal studies, many pesticides are carcinogenic, (eg., organochlorines, creosote, and sulfallate) while others (notably, the organochlorines DDT, chlordane, and lindane) are tumor promoters. Some contaminants in commercial pesticide formulations also may pose a carcinogenic risk. In humans, arsenic compounds and insecticides used occupationally have been classified as carcinogens by the International Agency for Research on Cancer. Human data, however, are limited by the small number of studies that evaluate individual pesticides. Epidemiologic studies, although sometimes contradictory, have linked phenoxy acid herbicides or contaminants in them with soft tissue sarcoma (STS) and malignant lymphoma; organochlorine insecticides are linked with STS, non-Hodgkin's lymphoma (NHL), leukemia, and, less consistently, with cancers of the lung and breast; organophosphorous compounds.

EPA working group. (1987) Health effects assessment for toxaphene. Environmental Protection Agency 6008-88.
The data base for toxaphene contained studies in rats and mice that indicated that toxaphene was carcinogenic, causing thyroid tumors in rats and liver tumors in mice. Using data for combined incidences of hepatocellular adenomas and carcinomas in male B6C3F1 mice from the Litton Bionetics, Inc. (1978) study, U.S. EPA (1980a) calculated a human carcinogenic potency factor of 1.131 (mg/kg/day)E-1.

Gaines, TB. (1969) Acute toxicity of pesticides. Toxicol Appl Pharmacol 14(3):515-534.

Goldsmith, D. (2000) Linking environmental cancer with occupational epidemiology research: The role of the international agency for research on cancer (iarc). J Environ Pathol Toxicol Oncol 19(1-2):171-175.
BACKGROUND: The International Agency for Research on Cancer (IARC) provides the most credible assessment of carcinogenicity for the scientific community. IARC Monographs also suggest areas where new laboratory and epidemiology research on cancer should be focused. REVIEW: This presentation examines two recent IARC reports on silica and coal dust (from 1997), and on occupational exposures to insecticide and pesticide applications (from 1991). RESULTS: From the Silica Monograph, the research implications suggest that laboratory and epidemiology studies would be useful focusing on mixtures of hazards where silica is a significant component of the respirable environment: in coal mining (which has an excess of gastric cancers) with variations in silica exposure; in uranium mining where there is silica dust plus radon decay products, in foundries and steel-making plants where silica exposure is common as are other carcinogenic hazards; in agriculture where dusty farming may be common, and comparisons are needed with other polymorphs of silica, including amorphous quartz. Additional studies of lymphatic, dermal, and gastrointestinal malignancies are needed to determine if the evidence of silicocarcinogenesis extends to these tumor sites. Finally, some fundamental studies of adsorptive capability of silica and resultant biologic activity, including biomarker studies, are needed. In the pesticide realm, there are many active ingredients that have been shown to be 2B (or possible) carcinogens based on animal studies (or other evidence). Industrial epidemiology studies of workers manufacturing or handling chemicals such as atrazine, chlordane, dichlorvos, 2,4-D, and DDT should be undertaken. Cancer epidemiology

associations have been demonstrated for chemicals such as phenoxy acid herbicides, 2,4,5-T, lindane, methoxychlor, toxaphene, and several organophosphate insecticides for which laboratory studies are needed. CONCLUSIONS: IARC reviews offer many leads for future research and insightful protocols that can provide new leads for studying these common exposures under novel environmental conditions.

Goodman, J; Brusick, D; Busey, W; et al. (2000) Reevaluation of the cancer potency factor of toxaphene: Recommendations from a peer review panel. Toxicol Sci 55(1):3-16.
This reevaluation of the current U.S. EPA cancer potency factor for toxaphene is based upon a review of toxaphene carcinogenesis bioassays in mice conducted by Litton Bionetics (unpublished report, 1978) and the National Cancer Institute (NCI) (Technical Report Series No. 37, conducted by Gulf South Research Institute, 1979). The mechanistic data available for toxaphene, including consideration of the potential of the compound to induce genotoxicity, was examined with an emphasis on whether this information supports a change in the cancer potency factor. If a quantitative dose-response assessment for toxaphene is to be performed, the data from both the NCI and Litton cancer bioassays should be used. Additionally, liver tumor results from female mice, rather than male mice, should be used for estimating potential human cancer risk because the background rate of liver tumors in females is lower and less variable than that exhibited by males. An ED(10) was estimated as the point of departure. The mechanistic data were not sufficient to fully support a margin of exposure approach. Therefore, we believe that applying a linear extrapolation from the ED(10) to the origin is an appropriate means to estimate risk at low doses. This is a highly conservative approach and, when it is applied, we conclude that the current EPA cancer potency factor should be reduced from 1.1 (mg/kg/day)(-1) to 0.1 (mg/kg/day)(-1). Also may be used in Section(s): 4.5

IARC (1979) Toxaphene (polychlorinated camphenes). IARC Monogr Eval Carcinog Risk Chem Hum 20:327-348.

IARC (1987) Iarc monographs on the evaluation of the carcinogenic risk of chemicals to humans: Overall evaluations of carcinogenicity: An updating of iarc monographs volumes 1 to 42 supplement. 7(177).

IARC (1990) Iarc monographs on the evaluation of carcinogenic risks to humans - volume 79: Some thyrotropic agents. This document presents the views and expert opinions of an IARC working group which met in Lyon, France, 10-17 October 2000. It contains 19 monographs on thyrotropic agents (methimazole, methylthiouracil, propylthiouracil, thiouracil, doxylamine succinate, phenobarbital and its sodium salt, griseofulvin, spironolactone, sulfomethazine and its sodium salt, sulfamethoxazole, amitrole, chlordane and heptachlor, hexachlorobenzene, toxaphene, kojic acid, 2,4-diaminoanisole and its salts, N,N'-diethylthiourea, ethylenethiourea and thiourea). Contents of each monograph: exposure data; studies of cancers in humans; studies of cancers in experimental animals; other data relevant to an evaluation of carcinogenicity; summary of data reported and evaluation.

IARC (2001) Toxaphene. IARC Monographs on the evaluation of the carcinogenic risk of chemicals to humans 79:569-604.
Exposure data. Toxaphene is a complex mixture of chlorinated hydrocarbons produced by the

chlorination of camphene. Toxaphene was widely used from the late 1940s as an insecticide on crops and to control parasites on livestock. The use of toxaphene is presently banned or restricted in many countries. Occupational exposure to toxaphene has occurred during its production and application. Human exposure to toxaphene is still possible owing to its persistence in the environment and its consequent continuing occurrence in fish, milk and other foodstuffs. In those countries in which its use has been banned, dietary intake has probably decreased in recent years. Human carcinogenicity data. One case-control study of non-Hodgkin lymphoma and one of leukaemia not otherwise specified in the same populations showed no significant increase in risk associated with exposure to toxaphene. Animal carcinogenicity data. Toxaphene has been tested for carcinogenicity by oral administration in one study in mice and one study in rats. It increased the incidence of hepatocellular adenomas and carcinomas combined in male and female mice. In rats, it produced thyroid follicular-cell adenomas and carcinomas in both males and females and pituitary adenomas in females. Other relevant data. Toxaphene is lipid-soluble and accumulates in animals. It is metabolized by dechlorination and excreted into the bile. Toxaphene is a well-known microsomal enzyme inducer that increases phase I and II drug-metabolizing enzymes, consistent with a phenobarbital-like effect. It also increases the size of the thyroid gland and thyroid-stimulating hormone concentrations. Toxaphene produced hepatotoxicity and immunotoxicity in experimental animals. No reproductive or developmental effects were seen in three multigeneration studies in rats. An increased frequency of chromosomal aberrations was observed in the lymphocytes of workers exposed to toxaphene in one study. In mammalian cells in vivo, toxaphene did not bind to DNA or produce dominant lethal mutations. In vitro, toxaphene was mutagenic to bacteria but did not induce mutations in mammalian cells. It induced micronuclei in the only assay for this end-point performed in mammalian cells. It also induced sister chromatid exchange and inhibited gap junctional intercellular communication in cultured mammalian cells. Evaluation. There is inadequate evidence in humans for the carcinogenicity of toxaphene. There is sufficient evidence in experimental animals for the carcinogenicity of toxaphene. Overall evaluation. Toxaphene is possibly carcinogenic to humans (Group 2B). Also may be used in Section(s): 3.2 & 3.3

Jowa, L; Faust, J. (2000) Re: "Reevaluation of the cancer potency factor of toxaphene: Recommendation from a peer review". Toxicol Sci 58(2):416.

OEHHA (CAL-EPA). (2003) Public health goal document for toxaphene in drinking water.

Pereira, M. (1985) Mouse liver tumor data assessment of carcinogenic activity. An International Symposium on Advances in Health Risk Assessment for Systemic Toxicants and Chemical Mixtures Toxicol Ind Health 1(4):311-334.

Saleh, M. (1991) Toxaphene: Chemistry, biochemistry, toxicity and environmental fate. Rev Environ Contam Toxicol 1181-85.
The chemistry of toxaphene is now well developed; 20 isomers have been isolated and identified. The molecular weight and molecular formula are known for the remaining major components. The major metabolic degradation mechanisms for toxaphene in all organisms from bacteria to primates are now believed to the reductive dechlorination, reductive dehydrochlorination, and in some cases, oxidative dechlorination to produce hydroxyl derivatives, acids or ketones. Earlier reports that toxaphene was biodegradable were published before the advent of state-of-the-art

analytical methodology which has permitted detection at levels in the range of ppb. Toxaphene residues have recently been documented throughout the biosphere as well as in human milk, even though its use was banned in 1982. This global persistence is against previous beliefs that toxaphene was easily biodegradable. During the last decade advances have been achieved in the selectivity, accuracy, and sensitivity of detection techniques so that the presence of toxaphene throughout the biosphere has been extensively documented. Through the use of GC/MS and electron capture GC, toxaphene can now be detected at ppb levels, making possible a more consistent and accurate assessment of the compound's presence in organisms as well as in soil, water, and ground water. Toxaphene residues have been detected in human populations, fish and wildlife, soil, water, and ground water as well as in food. An FDA Food Survey study found residues of toxaphene exceeding regulatory limits in only 1% of the 14,492 food samples. Toxaphene was reported to be among the most frequently occurring residues found in total dietary foods for the period 1982-84. It was found 48 times based on two food consumption surveys, a level higher than the frequency of DDT, DCPA, pentachloroaniline, and methoxychlor. Toxaphene has been detected in two large, pooled samples of human milk collected from mothers living in Uppsala and Stockholm at a concentration of 0.1 mg/kg of milk fat. Accumulation of toxaphene occurs in water in areas where the insecticide is in use, and it may be quite persistent. In some Canadian lakes it was found in toxic concentrations up to five yr after fish have been killed. Several studies have documented the presence of toxaphene in rain water, e.g. 9 ng/L in rain samples from Lake Michigan. It is now clear that toxaphene is a global pollutant like DDT, PCBs, and other organochlorines. Toxaphene is persistent in soils and lake sediments and has been found in fish, in the ringed seal, in rain water, and in human milk. Also may be used in Section(s): 4.2

Saleh, M; Casida, J. (1979) Toxaphene composition, structure-toxicity relations and metabolism. In: (Geissbuehler, H, ed. Advances in pesticide science. Vol. 3; pp. 562-566.
A brief review of composition, structure-activity toxicities and metabolism and photodecomposition studies of toxaphene is presented. The most toxic component of the polychlorinated camphene mixture to mice, goldfish and houseflies is 2,2,5-endo, 6-exo, 8,9,9,10-octa chlorobornane. Comparisons of excretion studies indicate that toxaphene is metabolized by several routes in chickens, rats, mice, hamsters and guinea pigs, but none of the metabolic sites of action are clearly defined. Also discussed are the possible carcinogenic activity of toxaphene and the prospects for its futural use as an agriculture insecticide.

Saleh, M; Turner, W; Casida, J. (1977) Polychlorobornane components of toxaphene: Structure-toxicity relations and metabolic reductive dechlorination. Science 198(4323):1256-1258.
2,2,5-endo,6-exo,8,9,10-Heptachlorobornane and four derivatives of this heptachlorobornane, with an additional chlorine atom at position 3-exo,8,9, or 10, account for a major portion of the acute toxicity of toxaphene and for up to 23 percent of toxaphene composition as analyzed by open tubular column gas-liquid chromatography with an electron capture detector. Both in several organisms and model environmental systems and on photolysis, this heptachlorobornane undergoes facile reductive dechlorination at the geminal-dichloro group and sometimes dehydrochlorination.

Simon, T; Manning, R. (2006) Development of a reference dose for the persistent congeners of weathered toxaphene based on in vivo and in vitro effects related to tumor promotion. Regul

Toxicol Pharmacol 44(3):268-281.
Toxaphene is a mixture of chlorinated camphenes and bornanes that was produced and used in the United States until 1982. 1.3 million tons of toxaphene have been released worldwide. "Technical" toxaphene (TT) consists of a mixture of up to 800 different chemicals, known as congeners. TT weathers in the environment by both biotic and abiotic processes. The human body burden of toxaphene consists of only five persistent congeners that are not metabolized; three of these occur in considerably greater amounts than the other two. Because of the rapid metabolism and excretion of the non-persistent congeners, the persistent congeners that make up the human body burden most likely play a role in eliciting any potential adverse effects. EPA's toxicity assessment for TT is based on the occurrence of liver cancer in rodents, and considerable doubt exists whether this assessment is applicable to weathered toxaphene (WT). Using experimental results from European Union scientists, a reference dose (RfD) was developed for WT based on the three most persistent congeners that comprise the human body burden. The critical effect chosen was tumor promotion and this endpoint is considered protective for other endpoints as well. Although RfDs are typically derived for non-carcinogenic effects, the endpoint of tumor promotion is appropriate for RfD development because the experimental data suggest a dose threshold. The RfD for weathered toxaphene represented by the sum of the three major persistent congeners (summation 3PC) is 2E-05 mg/kg-day. To apply this reference dose to a particular WT mixture, information is needed regarding the percentage of summation 3PC in the mixture.

USEPA (1995) Toxaphene: Drinking water health advisory. TD3: The Drinking Water Health Advisory, Office of Water, has issued its report on the chemical toxaphene. The report covers the following areas: the occurrence of the chemical in the environment; its environmental fate; the chemical's absorption, distribution, metabolism and excretion in the human body; and its health effects on humans and animals, including its mutagenicity and carcinogenicity characteristics. Also included are the quantification of its toxicological effects; standards; analytical methods; and environmental treatment technologies. Draft rept. Supersedes PB91-143404. Also may be used in Section(s): 4.2

USEPA (1976) Criteria document for toxaphene. EPA-440/9-76-014.
The properties, toxicity, and environmental fate and effects of toxaphene (8001352) are reviewed. The chemical and physical properties of the compound are presented. Toxaphene is a chlorinated camphene with 30 to 40 principal constituents and a chlorine content from 67 to 69 percent. The toxic effects of toxaphene in water are given for representative types of organisms present in fresh, marine, and estuarine systems. On five pure cultures of phytoplankton, toxaphene has been found to be the most potent of 17 chlorinated hydrocarbons tested. The median lethal concentrations (LC50) for various freshwater invertebrates and the toxicity of toxaphene to various freshwater fishes in static bioassays are tabulated. The LC50 values in blue fish at various temperatures for 24 hour exposures are 9.7, 6.8, and 6.6 micrograms per liter (microg/l) at 12.7, 18.3, and 23.8 degrees-C, respectively. At 96 hours, the LC50 values are 3.2, 2.6, and 2.4microg/l for the respective temperatures. Effects on birds are described, with decreases in egg laying and hatching and in food intake and weight gain, with greater mortality in young birds. The acute oral and dermal toxicities of toxaphene in rats are compared with DDT (50293), chlordane (12789036), aldrin (309002), dieldrin (60571) and endrin (72208). The LC50 values of toxaphene for rats, mice, dogs, guinea-pigs, cats, rabbits, cattle, goats, and sheep are

listed. The authors conclude that toxaphene is a powerful insecticide capable of persisting in the aquatic environment, soil, or animal tissues for long periods and can accumulate in fish at high concentrations. The potential danger to terrestrial predators, including humans, must be considered. Also may be used in Section(s): 4.2

USEPA. (1978) Occupational exposure to toxaphene. A final report by the epidemiological studies program. Oppts.

Van Ert, M; Sullivan, J, Jr. (1992) Organochlorine pesticides. In: (Sullivan, J, Jr.; Krieger, G, eds.) Hazardous materials toxicology, clinical principles of environmental health. Baltimore, Maryland: Williams and Wilkins; pp. 1027-1052.
The toxicology and adverse health effects associated with exposure to organochlorine pesticides were discussed. These insecticides have demonstrated neurotoxic effects ranging from central nervous system excitation and seizures to muscle tremors, confusion, agitation, and coma. The chemical and physical properties, exposure, distribution, absorption, metabolism and excretion, clinical toxicity, carcinogenic, reproductive, and immunotoxic effects and regulation of DDT (50293), hexachlorocyclohexane (319846), lindane (58899), chlordane (57749), heptachlor (76448), aldrin (309002), dieldrin (60571), endrin (72208), isobenzan (297789), endosulfan (115297), chlordecone (143500), kelevan (4234791), mirex (2385855), toxaphene (8001352), dicofol (115322), and methoxychlor (72435) were discussed. A review of studies examining the concentrations of organochlorine pesticides found in human tissues was presented. Also may be used in Section(s): 3.3 & 4.2

Wang, G. (1984) Evaluation of pesticides which pose carcinogenicity potential in animal testing. Ii. Consideration of human exposure conditions for regulatory decision making. Regul Toxicol Pharmacol 4(4):361-371.
In reaching a regulatory decision on the use of pesticides with carcinogenic potential, it is of great importance to investigate the extent of dermal exposure and absorption of a pesticide to users and field workers. By applying this information, along with the appropriate carcinogenicity categorization of a pesticide, a reasonably sound regulatory decision can be derived. Seven pesticides were selected, based on adequacy of tumor data, and were taken through the tumor evaluation system as reported in Part I 1984, Regul. Toxicol. Pharmacol. 4, 355-360). A step-by-step analysis on how a regulatory decision is reached on each pesticide by the EPA and CDFA was discussed. Also may be used in Section(s): 4.5

WHO Working Group. (1984) Camphechlor. Identity, properties and analytical methods: Camphechlor (toxaphene) (C10H10C18 approx.) is an amber, waxy solid consisting of a complex mixture of polychlorinated bicyclic terpenes. Gas chromatography with electron capture detection is the method of choice for the determination of camphechlor. Use and sources of exposure: Camphechlor is a non-systemic contact and stomach insecticide with some acaricidal action. It is often used in combination with other pesticides. The main source of exposure for the general population is the residues of camphechlor in food, but these are generally very low. Environmental concentrations and exposure: Camphechlor is broken down in the environment by sunlight (ultraviolet radiation), high temperature, and by biodegradation. There are no details on the relative breakdown of the components of the mixture. Camphechlor is readily lost from the soil by evaporation, butt once it penetrates the soil,it is tightly bound to soil particles and very

resistent to leaching. Its half-life in soil has been reported to vary from 70 days to 12 years, depending on the type and condition of the soil. Accumulation of camphechlor occurs in water in areas where the insecticide is in use, concentrations of 0.001-0.065 mg/litre were found. In some waters it has been shown to persist for years at concentrations that are toxic for fish. Camphechlor is rapidly removed from crops by weathering and evaporation. Concentrations of camphechlor in ambient air in unsprayed areas are in the ng/m3 range. It is toxic for aquatic species (Daphnia pulex 48-h EC50 = 15, Sheepshead minnow 96-h LC50 = 1,1, and Selenastrum capricornutum EC50 = 380 ug/litre) and some terrestrial species (honey bee, 48-h LD50 = 0.144 ug/bee) and has been shown to bioaccumulate, mainly in aquatic species (BCF in fish > 1300). It may present a major hazard for aquatic organisms. It also poses a threat to birds (LD50 = 10-20 mg/kg). Camphechlor is absorbed following ingestion and inhalation, as well as through the skin. Detailed information is lacking on its metabolism, probably because of its complex composition. Both hydroxylation and dechlorination products have been found as metabolites. Excretion takes place via both urine and faeces. Studies on experimental animals: Camphechlor is moderately toxic, i.e., the oral LD50 values in the rat range from 60 to 120 mg/kg body weight and can on acute oral overexposure give rise to salivation, vomiting, hyperexcitability, convulsions, and death. The lethal dose for man is estimated to be 2 - 7 g. It is an irritant for the skin. In short-term and long-term studies on animals, hypertrophy of the liver with increased microsomal enzyme activity and histological changes in the liver cells occurs at high dose levels (1000 mg/kg diet), depending on the test conditions and the species tested. Induction of microsomal enzyme activity in the rat has been found at levels of 5 mg or more/kg diet. Hypertrophy of the thyroid and adrenals and degeneration of the tubular epithelium of the kidney have also been reported. At near lethal dosages, excitation of the CNS may occur. Camphechlor has been shown not to have any effects on reproduction and was not found to be teratogenic. It was mutagenic in Salmonella typhimurium but results of a dominant lethal test on mice were negative. It is carcinogenic for both rats and mice. Effects on man: Several cases of poisoning have been described in man due to contamination of food with camphechlor or to accidental ingestion of camphechlor formulations. Symptomatology consists of gastrointestinal complaints, followed by motor seizures. Some incidents in children were lethal. Although a survey of a population of workers in a plant manufacturing camphechlor did not reveal any cases of ill-health referable to their employment, some illness has been reported in a few people coming into contact with this chemical. A group of 8 women exposed to camphechlor were reported to have a higher incidence of chromosome abnormalities than the controls. Available epidemiological studies are not adequate to evaluate the carcinogenicity of camphechlor for human beings. Also may be used in Section(s): 3.2, 4.1, & 4.2

3. TOXICOKINETICS

Andrews, P; Headrick, K; Pilon, J; et al. (1996) Capillary gc-ecd and ecni gcms characterization of toxaphene residues in primate tissues during a feeding study. Chemosphere 32(6):1043-1053. Toxaphene is a pesticide whose use was banned in North America because of concerns regarding its toxicity. To obtain better data on the metabolism and toxicity of toxaphene in primates, a one year feeding study was carried out in cynomologous monkeys at a dose of 1 mg/kg/day for one year. Levels of toxaphene residues in blood and adipose tissue during the dosing period were measured by GC-ECD and ECNI GCMS. The dosing toxaphene mixture was found to be

extensively metabolized. Four chlorinated bornane congeners were the predominate residues found in the tissue samples. Blood levels of toxaphene residues plateaued at 40 ppb, adipose levels at approximately 4000 ppb. Kidney, liver, feces and urine were analyzed for toxaphene residues after necropsy. Also may be used in Section(s): 3.2, 3.3, 3.4, & 4.2

Chaturvedi, A; Kuntz, D; Rao, N. (1991) Metabolic aspects of the toxicology of mixtures of parathion, toxaphene and/or 2,4-d in mice. J Appl Toxicol 11(4):245-251.
The effects of mixtures of parathion (PA;5 mg kg-1), toxaphene (TOX; 50 mg kg-1)and/or 2,4-dichlorophenoxyacetic acid (2,4-D; 50 mg kg-1) on the hepatic mixed-function oxygenase (MFO) system were studied in ICR male mice (21-24 g) by oral intubation daily for 7 days. In general, TOX and TOX-containing mixtures were found to induce the metabolism of amidopyrine (21-52%), aniline (58-72%), phenacetin (239-307%), pentobarbital (104-148%) and benzo[a]pyrene (143-304%) in the 9000 g liver supernatants and to increase the hepatic cytochrome P-450 contents (57-80%). Furthermore, the TOX pretreatment was effective in enhancing the biotransformation of PA or paraoxon (PO) in the supernatants. This enhancement was not altered significantly by 5 mM EDTA. Although TOX increased the aliesterase activity in the serum and liver homogenates and supernatants by 31-158%, the activity of paraoxonase was not affected in these preparations. The TOX-induced increase in the metabolism of PA or PO was, at least in part, associated with the MFO system, and paraoxonase did not have significant involvement in the increase. These findings suggest that the toxicity of the PA + TOX mixture would be lower than that of PA, as TOX has the ability to increase the biotransformation of PA, as well as of PO, and the levels of aliesterase, thereby providing a pool of noncritical enzymes for the binding of PO. Because of these properties of TOX, it is anticipated that the toxicity of the PA + TOX + 2,4-D mixture also would be lower than that of PA. Also may be used in Section(s): 3.1, 3.2, 3.3, 3.4, 4.2, & 4.5

Crowder, L; Dindal, E. (1974) Fate of (sup)36cl-toxaphene in rats. Bull Environ Contam Toxicol 12(3):320-327.
Male rats received (SUP)36Cl-toxaphene (20 mg/kg, p. o. via stomach tube). The amount of toxaphene excreted in urine was greater than that observed with either dieldrin or mirex. Both single-dosed and redosed rats showed 90% of the dose recovered in the water fractions of feces. In almost all cases the greatest concentration of radioactivity in various tissues over a period from 3 hr to 20 days occurred at 12 hr, followed by a rapid decrease. Blood cells peaked at 3 days. Less than 10% of the dose remained after day 1. Most of the large concentration up to day 1 could be accounted for by the amount in the stomach. With respect to the nervous system, brain tissue did not concentrate an extraodinary amount of radioactivity. Fat storage appeared non-significant. Tissues and organs of rats following a redose of (SUP)36Cl-toxaphene retained 6. 0%. At the end of 20 days, it was determined that redosed rats had a 20% less dose retention than single-treated animals. Thus, rats retained less in their tissues when they contained a previous body burden.

Crowder, L; Whitson, R. (1980) Fate of toxaphene, methyl parathion, and chlordimeform combinations in the mouse. Bull Environ Contam Toxicol 24(3):444-451.
Male Swiss mice were used in studies designed to determine if combinations of methyl parathion (MP), toxaphene (T), and chlordimeform (C) affect the excretion, retention or mortality of any of the individual compounds. Mice were orally dosed with each compound alone and in

combination with the other compounds at 25 mg/kg T, 12.5 mg/kg MP, and 3.25 mg/kg C. Urine and feces were collected and mortality counts made at various intervals. After 192 hr, one mouse from each replicate was sacrificed and later analyzed for tissue retention, and the remaining animals were given an additional dose (redosed). Radioassay of feces and tissue samples was performed using scintillation counting techniques. The excretion of radioactivity derived from 36Cl-T in the urine was not altered by combinations of C and/or MP, but in the feces, less 36Cl was excreted when combined with MP or C-MP. The excretion of 14C following a single oral dose of 14C-C was not altered by combination with T and/or MP; however, the excretion of PNP, a metabolite of MP, was decreased by the addition of T. With regard to retention, lipids displayed no significant changes as a result of combining T with C and/or MP. Addition of C to T resulted in more 36Cl being deposited in the brain, muscle and testes, and the T-MP combination resulted in more 36Cl retained by tissues increased after a redose. The addition of T and/or MP to C resulted in lower 14C deposition in some tissues. Mortality occurred only in treatments containing MP, and all mortality occurred within 3 hr of dosing.

Mohammed, A. (1989) Studies on the fate and biological effects of toxaphene polychlorinated terpenes in-vitro and in-vivo. Acta Pharm Nord 1(2):105-106.
Also may be used in Section(s): 3.3, 3.4, & 4.2

Mohammed, A; Andersson, O; Biessmann, A; et al. (1983) Fate and specific tissue retention of toxaphene in mice. Arch Toxicol 54(4):311-321.
Series of female virgin and pregnant albino mice were i.v. injected with 14C-labelled- or unlabelled toxaphene (16 mg/kg b.w.). After survival times ranging from 1 min to 32 days the toxaphene distribution in the body was studied using whole-body autoradiography and capillary gas-chromatography. Autoradiographic studies have shown that after an initial accumulation in the liver, brown fat, lung, brain, kidney, and ovaria (corpora lutea) there was a gradual redistribution of radioactivity to the white fat within 4 h postinjection. The labelling was then decreasing rapidly and only negligible amounts of the radioactivity were present in the adipose tissue after 32 days. In the fetus only the liver and adrenals showed a distinct labelling. A specific and persistent accumulation of the label was detected in some zones of the adrenal cortex suggesting a possible direct interference of toxaphene with adrenal steroid hormone synthesis. The gas chromatographic pattern of toxaphene-derived residues in the tissue samples resembled that of the technical toxaphene, but was changing in different tissues with the time. The liver chromatograms indicated more extensive formation of metabolites. Also may be used in Section(s): 3.3 & 3.4

Pollock, G; Kilgore, W. (1980) Excretion and storage of [14c]toxaphene and two isolated [14c]toxaphene fractions. J Toxicol Environ Health 6(1):127-140.
The 7-d urinary and fecal excretions of [14C]toxaphene and two isolated [14C]toxaphene fractions (polar fraction 7 and nonpolar fraction 2) were determined in orally dosed rats. The urinary, fecal, and total excretions of toxaphene were, respectively, 22.5, 35.7, and 58.2% of the administered dose. The total excretions of fractions 2 and 7 were, respectively, 69.4 and 65.0%, and the overall order of excretion was fraction 2 greater than toxaphene greater than fraction 7. All three groups had low toxaphene levels (below 0.2 ppm) in all tissues analyzed except for fat, where significant levels were detected. Hexane and chloroform extracts of the urine revealed that the activity was more polar than the parent material for all three groups. Apparently, toxaphene

must be metabolized before it can be excreted in the urine. When fat extracts were analyzed by thin-layer chromatography and autoradiography, differences were found between the parent material and the extracted activity. There was an increase in polar activity in the residue obtained from toxaphene-treated rats. The fat from the fraction 2 group contained fraction 2 and two additional more polar spots, which represented about 11% of the total activity. The fat from the fraction 7 group also contained two additional spots, but they were less polar than fraction 7. Apparently, the metabolism of fraction 7 results in some products that are less polar and, perhaps, more persistent. Also may be used in Section(s): 3.2 & 3.3

Pollock, G; Hillstrand, R. (1982) The elimination, distribution, and metabolism of 14c-toxaphene in the pregnant rat. J Environ Sci Health B 17(6):635-648.
Pregnant Sprague-Dawley rats were orally administered 14C-toxaphene in olive oil on day 15 of pregnancy and housed in glass metabolism cages. Urine, feces, and tissues were collected and assayed for radioactivity. The elimination was similar to that in virgin females with the majority of activity excreted in the feces (38.4%; five days) and less in the urine (23.7%; five days). The fetuses contained the lowest levels of radioactivity of all tissues tested (28 ppb; five days) and fat contained the highest levels (7476 ppb; five days). A comparison of the activity in the fetuses with that in the dam's fat showed slight differences, indicating the presence of more polar compounds (perhaps metabolites). Also may be used in Section(s): 3.3 & 4.3

Sandanger, T; Odland, J; Tkachev, A; et al. (2003) Persistent organic pollutants in plasma of delivering women from arkhangelsk. Sci Total Environ 306(1-3):171-178.
The high levels of persistent organic pollutants have caused concern about human health, especially the health of the foetus and newborn child. This has especially been the case for Greenlandic and Canadian Inuits, where elevated levels of PCB and p,p'-DDE have been reported. In recent studies from arctic Russia the levels of beta-HCH and the DDT-group have been reported to be high, whereas the levels of PCB are low. However, the information from Northern Russia is, so far, incomplete. In this study, 27 delivering women from the city of Arkhangelsk, Russia, participated. They completed a questionnaire before delivery and plasma samples were collected after delivery. The analytical method developed to support this study involved gel permeation chromatography and silica gel purification, in addition to a traditional GC-MS method, and thus include acid labile compounds. The arithmetic mean levels of p,p'-DDE, beta-HCH and p,p'-DDT were 5.42, 3.59 and 1.17 microg/l, respectively. Toxaphene 26 and 50 were the only toxaphenes above the limit of detection, with arithmetic mean levels of 0.05 and 0.09 microg/l, respectively. Among the PCB congeners, PCB 138/163 was the most abundant with an arithmetic mean of 0.53 microg/l. The elevated levels of beta-HCH and p,p'-DDT as well as a low DDE/DDT ratio is a strong indication of fresh and maybe local sources in this area.

3.1. ABSORPTION

3.2. DISTRIBUTION

Archer, T; Crosby, D. (1966) Gas chromatographic measurement of toxaphene in milk, fat,

blood, and alfalfa hay. Bull Environ Contam Toxicol 170-75.

Barr, J; Woolfitt, A; Maggio, V; et al. (2004) Measurement of toxaphene congeners in pooled human serum collected in three U.S. Cities using high-resolution mass spectrometry. Arch Environ Contam Toxicol 46(4):551-556.
Because human toxaphene exposure data are largely lacking, we surveyed human serum pools collected from U.S. residents to determine the feasibility of measuring toxaphene in human samples and to determine whether additional analytical requirements were needed for routine measurement of toxaphene. We report a method for quantification of toxaphene congeners in human serum using a mixed-bed gradient solid-phase extraction and analysis using gas chromatography-high-resolution mass spectrometry with electron-impact ionization. In this method, we monitored low-mass fragment ions that were common to all 22 congeners. To verify the specific congeners detected, we further analyzed the extract using negative methane chemical ionization. We used this method to measure two specific congeners, Parlar 26 and 50, at concentrations ranging from about 3 to 30 pg/ml (0.7-7 ng/g lipid) in pooled human serum collected in Atlanta, Chicago, and Cincinnati. We identified several analytical parameters that must be strengthened to routinely measure toxaphene congeners in human samples. Also may be used in Section(s): 3.3

Bjerregaard, P; Dewailly, E; Ayotte, P; et al. (2001) Exposure of inuit in greenland to organochlorines through the marine diet. J Toxicol Environ Health A 62(2):69-81.
High organochlorine concentrations have been found among the Inuit in eastern Canada and in Greenland. The present study was undertaken to assess the exposure to organochlorines in relation to age, sex, and diet in a general population sample of Inuit from Greenland. Survey data and plasma concentrations of 14 polychlorinated biphenyl (PCB) congeners and 16 pesticides, including 5 toxaphene congeners, were recorded in a random population survey of 408 adult indigenous Greenlanders. In a two-stage design, the survey response rate was 66%, and 90% of those randomly selected for blood testing participated. This was equivalent to an overall response rate of 59%. The median plasma concentration of the sum of PCB congeners was 13.3 microg/L; the lipid-adjusted value was 2109 microg/kg. The PCB concentration was twice as high as among the Inuit of Nunavik, Canada, 25 times higher than in a control group from southern Canada, and several times higher than the values found in European studies. Concentrations were similarly elevated for all PCB congeners and pesticides. The PCB congener pattern was similar to previous observations from the eastern Canadian Arctic and Greenland. Concentrations showed statistically significant positive associations with age, marine diet, and male sex in multiple linear regression analyses. The exceptionally high plasma concentrations of several organochlorines among the Inuit of Greenland are attributed to a lifelong high intake of seafood, in particular marine mammals. Concentrations of PCB adjusted for the consumption of marine food increased until approximately 40 yr of age, which is equivalent to the birth cohorts of the early 1950s. The age pattern indicates that bioaccumulation of PCB started in the 1950s, which is a likely date for the introduction of the compounds into the Arctic environment.

Butler Walker, J; Seddon, L; McMullen, E; et al. (2003) Organochlorine levels in maternal and umbilical cord blood plasma in arctic canada. Sci Total Environ 302(1-3):27-52.
A baseline for exposure to organochlorine and metal contaminants has been established for mothers and newborns in the Northwest Territories and Nunavut areas of Arctic Canada.

Maternal and umbilical cord blood plasma organochlorine levels are described for Inuit, Dene, Metis, Caucasian and Other non-Aboriginal participants. Overall, 523 women volunteered to participate by giving their written informed consent between May 1994 and June 1999, resulting in the collection of 386 maternal blood samples, 407 cord blood samples and 351 maternal/cord pairs. Nearly half of all the participants regularly smoked cigarettes, including 77% of the Inuit participants. Maternal and cord results are presented for PCBs (as Aroclor 1260 and 14 congeners) and organochlorine pesticides, including p,p'-DDT, p,p'-DDE, beta-hexachlorocyclohexane (beta-HCH), hexachlorobenzene (HCB), cis and trans nonachlor, heptachlor epoxide, oxychlordane, mirex, dieldrin and toxaphene. Maternal PCB levels (as Aroclor 1260) averaged 4.42 (+/-9.03) microg/l in Inuit, which was 3.3 times higher than those found in Dene/Metis, and 3.4 times higher than levels in Caucasians. Mean DDE levels were 2.8 times higher in the Other non-Aboriginal group (Chinese, Filipino, East Indian and multiple ethnicity) than in the Inuit group, at 3.99 microg/l and 1.42 microg/l, respectively. Cord blood PCB levels (as Aroclor 1260) averaged 1.16 (+/-2.42) microg/l for Inuit participants, which was 3.3-4 fold higher than the other ethnic groups. PCBs, p,p'-DDE and hexachlorobenzene were detected in all maternal samples, and p,p'-DDE was detected in all cord samples. Regression coefficients for maternal/cord pairs are presented for selected organochlorines. Other results from this study, including maternal and cord metals data, will be presented elsewhere. Also may be used in Section(s): 3.3

Chan, H; Zhu, J; Yeboah, F. (1998) Determination of toxaphene in biological samples using high-resolution gc couples with ion trap ms/ms. Chemosphere 362135-2148.

Cooke, G; Newsome, W; Bondy, G; et al. (2001) The mammalian testis accumulates lower levels of organochlorine chemicals compared with other tissues. Reprod Toxicol 15(3):333-338. Tissues were obtained from three separate experiments in order to quantify the tissue distribution of organochlorine chemicals that are thought to be potential reproductive toxicants in males: 1) Sprague Dawley rats received 1 microCi of 14C-Aldrin or 14C-Dieldrin (20.6 microCi/micromole) i.p. once a week for three weeks. One week and four weeks after the last injection, tissues were harvested and stored at -80 degrees C. Tissue 14C levels were quantified by scintillation spectrometry. 2) Cis- or trans-nonachlor (0, 0.25, 2.5, 25 mg/kg body weight) were administered daily in corn oil to male rats by gavage for 28 days. Tissues were harvested and frozen at -80 degrees C on the 29th day. Organochlorine residues were extracted and quantified by gas chromatography with electron capture detection. 3) Technical grade toxaphene (0, 0.1, 0.4 or 0.8 mg/kg body weight) was ingested daily by female cynomolgus monkeys of reproductive age for 18 months prior to being mated with control males. Dosing continued during pregnancy and lactation. Their infants received toxaphene via breast milk, and upon weaning, they ingested the same dose as their mothers for 48 to 49 weeks until, at 77 to 80 weeks of age, tissues were harvested and stored at -80 degrees C. Organochlorine residues were extracted and quantified as previously stated. In all three experiments, organochlorine residues in the testis were lower than in most of the other reproductive tract and nonreproductive tract tissues we examined. For example, testicular aldrin and dieldrin levels were <5% the epididymal content; testicular cis- and trans-nonachlor were <25% the epididymal content and, testicular toxaphene levels were <15% of the epididymal content. The reasons for the low degree of accumulation by the testis in comparison with other tissues are unknown. However, the lower testicular content may afford germ cells some protection from the potentially toxic effects of

these chemicals. Also may be used in Section(s): 3.3

Cuadra, S; Linderholm, L; Athanasiadou, M; et al. (2006) Persistent organochlorine pollutants in children working at a waste-disposal site and in young females with high fish consumption in managua, nicaragua. Ambio 35(3):109-116.
The aim of this study was to assess persistent organochlorine pollutant (POP) levels in serum collected from children (11-15 years old) working and sometimes also living at the municipal waste-disposal site in Managua, located at the shore of Lake Managua, and in nonworking children living both nearby and also far away from the waste-disposal site. The influence of fish consumption was further evaluated by assessing POPs levels in serum from young women (15-24 years old) with markedly different patterns of fish consumption from Lake Managua. 2,2-bis(4-chlorophenyl)-1,1,1-trichloro-ethane (4,4'-DDT) and 2,2-bis(4-chlorophenyl)-1,1-dichloro-ethene (4,4'-DDE), gamma-hexachlorocyclohexane (gamma-HCH), polychlorinated biphenyls, pentachlorophenol, and polychlorobiphenylols were quantified in all samples. In general, the levels observed were higher than those reported in children from developed countries, such as Germany and United States. Toxaphene, aldrin, dieldrin, and beta-HCH could not be identified in any sample. The children working at the waste-disposal site had higher levels of POPs compared with the nonworking reference groups. In children not working, there were also gradients for several POPs, according to vicinity to the waste-disposal site. Moreover, in children, as well as in young women, there were gradients according to fish consumption. The most abundant component was 4,4'-DDE, but at levels still lower than those reported in children from malarious areas with a history of recent or current application of 4,4'-DDT for vector control. Also may be used in Section(s): 3.1 & 4.1

Deboer, J; Wester, P. (1993) Determination of toxaphene in human milk from nicaragua and in fish and marine mammals from the northeastern atlantic and the north sea. Chemosphere 27(10):1879-1890.
Concentrations of toxaphene (polychlorinated monoterpenes, chlorobornanes) were determined in human milk samples from Nicaragua and in fish from the North Sea. Relatively high toxaphene levels were found in the Nicaraguan human milk samples. The lack of correlation between the number of children of the mothers and toxaphene levels in their milk suggests a compensation of the elimination of toxaphene by a regularly high toxaphene intake. The increasing trend of toxaphene concentrations in North Sea fish sampled further away from the European coast suggests an aerial transport of toxaphene from the American continent to Europe. Also may be used in Section(s): 3.4

Ejobi, F; Kanja, L; Kyule, M; et al. (1996) Organochlorine pesticide residues in mothers' milk in uganda. Bull Environ Contam Toxicol 56(6):873-880.
Biosis copyright: biol abs. rrm research article human lindane aldrin hexachlorobenzene camphechlor chlordane heptachlor contamination. Also may be used in Section(s): 3.3

Gill, U; Schwartz, H; Wheatley, B. (1995) Toxaphene (polychlorinated camphenes) analysis in human blood Int J Environ Anal Chem.

Gill, U; Schwartz, H; Wheatley, B; et al. (1996) Congener specific analysis of toxaphene in serum using ecni-ms. Chemosphere 33(6):1021-1025.

A method for the determination of environmentally relevant toxaphene congeners (eg chlorinated bornanes (CHBs)) in serum is described. Four chlorinated bornane congeners are predominant in serum. Also may be used in Section(s): 3.3

Klisenko, M; Kuz'minskaya, U; Novachik. (1972) Distribution of polychlorocamphene in lipid fractions of tissues. Gig Sanit 37(12):96-97.
The distribution of polychlorocamphene (toxaphene) was studied by thin-layer chromatography in lipid fractions of liver, brain, and medulla oblongata tissues of albino rats fed single 120 and 24 mg/kg, or daily 2.4 mg/kg doses of polychlorocamphene for 3-6 months. Liver tissues contained polychlorocamphene only in free form, not associated with any lipid fraction. After administration of a single 24 mg/kg dose, the hepatic residue content decreased to 1.1 mg/kg from 2.25 mg/kg between the 1st and the 5th day; residues disappeared completely in 15 days. A close relationship between the hepatic residue content and dose was established. The residue level was independent of the duration of exposure in the chronic feeding test.
Polychlorocamphene appeared in lipid fractions of the brain and medulla oblongata 15 days after intake of a single 120 mg/kg dose. The residue levels in phospholipids, free cholesterol, triglycerides, and cholesterol esters were 0.9 mug/g, 0.2 mug/g, and 1.08 mug/g. The polychlorocamphene level in the brain phospholipid fraction increased by 66% as the administration of daily 2.4 mg/kg doses was extended from 3 to 6 months. The corresponding increase in the polychlorocamphene residue levels in phospholipids, free cholesterol, and another unidentified lipid fraction of the medulla oblongata averaged 65%.

Kutz, F; Wood, P; Bottimore, D. (1991) Organochlorine pesticides and polychlorinated biphenyls in human adipose tissue. Rev Environ Contam Toxicol 1201-82.
Halogenated organic compounds are highly lipophilic chemicals that are persistent in the environment as a result of their use and chemical stability. Some of these compounds are also present in the environment as metabolites or oxidation products of a parent compound or as by-products formed in the production of chlorinated compounds. Chronic exposure to the general population results mainly through the food chain. Because they are lipophilic, and because many are metabolized slowly, these chemicals tend to concentrate in body fat tissue. This contribution has described these halogenated organic compounds, discussed their use, regulation and prohibition throughout the world, and reviewed published studies on the levels of these chemicals found in the adipose tissue of humans and animals. For many years, residues of halogenated organic compounds have been detected in the human adipose tissue of individuals in a number of countries, including those in Europe, Asia, and Africa, as well as in the U.S. The levels detected have been used as an index of the level of general population exposure of these compounds over time. Over the past two decades, most countries have observed a steady decline of this level of exposure, reflecting a reduction in the use of these compounds, restrictions on or banning of their use, and a corresponding decrease in their environmental levels. The levels of concentrations vary from chemical to chemical as well as from isomer to isomer. Since the use of aldrin and dieldrin has now been banned or restricted in the U.S. and a number of other countries, residue levels have slowly decreased. Mean values in human adipose tissue in the U.S. and some foreign countries ranged from 0.04 to 0.40 ppm for dieldrin. Aldrin was detected only in Argentina and Poland in the 1970s and endrin was not detected anywhere at anytime. By 1978, all products containing BHC registered in the U.S. has been either discontinued or reformulated to incorporate lindane rather than BHC. The potential for exposure to BHC is

virtually nonexistent in the U.S.; however, exposure to lindane is possible since products containing this chemical are still marketed, and used particularly in the manufacture of human medicine. DDT was banned for agricultural purposes in the U.S. in 1972, although it is still used elsewhere for public health vector control. Since the decline in use of DDT, however, the average levels of concentration have also declined. Heptachlor, chlordane, and trans-nonachlor (a component of both heptachlor and chlordane) are chlorinated cyclodienes.

Kuz'Minskaya, U; Novachik, V; Klisenko, M. (1972) Distribution of polychlorocamphene in lipid fractions of tissues. Gig Sanit 37(12):96-97.
Experiments on rats demonstrated that the prolonged oral administration of the insecticide polychlorocamphene (2.4 mg/kg daily for 6 mo.) led to an increase of the permeability of the blood-brain barrier and to selective accumulation of the preparation in lipids of the brain and especially the spinal cord. Also may be used in Section(s): 4.4

Lacayo Romero, M; Dorea, J; Granja, A. (2000) Concentrations of organochlorine pesticides in milk of nicaraguan mothers. Arch Environ Health 55(4):274-278.
Breast-milk samples from 101 mothers from the basin of Rio Atoya, Nicaragua, were collected on two occasions within the first trimester of lactation. Milk samples were analyzed for 13 organochlorine pesticides: (1) p,p'-dichlorophenyldichloroethylene; (2) p,p'-dichlorophenyltrichloroethane; (3) p,p'-dichlorophenyldichlorodiene; (4) α-hexachlorocyclohexane; (5) β-hexachlorocyclohexane; (6) y-hexachlorocyclohexane; (7) δ-hexachlorocyclohexane; (8) toxaphene; (9) dieldrin; (10) endrin; (11) aldrin; (12) heptachlor; and (13) heptachlor-epoxide. Organochlorines of the dichlorodiphenylethane class (i.e., p,p'-dichlorodiphenylethane and p,p'-dichlorodiphenylethane) were found in all samples and at the highest mean concentrations observed in the study. Chemicals in the hexachlorocyclohexane family (i.e., α- and δ-hexachlorocyclohexane) were not found at all (0%), and the other hexachlorocyclohexane compounds (i.e., β > y) were found in less than 6% of the samples. Twenty percent or less of the sample contained chlorinated cyclodienes (i.e., dieldrin > endrin > heptachlor-epoxide > heptachlor). No measurable concentrations of α-hexachlorocyclohexane, aldrin, p,p'-dichlorophenyldichlorodiene, and toxaphene were found in the breast milk samples. Analysis of variance demonstrated that only the concentration of p,p'-dichlorophenyldichloroethylene p,p'-dichlorophenyltrichloroethane, and endrin were affected significantly by maternal age. Overall, with the exception of p,p'-chlorophenyldichloroethylene, and p,p'-dichlorophenyltrichloroethane, the mean concentrations of the analyzed pesticides were low. Total p,p'-dichlorophenyltrichloroethane concentrations that exceeded the allowed daily intake set by the World Health Organisation were found in 5.9% of the samples.

Marth, E. (1965) Residues and some effects of chlorinated hydrocarbon insecticides in biological material. Residue Rev 91-89. Also may be used in Section(s): 4.2

Mohammed, A; Hallberg, E; Rydstrom, J; et al. (1985) Toxaphene: Accumulation in the adrenal cortex and effect on acth-stimulated corticosteroid synthesis in the rat. Toxicol Lett 24(2-3):137-143.
Uptake and distribution of [14C]toxaphene was studied in the adrenals of rats using whole-body autoradiography. An accumulation of radioactivity was seen in the adrenal cortex (zona fasciculata) 1-24 h after a single gavage of [14C]toxaphene (16 mg/kg b.w.). In in vitro studies

toxaphene was found to inhibit ACTH-stimulated corticosterone synthesis in the cultured rat adrenocortical cells (IC50 2.8 X 10(-5) M). Moderate but significant inhibition (P less than 0.001) of ACTH-stimulated corticosterone synthesis was also observed in the adrenocortical cells isolated from rats after a prolonged exposure (5 weeks) to low levels (1.2 ppm) of toxaphene in feed. The results indicate a direct adrenotoxic effect of toxaphene. Also may be used in Section(s): 4.2 & 4.4

Mohammed, A; Eklund, A; Ostlund-Lindqvist, A; et al. (1990) Distribution of toxaphene, ddt, and pcb among lipoprotein fractions in rat and human plasma. Arch Toxicol 64(7):567-571.
The distribution of 14C-toxaphene, 14C-DDT, and 14C-PCB among lipoprotein fractions was studied in vitro and in vivo using rat and human plasma. The association of these substances with rat plasma fractions was similar in both in vitro and in vivo experiments. Thirty-seven to fifty-two per cent of the total radioactivity was associated with the cholesterol-rich high density lipoproteins (HDL2, d = 1.075-1.21 g/ml) and 18-52% was recovered in the albumin-rich bottom fraction (BF, d greater than 1.21 g/ml). A time-dependent redistribution of the radioactivity from the lipoprotein fractions to the BF was also observed in the in vivo studies. In human plasma, the distribution of the three compounds was different and uncorrelated to the cholesterol level of the individual lipoprotein fractions. Toxaphene was almost equally distributed between BF (d greater than 1.21 ml), HDL (d = 1.063-1.21 g/ml) and low density lipoproteins (LDL, d = 1.006-1.063 g/ml) (26%, 27% and 29%, respectively), while only 18% appeared in the very low density lipoprotein (VLDL, d less than 1.006) fraction. In contrast, a large proportion of DDT and PCB radioactivity was recovered in the BF (52% and 62%, respectively) while only 38-48% was present in lipoprotein fractions. The complex nature of the interaction between xenobiotics and plasma lipoproteins is discussed.

Mohammed, A; Eklund, A; Ostlund-Lindqvist, A; et al. (1990) Tissue accumulation of lipoprotein associated toxaphene in normo- and hypolipidemic mice. Arch Toxicol 64(1):38-42.
Normo- and hypolipidemic mice were given a single i.v. injection of 14C-toxaphene associated with low density lipoprotein (LDL), high density lipoprotein (HDL) or dimethyl sulfoxide (DMSO). The tissue distribution of radioactivity was studied 20 min and 4 h after the application. In the normolipidemic mice at 20 min postinjection there was high uptake of the 14C-toxaphene preparations in the liver and adrenals followed after 4 h by a redistribution to the adipose tissues. In the hypolipidemic mice, proportionally less label accumulated initially in the liver and adrenals while more radioactivity was seen in the kidneys and heart. The radioactivity then redistributed to the liver with a very small uptake in the adipose tissue compared to the normolipidemic mice after 4 h. The results indicate that changes in the lipid pattern, e.g. hypolipidemic conditions, may influence the tissue distribution of lipophilic xenobiotics.

Mount, M; Oehme, F. (1981) Insecticide levels in tissues associated with toxicity: A literature review. Vet Hum Toxicol 23(1):34-42.
Extensive residue studies have been done with most of the organochlorine insecticides. The brain is a reliable tissue to determine lethal or exposure residues of the persistent organochlorine insecticides. Fewer studies have been done with organophosphate residues. residues of organophosphate insecticides are useful indicators of poisoning in tissues of exposed animals. Metabolite determination and identification is a necessary consideration since metabolic activation is required for several of the organophosphate insecticides. No studies of tissue residue

evaluation of carbamate insecticides are available. Also may be used in Section(s): 3.3 & 4.2

Mussalo-Rauhamaa, H; Pyysalo, H; Antervo, K. (1988) Relation between the content of organochlorine compounds in finnish human milk and characteristics of the mothers. J Toxicol Environ Health 25(1):1-19.
Neutral organochlorine pesticide and PCB residues were analyzed by GC-MS technique in 183 human milk samples obtained in 1984-1985 from 165 women living in different parts of Finland. The effect of the donors' age, body mass, place of residence, number of children, dietary habits, smoking habits, occupational history, and weight loss on the organochlorine content of human milk were studied. Of all the milk samples analyzed, p,p'-DDE concentrations were above the detection limit in 99.5%, p,p'-DDD + p,p'-DDT in 57.9%, isomers of HCH in 30.0%, cis-chlordane in 4.9%, oxychlordane in 3.3%, trans-nonachlor in 6.0%, heptachlor in 12.0%, and heptachlor epoxide in 6.6%. Mirex was not found in any of the milk samples, whereas the signals of chlorinated terpenes (toxaphenes) were detected but could not be quantitatively determined. The mean fat adjusted residue levels above the detection limit in Finnish human milk samples of primipara mothers were 0.66 ppm for total DDT compounds, 0.08 ppm for HCB, 0.93 ppm for PCBs, 0.41 ppm for chlordane compounds, 0.20 ppm for isomers of HCH, and 0.10 ppm for heptachlor epoxide. The geometric means were 0.46, 0.06, 0.57, 0.02, 0.02, and 0.01 ppm, respectively. The age of the mothers positively correlated with the DDE concentrations in human milk. The residues of OC compounds in human milk did not differ in women living in plywood industry regions, those actually working in the industry, and other mothers. Small differences were detected in the levels of organochlorine compounds in different parts of Finland. No relation was found between the OC content and the fish consumption, smoking habits, weight loss, or social group of the donors. Also may be used in Section(s): 4.1

Newsome, W; Ryan, J. (1999) Toxaphene and other chlorinated compounds in human milk from northern and southern canada: A comparison. Chemosphere 39(3):519-526.
Human milk from residents of northern Canada (Keewatin) was compared to that in national surveys of southern Canada with respect to residues of toxaphene, PCBs, PCDD/PCDFs, chlordane, and several other persistent organic compounds. Concentrations of toxaphene were approximately ten-fold higher in specimens from Keewatin than from the south. Toxaphene concentrations in samples from the Great Lakes Basin collected in 1992 were not significantly ($p < 0.05$) different from those of the rest of Canada; however they were significantly ($p < 0.05$) lower than concentrations reported in a 1986 survey. Hexachlorobenzene, trans nonachlor and oxychlordane were three to five times higher in concentration in the Keewtin samples than in samples reported in the 1992 national survey. Total PCB congeners, DDTs, PCDD/PCDFs, and other chlorinated compounds were not significantly higher in northern samples. Also may be used in Section(s): 3.3

Niessen, K; Helbich, H; Teufel, M; et al. (1998) Familiar harmful substances and newly discovered toxaphenes in the adipose tissue of children. Monatsschr Kinderheilkd 46(3):271-301. Also may be used in Section(s): 4.1 & 4.8.

Patel, M; Berner, J; Sjodin, A; et al. (2004) Detection of toxaphene congeners in native alaskan women. J Toxicol Clin Toxicol 42(5):804-805.
Background: The insecticide Toxaphene has been banned in many countries during the last two

decades because of its carcinogenicity in experimental animals, environmental persistence, bioaccumulation, and potential for global dispersion. However, recent detection of Toxaphene in freshwater fish from the Arctic, an area where Toxaphene was never used, prompts concern about potential on-going human exposure. Using a newly developed laboratory method, we determine whether Toxaphene is present in Alaska Native women and, if so, whether levels correlate with age and proximity to freshwater. Methods: Thirty-six serum pools were formed from 108 individual samples of a prospective cohort of pregnant women in Barrow and Bethel, Alaska. Samples were stratified by subject's age, location, and proximity to fresh vs. saltwater. Three Toxaphene congeners [Parlar (P) 26, P50, P62] were measured using gas chromatography/high-resolution mass spectroscopy. Results: Two toxaphene congeners were detected in more than 50% of the samples [Geometric mean (GM) of p26=1.10 ng/g lipid-weight (LW) (95% CI=0.66–1.84) and GM of p50=1.61 ng/g LW (0.96–2.72)]. There was a significant correlation between congener levels and age [r=0.60, $p < 0.0001$ (P26) and r=0.59, $p < 0.0001$ (P50)] but no correlation with proximity to freshwater. Conclusion: Detection of Toxaphene congeners in people temporally and geographically remote from any exposure source reaffirms the biological persistence and global distribution of this chemical. Future studies should investigate whether there is a correlation between exposure to low levels of Toxaphene and adverse health effects. Also may be used in Section(s): 4.1

Polder, A; Odland, J; Tkachev, A; et al. (2003) Geographic variation of chlorinated pesticides, toxaphenes and pcbs in human milk from sub-arctic and arctic locations in russia. Sci Total Environ 306(1-3):179-195.
The concentrations of HCB, alpha-, beta- and gamma-HCH, 3 chlordanes (CHLs), p,p'-DDE, p,p'-DDD, p,p'-DDT, and 30 PCBs (polychlorinated biphenyls) were determined in 140 human milk samples from Kargopol (n=19), Severodvinsk (n=50), Arkhangelsk (n=51) and Naryan-Mar (n=20). Pooled samples were used for determination of three toxaphenes (chlorobornanes, CHBs). The concentrations of HCB, beta-HCH and p,p'-DDE in Russian human milk were 2, 10 and 3 times higher than corresponding levels in Norway, respectively, while concentrations of sum-PCBs and sum-TEQs (toxic equivalent quantities) of the mono-ortho substituted PCBs were in the same range as corresponding levels in Norway. The PCB-156 contributed most to the sum-TEQs. Highest mean concentrations of HCB (129 microg/kg milk fat) and sum-PCBs (458 microg/kg milk fat) were detected in Naryan-Mar, while highest mean concentrations of sum-HCHs (408 microg/kg milk fat), sum-CHLs (48 microg/kg milk fat), sum-DDTs (1392 microg/kg milk fat) and sum-toxaphenes (13 microg/kg milk fat) were detected in Arkhangelsk. An eastward geographic trend of increasing ratios of alpha/beta-HCH, gamma/beta-HCH, p,p'-DDT/p,p'-DDE and PCB-180/28 was observed. In all areas the levels of sum-HCHs decreased with parity (number of children born). Considerable variation in levels of the analysed organochlorines (OCs) was found in all the studied areas. Breast milk from mothers nursing their second or third child (multiparas) in Naryan-Mar showed a significant different PCB profile compared to mothers giving birth to their first child (primiparas) from the same area and to primi- and multiparas in the other areas. Both p,p'-DDE and p,p'-DDT showed a significant, but weak, negative correlation with the infants birth weight.

Skopp, S; Oehme, M; Drenth, H. (2002) Study of the enantioselective elimination of four toxaphene congeners in rat after intravenous administration by high resolution gas chromatography negative ion mass spectrometry. Chemosphere 46(7):1083-1090.

This study was performed to investigate the possible enantioselective metabolism of the four chlorinated bornanes: #26, #32, #50 and #62 (according to the Parlar nomenclature) by rats. Rats were exposed to a mixture of these toxaphenes by a single intravenous injection. Enantiomer ratios (ER) as well as the enantiomer fractions (EF) were determined in brain, adipose tissue and liver samples at six time intervals by high resolution gas chromatography (HRGC) coupled to negative ion chemical ionization (NICI) mass spectrometry (MS). Capillaries coated with heptakis-(2,3,6-O-tert-butyldimethylsilyl)-beta-cyclodextrin (TBDMS-CD) or octakis-(2,3,6-tri-O-ethyl)-gamma-cyclodextrin (TEG-CD) were used for the enantioselective separations. Significant time-dependent changes of ER and EF were found in all the three tissues for #26, #50 and #62. Greatest deviations from racemic composition were found in the liver, which is known to be the major metabolizing organ for toxaphenes. #32 was metabolized the fastest, but showed no changes in ER. Brief information is also included about the possible reasons for the different behaviors of the four congeners in the studied tissues. Also may be used in Section(s): 3.3

Skopp, S; Oehme, M; Furst, P. (2002) Enantiomer ratios, patterns and levels of toxaphene congeners in human milk from germany. J Environ Mont 4(3):389-394.
High resolution gas chromatography (HRGC) coupled to quadrupole negative ion chemical ionization (NICI) mass spectrometry (MS) was used to investigate congener patterns, levels and enantiomer distribution of selected toxaphene congeners (#26, #41, #44, #50, #63, B7-1453) in human milk from Germany. #50 and #26 were the most abundant congeners. Furthermore, the identification of B7-1453, B8-1412, #41, #42, #44 and #63 was possible. Levels for the sum of #26, #41, #44 and #50 ranged from 7 to 24 microg kg(-1) milk fat and contributed between 2 and 9% to the total burden of investigated organochlorines such as selected compounds of the chlordane group, HCH, DDT and polychlorinated biphenyls (PCB). Capillaries coated with heptakis-(2,3,6-O-tert-butyldimethylsilyl)-beta-cyclodextrin (TBDMS-CD) or octakis-(2,3,6-tri-O-ethyl)-gamma-cyclodextrin (TEG-CD) were used for the enantioselective separations. Enantiomer ratios (ER) and enantiomer fractions (EF) of the abundant toxaphene congeners #26 and #50 as well as of B7-1453, #41 and #63 were determined. Greatest deviations from a racemic composition in individual human milk samples were found for #41 (1.54-2.37), #50 (1.37-1.72) and #63 (0.53-0.71) whereas ERs for #26 were close to 1. Compared to wildlife biota such as fish and raptors ER changes were more pronounced in human milk but comparable to human adipose tissue. Also may be used in Section(s): 3.3

Vaz, R; Blomkvist, G. (1985) Traces of toxaphene components in swedish breast milk analysed by capillary gc using ecd, electron impact and negative ion chemical ionization ms. Bull Environ Contam Toxicol 20445-446.
Also may be used in Section(s): 3.3

Vetter, W; Scholz, E; Luckas, B; et al. (2001) Structure of a persistent heptachlorobornane in toxaphene (b7-1000) agrees with molecular model predictions. J Agric Food Chem 49(2):759-765.
A Cl(7) component of technical toxaphene (CTT), previously detected in marine mammals and fish and referred to as "7-1", was isolated from contaminated estuarine sediment using preparative solid-liquid chromatography followed by reversed-phase HPLC. The structure of this compound, elucidated by GC/MS and (1)H NMR, was 2-endo,3-exo,5-endo,6-exo,8,8,10-heptachlorobornane (hereafter referred to as B7-1000). This newly identified CTT eluted in the

nonpolar fraction from silica and shares the alternating endo-exo chlorine substitution pattern with other relatively nonpolar, persistent congeners (e.g., B8-1413 and B9-1679). Based on ECNI-MS response, levels of B7-1000 in tissue samples of various higher organisms including humans were as high as 16% of B8-1413. Enantioselective determination of B7-1000 using a modified cyclodextrin chiral stationary phase (beta-BSCD) resulted in enantiomer ratios that were depleted in adipose tissue of a marine bird (skua) and Weddell seal blubber (0.3 and 0.5, respectively), but not in elephant seal blubber (1.1). Elucidation of the structure of B7-1000 thus validates previous predictions of persistence based on structure-activity relationships, chromatographic properties, and molecular modeling. Also may be used in Section(s): 3.3

Walker, J; Seddon, L; McMullen, E; et al. (2003) Organochlorine levels in maternal and umbilical cord blood plasma in artic canada. Sci Total Environ 30227-52.

Witt, K; Niessen, K. (2000) Toxaphenes and chlorinated naphthalenes in adipose tissue of children. J Pediatr Gastroenterol Nutr 30(2):164-169.
BACKGROUND: Chlorinated hydrocarbons are ingested by humans in food and accumulate in adipose tissue. At the University Kinderklinik, Mannheim, previously unknown substances have been found in children (e.g., the pesticide toxaphene and chlorinated naphthalenes). These substances have been widely used for industrial purposes in the past. Samples from West and East Germany; Saratov, Russia; and Almaty, Kazakhstan were examined to determine whether these substances are ubiquitous. METHODS: After Soxhlet extraction, the extracts were cleaned up using a liquid chromatographic technique. Measurement was performed by gas chromatography-mass spectrometry using negative chemical ionization in the single-ion-monitoring mode. RESULT: In specimens from all cities, toxaphene congeners Parlar 26 and Parlar 50 and six chlorinated naphthalenes were traced. Highest median load of toxaphene was 1.97 microg/kg for Parlar 26 and 2.36 microg/kg for Parlar 50 in Stralsund, East Germany. For chlorinated naphthalenes, the median was highest in Mannheim, West Germany, with 12.0 microg/kg. CONCLUSION: These findings show that monitoring these toxic substances remains necessary. Even though the use and as a consequence the amount of chlorinated hydrocarbons were reduced, these substances have by no means disappeared from the environment. Also may be used in Section(s): 3.3

Zavon, M; Tye, R; Latorre, L. (1969) Chlorinated hydrocarbon content of the neonate. Ann N Y Acad Sci 160(1):196-200.
The amounts of chlorinated hydrocarbon insecticides with which the human organism commences life was investigated. Skin, fat and attached subcutaneous tissue from 68 neonates from 13 cities in the United States were collected. The specimens, averaging 2 g in size, were chopped, extracted with hexane and cleaned up by distribution with acetonitrile and chromatography on a Florisil column. This latter step separated heptachlor epoxide and DDE. Analysis was by electron-capture chromatography. Quantitation of the analytical sample was based on peak height, assuming linearity of response between the sample and the quantitatively similar standard. These methods revealed heptachlor epoxide, dieldrin, DDE, o,p'-DDT and p,p'-DDT. They did not show benzene hexachloride or any of its isomers or methoxychlor and toxaphene. Fifty-six of the specimens received were from children who were stillborn or died within 1 week of birth. Tabulated data indicate that all children born in the United States are likely to have trace quantities of chlorinated hydrocarbon insecticides in their tissues since

placental passage of these pesticides apparently does occur. Averages of results based on total weight of samples demonstrated 0.060, 0.045, 0.962, 0.230 and 0.415 ppm of heptachlor epoxide, dieldrin, DDE, o,p'-DDT and p,p'-DDT, respectively. The differences between males and females were inconsequential and the number of samples from each city were too small to warrant comparison. The concnetration of the compounds detected are slightly lower than in studies of adult populations done previously.

3.3. METABOLISM

Casida, J; Holmstead, R; Khalifa, S; et al. (1975) Toxaphene composition and metabolism in rats. Environ Qual Saf Suppl 3:346-349.
Also may be used in Section(s): 3.1 & 3.4

Casida, J; Holmstead, R; Khalifa, S; et al. (1974) Toxaphene insecticide: A complex biodegradable mixture. Science 183(124):520-521.
Adsorption and gas-liquid chromatography separate toxaphene into at least 175 polychlorinated 10-carbon compounds including Cl(6), Cl(7), Cl(8), Cl(9), and Cl(10) derivatives. One toxic component is 2,2,5-endo,6-exo,8,9,10-heptachlorobornane. Rats metabolically dechlorinate toxaphene, removing about half of the chlorine from the technical insecticide and from each of seven subfractions of varying composition and toxicity.

Casida, J; Holmstead, R; Khalifa, S; et al. (1974) Toxaphene composition and metabolism in rats. Coulston, Frederick And Friedhelm Korte365-369.
Mouse house fly insecticide food residues environmental fate toxicity ld-50 gas chromatography chemical ionization mass spectrometry.

Chandurkar, P. (1978) Metabolism of toxaphene components in rats. Diss Abstr Int B 38(10):4626-4627.
To know more precisely the route of toxaphene metabolism, two of the isolated toxic components of toxaphene, hepta chlorobornane (toxicant B) and nona chlorobornane (toxicant C) were used as the substrates for in vitro studies. Toxicant C was found to be metabolized to a major dechlorination product, octachlorobornane. This is the only major product in the solvent extract of NADPH fortified incubates. This is the first time that such a toxaphene metabolite has been completely characterized. In addition, four hydroxylation products at 2, 3, 5, 6 carbon positions and one hydroxylation product at the bridge head methyl group were found among toxicant C metabolites. Toxicant B, on the other hand, produced five products with shorter GC retention times, all of which were found to be nonhydroxylated compounds. This data along with studies using 36Cl-toxaphene indicate that dechlorination and/or dehydrochlorination processes are also active in degrading some of the toxaphene components. (Author abstract by permission. Copies of the thesis are available from University Microfilms, order No. 7725812).

Chandurkar, P; Matsumura, F. (1979) Metabolism of toxaphene components in rats. Arch Environ Contam Toxicol 8(1):1-24.
The metabolism of toxaphene (8001352) and two of its toxic components, 2,2,5-endo,6-exo,8,9,10-heptachlorobornane (toxicant 1) and 2-endo,3,3,5,6-exo-8,9,10,10-nonachlorobornane

(toxicant 2), was studied in rat liver. Male albino Sprague-Dawley-rats were used for preparation of liver homogenate and differential centrifugation. For in-vitro metabolic studies, 4.2 micrograms (microg) of labeled toxaphene or 3.5microg of non radioactive toxicant 1 or toxicant 2 were added to an assay tube. The reaction mixture was incubated and extracted in the presence of glutathione (GSH) and reduced nicotinamide-adenine-diphosphate (NADPH) inhibitors. Four rats were given a single oral dose of labeled toxaphene at 15 milligrams per kilogram (mg/kg) by stomach tube; urine and feces were collected separately at 24 hour intervals for 5 days for analysis of metabolites. The liver microsomal fraction (in the presence of NADPH) and the liver soluble fraction (in the presence of GSH) converted 9.5 and 4.8 percent, respectively, of the labeled toxaphene into water soluble metabolites; NADPH had a more stimulatory effect than GSH. A total of 16, 24, and 49 new compounds were detected by gas liquid chromatography of solvent extracts of control, GSH, and NADPH incubate, respectively. Following beta-glucuronidase treatment, the extractable radioactivity of water soluble metabolites of labeled toxaphene increased from 41.6 percent in controls to 57.5 percent in NADPH incubate. Approximately 56.5 percent of the toxaphene was excreted in feces; 9 percent of the dose was excreted in urine. Approximately 8.94 percent of the total urinary metabolites and 0.7 percent of the total fecal metabolites were sulfate conjugates; 9.47 percent urinary and 7.54 percent fecal metabolites were acid hydrolyzable products. The authors conclude that the oxidative metabolism of toxaphene by NADPH dependent mixed function oxidases from rat liver microsomes plays an important role in the total metabolism of toxaphene. Also may be used in Section(s): 3.4

Chandurkar, P; Matsumura, F. (1979) Metabolism of toxicant b and toxicant c of toxaphene in rats. Bull Environ Contam Toxicol 214-5.
The metabolism of toxicant-B and toxicant-C, components of toxaphene (8001352), was studied in-vitro. The 20,000 times the force of gravity (20,000g) supernatant from centrifuged rat livers was incubated with 3.5 micrograms of toxicant-B or toxicant-C in the presence or absence of 0.001 molar reduced nicotinamide-adenine-dinucleotide-phosphate (NADPH). The reaction mixtures were analyzed for metabolites using thin layer and gas liquid chromatography, and proton nuclear magnetic resonance spectroscopy. After reaction in the media without NADPH, the recoveries of toxicant-B and toxicant-C were 53.60 and 46.68 percent, respectively. The corresponding recoveries for incubation in the presence of NADPH were 27.30 and 43.90 percent. The major metabolic products of toxicant-C and the metabolite were presented. Toxicant-C was also metabolized to five hydroxylated compounds, one of which had a hydroxyl group at the bridge head position. The others had hydroxyl groups at the C2, C3, C5, or C6 positions. No hydroxyl metabolites of toxicant-B were found. The authors question the importance of oxidative degradation processes in toxaphene metabolism.

Dorea, J; Cruz-Granja, A; Lacayo-Romero, M; et al. (2001) Perinatal metabolism of dichlorodiphenyldichloroethylene in nicaraguan mothers. Environ Res 86(3):229-237.
Umbilical cord and venous blood samples were collected at the time of delivery from 52 mothers living in urban and rural areas of the Atoya River basin, Nicaragua. In a subsample of 24 mothers that delivered by Cesarean section, abdominal adipose tissue samples were also collected, as was breast milk later in lactation. Cord and venous blood sera were analyzed for 13 organochlorine pesticides: 1,1,1-trichloro-2,2-bis(4-chlorophenyl)ethane (pp'-DDT); 1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene (pp'-DDE); pp'-dichlorophenyldichlorodiene (pp'-

DDD); alpha-hexachlorocyclohexane (alpha-HCH); beta-hexachlorocyclohexane (beta-HCH); gamma-hexachlorocyclohexane (gamma-HCH); delta-hexachlorocyclohexane (delta-HCH); toxaphene; dieldrin; endrin; aldrin; heptachlor; and heptachlor epoxide. In venous blood only pp'-DDE (100% of samples), pp'-DDT (1.92%), dieldrin (15.38%), heptachlor (15.38%), gamma-HCH (7.69%), beta-HCH (11.53%), and delta-HCH (1.92%) were found, whereas in cord blood only pp'-DDE (100%), pp'-DDT (3.84%), dieldrin (19.23%), and heptachlor (9.16%), were found. The persistent DDT metabolite pp'-DDE, present in all samples of blood serum, adipose tissue, and breast milk, was studied in relation to maternal characteristics such as body mass index (BMI), age, lactation experience, and fetal pesticide acquisition. Mean venous (7.12 microg/g) and cord (6.39 microg/g) pp'-DDE concentrations were not significantly different but were significantly correlated. pp'-DDE in maternal adipose tissue was positively correlated with pp'-DDE in cord blood (P=0.0001) and breast milk (P<0.0001) and marginally correlated with changes in BMI (r=-0.03088; P=0.06). There was a higher proportion of samples (58%) with a greater concentration of DDE in venous than in cord blood. Although DDE accumulation may be less during fetal development than during breast feeding, exposure during embryogenesis may be more important than during the postnatal period. Also may be used in Section(s): 4.1

Haake, J; Kelley, M; Keys, B; et al. (1987) The effects of organochlorine pesticides as inducers of testosterone and benzo[a]pyrene hydroxylases. Gen Pharmacol 18(2):165-169.
p,p'-DDE, phenobarbital, dieldrin heptachlor, chlordane and toxaphene induced rat liver microsomes exhibited increased formation of the 4,5-dihydrodiol, 3,6-quinone, 9- and 3-hydroxymetabolites of benzo[a]pyrene and the latter three compounds also induced an increase in the rate of formation of the 9,10-dihydrodiol metabolite. Lindane was inactive as an inducer of benzo[a]pyrene hydroxylase. With the exception of lindane, all the organochlorine pesticides and PB induced testosterone 16 alpha- and 16 beta-hydroxylases; in contrast lindane induced testosterone 6 alpha-, 7 alpha- and 6 beta-hydroxylases and PB also induced testosterone 15 beta-hydroxylase and androstenedione formation. Using a battery of monooxygenase enzyme assays it was evident that there were significant differences between PB and several organochlorine pesticides as inducers of rat hepatic cytochrome P-450-dependent monooxygenases.
Hallikainen, A; Salminen, S; eds. (1986) Foods food additives and contaminants in gastrointestinal toxicology. Amsterdam, Netherlands Elsevier Science Publishers B.V; 338-362.

Khalifa, S; Holmstead, R; Casida, J. (1976) Toxaphene degradation by iron(ii) protoporphyrin systems. J Agric Food Chem 24(2):277-282.

Nesnow, S; Leavitt, S. (1979) Application of in-vitro transformation and metabolism to the study of co carcinogenesis. In Vitro 15(3):208.
Mouse Embryo Fibroblast P P Ddt Toxaphene Insecticide Trifluralin Aroclor 1254 Pheno Barbital Benz A Anthracene 5 6 Benzo Flavone Pregnenolone 16-Alpha Carbonitrile.
Also may be used in Section(s): 4.5

Ohsawa, T; Knox, J; Khalifa, S; et al. (1975) Metabolic dechlorination of toxaphene in rats. J Agric Food Chem 23(1):98-106.
Also may be used in Section(s): 3.1

Pollock, G; Kilgore, W. (1976) The metabolism of toxaphene components. Toxicol Appl

Pharmacol 37(1):138-139.
Toxaphene is a chlorinated hydrocarbon insecticide synthesized by the chlorination of camphene. It is a very complex mixture of compounds containing primarily polychlorobornanes and polychlorodihydrocamphenes. Female rats were orally intubated with (14C)toxaphene and several isolated toxaphene components. The animals were housed in glass metabolism chambers and the urine and feces were collected and extracted. The extracts were spotted and developed on TLC plates and analyzed by a combination of TLC scanning and liquid scintillation counting. In addition, in vitro metabolism using liver homogenates was studied. The results show that there are differences in the excretion between some of the toxaphene components. These differences could be due to the metabolism of the various toxaphene components. Thus, these results raise questions about the possible selective accumulation of specific components within the parent mixture. An experimental model using selected purified components will be presented.

Pollock, G; Kilgore, W. (1978) The metabolism and excretion of toxaphene and selected toxaphene fractions. Toxicol Appl Pharmacol 45(1):235. Also may be used in Section(s): 3.4

Saleh, M; Casida, J. (1978) Reduction dechlorination of the toxaphene component 2,2,5-endo,6-exo,8,9,10-heptachlorobornane in various chemical, photochemical, and metabolic systems. J Agric Food Chem 26583-599.

Saleh, M; Skinner, R; Casida, J. (1979) Comparative metabolism of 2,2,5-endo,6-exo,8,9,10-heptachlorobornane and toxaphene in six mammalian species and chickens. J Agric Food Chem 27(4):731-737.

3.4. ELIMINATION

3.5. PHYSIOLOGICALLY-BASED PHARMACOKINETIC (PBPK) MODELS

Wen, Y; Chan, H. (2000) A pharmacokinetic model for predicting absorption, elimination, and tissue burden of toxaphene in rats. Toxicology and Applied Pharmacology 168(3):235-243.
A two-compartment pharmacokinetic model was formulated to predict absorption, elimination, and tissue burden of toxaphene in rats. The model was constructed based on the database of Crowder and Dindal (Bull. Environ. Contam. Toxicol. 12, 320-327, 1974) and included six tissue compartments: blood, brain, liver, muscle, fat, and carcass. The pharmacokinetically based dosimetry indicated that absorption of toxaphene was fast in fat, whole body, carcass, and blood, relatively slow in liver and muscle, and slow in brain. In contrast, the elimination rate was rapid in whole body, muscle, and blood, moderate in carcass and brain, and slow in liver and fat. Tissue burden was highest in fat, whole body, and blood, intermediate in liver, and lowest in brain. The model performance was evaluated by the data set of Pollock and Hillstrand (J. Environ. Sci. Health B 17, 635-648, 1982) on toxaphene absorption and elimination in pregnant rats. Validity of the model was confirmed by the close agreement between the predicted and observed tissue burdens of toxaphene in target tissues. Disposition of toxaphene via feces was a dominant excretory pathway while urinary excretion was a minor elimination route in male rats. However, for pregnant rats, excretion of toxaphene both in urine and feces were of similar magnitude. These characteristics of elimination are valuable for understanding the metabolism of

toxaphene in pregnant rats. The model serves as a starting point for a quantitative, mechanism-based understanding of the processes that influence the pharmacokinetics of toxaphene in mammalian systems. Also may be used in Section(s): 3.1, 3.2, 3.3, & 3.4

4. HAZARD IDENTIFICATION

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

Barthel, E. (1976) [high incidence of lung cancer in persons with chronic professional exposure to pesticides in agriculture (author's transl)]. Z Erkr Atmungsorgane 146(3):266-274.
In an epidemiological study in the Neubrandenburg district among 316 long-term exposed pesticide workers the incidence of tumors was investigated. There were 30 cases of tumors, of which 11 were lung cancers. The incidence of lung cancers was in contrast to age-specific population twenty times higher. The average exposure against pesticides amounted to 14.1 +/- 4.7 (6-23) years, the latency period between exposition start and tumor manifestation to 17.9 +/- 6.0 (6-23) years. The exposure occurred mainly to the following agents: herbicides, such as derivatives of phenoxyacetic acid (2,4 D and MCPA); insecticides, such as chlorinated hydrocarbons (DDT, HCH and Toxaphen), organic phosphorus compounds (Parathion) and organic nitro derivatives (DNOC) as well as fungicides, such as copper containing and organic synthetic agents. Between 1950 and 1956 some pesticide workers were also exposed to arsenic containing agents. As the workers were exposed to various chemical compounds simultaneously or alternatively, no carcinogenic effect can be determined by specific individual pesticides. The investigations are discussed in detail on the today knowledge about cancer hazards associated with exposure to pesticides, and respective conclusions are drawn for preventive measures.

Cantor, K; Blair, A; Everett, G; et al. (1992) Pesticides and other agricultural risk factors for non-hodgkin's lymphoma among men in iowa and minnesota. Cancer Res 52(9):2447-2455.
Data from an in-person interview study of 622 white men with newly diagnosed non-Hodgkin's lymphoma and 1245 population-based controls in Iowa and Minnesota were used to measure the risk associated with farming occupation and specific agricultural exposures. Men who ever farmed were at slightly elevated risk of non-Hodgkin's lymphoma (odds ratio = 1.2, 95% confidence interval = 1.0-1.5) that was not linked to specific crops or particular animals. Elevated risks were found, with odds ratio generally 1.5-fold or greater, for personal handling, mixing, or application of several pesticide groups and for individual insecticides, including carbaryl, chlordane, dichlorodiphenyltrichloroethane, diazinon, dichlorvos, lindane, malathion, nicotine, and toxaphene. Associations were generally stronger for first use prior to 1965 than more recently, and when protective clothing or equipment was not used. Small risks were associated with the use of the phenoxyacetic acid herbicide 2,4-dichlorophenoxyacetic acid, but the risks did not increase with latency or failure to use protective equipment. Exposure to numerous pesticides poses problems of interpreting risk associated with a particular chemical, and multiple comparisons increase the chances of false-positive findings. In contrast, nondifferential exposure misclassification due to inaccurate recall can bias risk estimates toward the null and mask positive associations. In the face of these methodological and statistical issues, the consistency of several findings, both within this study and with observations of others,

suggests an important role for several insecticides in the etiology of non-Hodgkin's lymphoma among farmers.

Copeland, A. (1988) Organophosphate related fatalities a violational biohazard. Forensic Sci Int 39(2):155-162.
A study of deaths due to organophosphate and related "cholinesterase-inhibiting" pesticides was performed on the case files of the office of the Medical Examiner in Metropolitan Dade County in Miami, Florida, USA. Briefly, a comparison was performed between cases which occurred between the years 1961-1965, when such pesticides were used indiscriminately and before stricter laws regulating their use were enacted, and with a series of cases occurring between the years, 1981-85, after such stricter laws were enacted. The occurrence of such deaths dropped dramatically with the decease in organophosphate use. A discussion ensues, along with specific information for the reader, on how the forensic scientist may help ameliorate their environment.

De Mesquita, H; Doornobos, G; van der Kuip, D; et al. (1993) Occupational exposure to phenoxy herbicides and chlorophenols and cancer mortality in the netherlands. Am J Ind Med 23289-300.

Deichmann, W. (1973) The chronic toxicity of organochlorine pesticides in man. In Proceedings from hte 8th Pesticide Symposium Collected Papers Inter-Am conf Toxicol Occup Med; pp. 347-410.

Deichmann, W; Macdonald, W. (1976) Liver cancer deaths in the continental usa from 1930 to 1972. Am Ind Hyg Assoc J 37(9):495-498.
EIS: Epidemiology Information System.

Dick, R; Ahlers, H. (1998) Chemicals in the workplace: Incorporating human neurobehavioral testing into the regulatory process. Am J Ind Med 33(5):439-453.
In February 1996, the United Kingdom Health and Safety Executive sponsored a workshop on the role of human neurobehavioral tests in the regulation of chemical exposures in the workplace. This paper presents the review of neurobehavioral testing that was initially prepared for the workshop but has been expanded and updated for publication. Information sources for the review were drawn from "preamble to the regulation," in the 1989 air contaminants project, an attempt by the Occupational Safety and Health Administration to update the 1968 regulatory limits of workplace exposures. The scientific citations listed in the preamble provide a chemical database to review for evidence of neurobehavioral testing to support limit setting. Several conclusions emerged: 1) A wide range of nervous system effects were reported in the scientific citations for the 172 chemicals identified with effects on the nervous system; 2) Citations of studies with human neurobehavioral test results a. Also may be used in Section(s): 4.4

Embry, T; Morgan, D; Roan, C. (1972) Search for abnormalities of heme synthesis and sympathoadrenal activity--in workers regularly exposed to pesticides. J Occup Med 14(12):918-921.

Gray, L, Jr.; Monosson, E; Kelce, W. (1996) Emerging issues the effects of endocrine disrupters on reproductive development. Di Giulio, R T and E Monosson (Ed) Chapman and Hall

Ecotoxicology Series, 3 Interconnections between Human and Ecosystem Health Xvii+275p Chapman and Hall Ltd: London, England, Uk NEW YORK, NEW YORK, USA. ISBN 0-412-62400-1.; 3(0):45-82.
Book chapter organism male female reproductive development endocrine disrupters sexual differentiation endocrine toxicity toxicology reproductive system.

Haun, E; Cueto, C, Jr. (1967) Fatal toxaphene poisoning in a 9-month-old infant. Am J Dis Child 113(5):616-619.

Hyde, KM; Crandall, JC; Kortman, KE; et al. (1978) Eeg, ecg, and respiratory response to acute insecticide exposure. Bull Environ Contam Toxicol 19(1):47-55.

Jeffery, W; Ahlin, T; Goren, C; et al. (1976) Loss of warfarin effect after occupational insecticide exposure. JAMA 236(25):2881-2882.
Also may be used in Section(s): 4.5

Karstadt, M; Bobal, R; Selikoff, I. (1981) A survey of availability of epidemiologic data on humans exposed to animal carcinogens. Peto, R. And M. Schneiderman (Ed.). Banbury Report, Vol. 9. Quantification Of Occupational Cancer; Meeting, March 29-April 2, 1981. Xx+756p. Cold Spring Harbor Laboratory: Cold Spring Harbor, N.Y., Usa. Illus. Isbn 0-87969-208-1.; 0 (0). 1981 (Recd. 1982). P223-246.
Review occupational exposure international agency for research on cancer who.

Longnecker, M; Rogan, W; Lucier, G. (1997) The human health effects of ddt dichlorodiphenyl-trichloroethane and pcbs polychlorinated biphenyls and an overview of organochlorines in public health. Fielding, J E (Ed) Annual Review of Public Health, Vol 18 Xi+605p Annual Reviews Inc: Palo Alto, California, USA Isbn 0-8243-2718-7 18(0):211-244.
Book chapter literature review human patient public health environmental health occupational health health effects ddt carcinogens endocrine disruptor organochlorine ddt p p'-dde dichlorodiphenyldichloroethene polychlorinated biphenyls pcbs toxicology adverse effects cancer epidemiology dioxin toxicity neoplastic disease usa north america.

Mc, GL; Reed, HL; Fleming, JP. (1952) Accidental poisoning by toxaphene; review of toxicology and case reports. Journal of the American Medical Association 149(12):1124-1126.

McConnell, R; Pacheco, F; Wahlberg, K; et al. (1999) Subclinical health effects of environmental pesticide contamination in a developing country: Cholinesterase depression in children. Environ Res 81(2):87-91.
The effect of exposure to pesticides among children in a Nicaraguan community in the path of rain water runoff from a large crop-dusting airport was evaluated by measuring plasma cholinesterase. Mean cholinesterase activity in 17 children in the path of runoff was 2.4 international units/ml blood/min, lower than the 2.9 IU/ml/min measured in a group of 43 children from an unexposed community (difference=0.49 IU/ml/min; 95% C.I. 0.24, 0.76). Six (35%) of the 17 exposed children had abnormally low cholinesterase levels. A possible explanation for this physiological effect of exposure to pesticides is the dermal absorption which may have occurred among children playing barefoot in puddles grossly contaminated by runoff

from the airport. Drinking water from a well in the exposed community demonstrated low level residues of cholinesterase-inhibiting pesticides, although contamination with toxaphene (not a cholinesterase inhibitor) exceeded by over 8-fold the United States Environmental Protection Agency maximum permissible concentration in drinking water. The difficulty in measuring health effects resulting from environmental pesticide contamination, and in controlling exposure resulting from the rapidly increasing use of pesticides, is a growing problem for developing countries like Nicaragua. Also may be used in Section(s): 3.1 & 4.7

Miller, AB; Gaudette, LA. (1996) Breast cancer in circumpolar inuit 1969-1988. Acta oncologica (Stockholm, Sweden) 35(5):577-580.
Breast cancer was studied over a 20-year period in Inuit populations in the Circumpolar region. A total of 193 breast cancers were observed in women. The incidence increased from 28.2 per 100 000 in 1969-1973 to 34.3 per 100 000 in 1984-1988. However, the incidence is low, about half what could be expected based on the rates in Denmark, Canada and Connecticut (USA). The low incidence could be explained by the Inuit diet and other lifestyle factors. These benefits should be preserved, in particular in the young, to maintain a low breast cancer incidence.

Mills, P; Yang, R. (2006) Regression analysis of pesticide use and breast cancer incidence in california latinas. J Environ Health 68(6):15-22; quiz 43-14.
An evaluation of pesticide use data and breast cancer incidence rates in California Hispanic females was conducted via a regression analysis. The analysis used 1988-2000 data from the California Cancer Registry, the population-based cancer registry that monitors cancer incidence and mortality in California. It also used pesticide use data from 1970-1988 from the California Department of Pesticide Regulation. California is the leading agricultural state in the United States, and more than a quarter of all pesticides in the United States are applied there. Hispanic (Latina) females are commonly employed in agricultural operations. The authors performed regression analysis of county-level specific pesticide use data (pounds of active ingredients applied) for two classes of pesticides, organochlorines and triazine herbicides, against the breast cancer incidence rates among Latinas, controlling for age, socioeconomic status, and fertility rates, using negative binomial regression models. A total of 23,513 Latinas were diagnosed with breast cancer in California during the years 1988-1999. Risk of breast cancer was positively and significantly associated with age and socioeconomic status, and inversely and significantly associated with fertility levels. With respect to pesticides, breast cancer was positively associated with pounds of the organochlorines methoxychlor (adjusted incidence rate ratio [IRR] for highest quartile = 1.18; confidence interval [CI] = 1.03-1.35) and toxaphene (IRR = 1.16; CI = 1.01-1.34). No significant associations were found for the triazine herbicides atrazine and simazine.

Mills, P; Yang, R; Riordan, D. (2005) Lymphohematopoietic cancers in the united farm workers of america (ufw), 1988-2001. Cancer Causes Control 16(7):823-830.
OBJECTIVE: Agricultural risk factors for lymphohematopoietic cancers (LHC) in Hispanic farm workers in California were examined in a nested case-control study embedded in a cohort of 139,000 ever members of a farm worker labor union in California. METHODS: Crop and pesticide exposures were estimated by linking county/month and crop specific job history information from union records with California Department of Pesticide Regulation pesticide use reports during the 20-year period prior to cancer diagnosis. RESULTS: A total of 131 LHC diagnosed in California between 1988 and 2001 were included in the analysis. Analyses were

conducted by gender and subtype of non-Hodgkins lymphoma (nodal, extra nodal) and by leukemia histology (lymphocytic, granulocytic). Odds ratios were calculated by stratification and by unconditional logistic regression. Risk for all LHC was elevated in workers cultivating vegetables (OR = 1.67, 95% CI = 1.12-2.48). Risk of leukemia was associated with exposure to the pesticides mancozeb (OR = 2.35, 95% CI = 1.12-4.95) and toxaphene (OR = 2.20, 95% CI = 1.04-4.65) while NHL risk was increased in association with 2,4-D (OR = 3.80, 95% CI=1.85-7.81). Risk of leukemia was particularly elevated among female workers and for granulocytic versus lymphocytic leukemia for several chemicals. No associations were noted for multiple myeloma. CONCLUSIONS: California farm workers employed where mancozeb and toxaphene were used had an increased risk of leukemia compared to farm workers employed elsewhere. Employment in farms using 2,4-D was associated with an increased risk of NHL.

Montesano, R; Cabral, J; Wilbourn, J. (1988) Environmental carcinogens using pesticides and nitrosamines as paradigms. Maltoni, C and I J Selikoff (Ed) Annals of the New York Academy of Sciences, Vol 534 Living in a Chemical World: Occupational and Environmental Significance of Industrial Carcinogens International Conference, Bologna, Italy, October 6-10, 1985. New York Academy of Sciences: New York, New York, USA. ISBN 0-89766-465-5(paper); ISBN 0-89766-464-7(Cloth):67-73.
Human occupational exposure environmental exposure insecticides herbicides fungicides fumigants.

Morgan, DP; Roan, CC. (1973) Adrenocortical function in persons occupationally exposed to pesticides. J Occup Med 15(1):26-28.

Morris, P; Koepsell, T; Daling, J; et al. (1986) Toxic substance exposure and multiple myeloma a case-control study. Journal of the National Cancer Institute 76(6):987-994.
Biosis copyright: biol abs. rrm human pesticide carbon monoxide painter metal polymer.

Multigner, L; Thonneau, P; Ducot, B; et al. (1996) Pesticides and male fertility current knowledge and epidemiological approach. Hamamah, S and R Mieusset Research in Male Gametes: Production and Quality Meeting, Tours, France, December 1995. Xvi+318p. Inserm(Institut National De La Sante Et De La Recherche Medicale): Paris, France. Isbn 2-85598-680-X; Isbn 2-85598-667-2.; 0 (0):159-165.
Biosis copyright: biol abs. rrm book meeting paper human medical sciences-human medicine-urology reproduction-reproductive system male fertility pesticides toxin infertility toxicology reproductive system disease-male.

Mussalo-Rauhamaa, H; Pyysalo, H; Antervo, K. (1988) Relation between the content of organochlorine compounds in finnish human milk and characteristics of the mothers. Journal of Toxicology and Environmental Health 25(1):1-20.
Polychlorinated biphenyl pesticide cis chlordane oxychlordane trans nonachlor heptachlor mirex toxaphene occupational exposure dietary habit parity weight loss. Also may be used in Section(s): 3.1 & 3.2

Nielsen, NH; Storm, HH; Gaudette, LA; et al. (1996) Cancer in circumpolar inuit 1969-1988. A summary. Acta oncologica (Stockholm, Sweden) 35(5):621-628.

The results of an international, collaborative study of cancer in Circumpolar Inuit in Greenland, Canada, Alaska and Russia are summarized. A total of 3 255 incident cancers were diagnosed from 1969 to 1988 among 85 000-110 000 individuals. Indirect standardization (SIR) based on comparison populations in Connecticut (USA), Canada and Denmark showed excess risk of cancer of the lung, nasopharynx, salivary glands, gallbladder and extrahepatic bile ducts in both sexes, of liver and stomach cancer in men, and renal and cervical cancer in women. Low risk was observed for cancer of the bladder, breast, endometrium and prostate, and for non-Hodgkin lymphoma, Hodgkin's disease, leukaemia, multiple myeloma and melanoma. Age-standardized incidence rates (ASRs) of cancer of lung, cervix, nasopharynx and salivary glands among Inuit were among the world's highest as were rates in women of oesophageal and renal cancer. Regional differences in ASRs within the Circumpolar area were observed for cancer of the cervix, lung, colon and rectum, liver, gallbladder and breast. The differences in the Inuit cancer incidence pattern to some extent reflect known variations in lifestyle, diet and other exposures, as well as implementation of cancer control measures. Future research addressing possible individual differences are needed to evaluate environmental and genetic factors in etiology and evaluate intervention studies.

Perera, F; Boffetta, P. (1988) Perspectives on comparing risks of environmental carcinogens. J Natl Cancer Inst (Bethesda) 80(16):1282-1293.
Review human exposure rodent potency industry pesticides pollution diet.

Philip, R. (1995) Environmental hazards and human health. Philp, R B Environmental Hazards and Human Health Xiii+306p Crc Press: London, England, Uk CRC Press Publishers: London, England, UK. ISBN 1-56670-133-3
Book human pollution assessment control and management toxicology environmental hazards natural synthetic.

Purdue, M; Hoppin, J; Blair, A; et al. (2007) Occupational exposure to organochlorine insecticides and cancer incidence in the agricultural health study. Int J Cancer 120(3):642-649.
Organochlorine (OC) insecticides have been regulated as possible human carcinogens primarily on the basis of animal studies. However, the epidemiologic evidence is inconsistent. We investigated the relationship between cancer incidence and OC insecticide use among pesticide applicators enrolled in the Agricultural Health Study, a prospective cohort study of 57,311 licensed applicators in Iowa and North Carolina enrolled between 1993 and 1997. Information on ever use of 7 OC insecticides (aldrin, chlordane, DDT, dieldrin, heptachlor, lindane, toxaphene) was collected from a self-administered questionnaire at enrollment. Lifetime exposure-days to OC insecticides were calculated using additional data from a take-home questionnaire completed by 25,291 participants (44% of total). We found no clear evidence of an association between use of OC insecticides and incident cancers (N = 1,150) ascertained through December, 2002. When we focused on individual insecticides and structurally similar groups (aldrin and dieldrin; chlordane and heptachlor), significantly increased relative risks of some cancers were observed for use of some chemicals (rectal cancer and chlordane, lung cancer and dieldrin, non-Hodgkin lymphoma (NHL) and lindane, melanoma and toxaphene, leukemia and chlordane/heptachlor). Some significant decreased relative risks were also observed (colon cancer and aldrin; overall cancer and heptachlor). In conclusion, we did not observe any clear relationship between cancer risk and the use of OC insecticides. Our chemical-specific findings are based on small numbers

and multiple comparisons, and should be interpreted with caution; however, some observed associations (lindane and NHL, chlordane/heptachlor and leukemia) are supported by previous evidence.

Ritter, L. (1997) Report of a panel on the relationship between public exposure to pesticides and cancer. Cancer 80(10):2019-2033.
Background: Pesticides, which by their nature are biologically active compounds, continue to raise public concern regarding their possible role as important etiologic agents in the development of human cancer. Methods: To examine this potential role. the National Cancer Institute of Canada convened an Ad Hoc Panel on Pesticides and Cancer to examine the possible contribution of pesticide exposure, particularly in the general population, to the development of human cancer. Results: The Panel focused primarily on exposure in the general population and reviewed a range of studies that addressed issues related to dietary exposure as well as incidental home and garden uses. In addition, the Panel examined the regulatory framework that exists to safeguard the public from potentially carcinogenic pesticides and also reviewed some potential benefits of pesticide use, including the availability of an abundant and low cost supply of fresh fruits and vegetables as an important str.

Smith, E. (1988) Causes of human cancer what is known and what is knowable evaluation by international program on chemical safety ipcs expert committees. Maltoni, C and I J Selikoff (Ed) Annals of the New York Academy of Sciences, Vol 534 Living in a Chemical World: Occupational and Environmental Significance of Industrial Carcinogens International Conference, Bologna, Italy, October 6-10, 1985. Xxv+1045p. New York Academy Of Sciences: New York, New York, Usa. Illus. Maps. Isbn 0-89766-465-5(Paper); Isbn 0-89766-464-7(Cloth).; 0(0):39-43.

Soboleva, L. (1975) Viscoelastic properties of the arterial vessels in persons in contact with some pesticides. Gig Tr Prof Zabol 1151-53.
Contact with BHC, polychlorocamphene, TMTD (thiram) or polychloropinene was accompanied in humans by an increased pulse wave distribution rate, primarily along vessels of the muscular rather than elastic type. The observed effect occurred regardless of the type of pesticide or the duration and intensity of exposure, and was stable and persistant. Among the possible mechanisms of the development of this vascular reaction is an increased blood level of some biogenic amines: adrenaline in the case of contact with polychloropinene and polychlorocamphene, and serotonin in the case of contact with TMTD. The pesticides may disturb metabolic processes of vascular wall muscle fibers, which would explain why their effect was more expressed in vessels of the muscular type. Alteration of the viscoelastic properties of the arterial vessels was in a number of cases a burden which led to hemodynamic changes.

Van Oostdam, J; Gilman, A; Dewailly, E; et al. (1999) Human health implications of environmental contaminants in arctic canada: A review. Sci Total Environ 230(1-3):1-82.
This paper assesses the impact on human health of exposure to current levels of environmental contaminants in the Canadian Arctic, and identifies the data gaps that need to be filled by future human health research and monitoring. The concept of health in indigenous groups of the Arctic includes social, cultural, and spiritual dimensions. The harvesting, sharing and consumption of traditional foods are an integral component to good health among Aboriginal people influencing

both physical health and social well-being. Traditional foods are also an economic necessity in many communities. Consequently, the contamination of country food raises problems which go far beyond the usual confines of public health and cannot be resolved by health advisories or food substitutions alone. The primary exposure pathway for the contaminants considered in this paper is through the traditional northern diet. For the Inuit, the OCs of primary concern at this time from the point of view of exposure are chlordane, toxaphene, and PCBs. Exposures are higher in the eastern than in the western region of the North. For Dene/Metis, exposure to OCs is in general below a level of concern. However, estimated intake of chlordane and toxaphene has been found to be elevated for certain groups and is a cause for concern if exposures are elevated on a regular basis. The developing foetus and breast-fed infant are likely to be more sensitive to the effects of OCs and metals than individual adults and are the age groups at greatest risk in the Arctic. Extensive sampling of human tissues in the Canadian north indicate that a significant proportion of Dene, Cree and Inuit had mean maternal hair mercury levels within the 5% risk-range proposed by the WHO for neonatal neurological damage. Based on current levels, lead does not appear to pose a health threat while cadmium is likely only a major risk factor for heavy smokers or consumers of large amounts of organ meats. Consumers of traditional foods are exposed to an approximately seven-fold higher radiation dose than non-consumers of traditional foods due predominantly to the bioaccumulation of natural radionuclides in the food chain. Risk determination for contaminants in country food involves a consideration of the type and amounts of food consumed and the sociocultural, nutritional, economic, and spiritual benefits associated with country foods. Risk management options that minimize the extent to which nutritional and sociocultural aspects of Aboriginal societies are compromised must always be considered. Also may be used in Section(s): 3.2 & 4.4

Van Oostdam, J; Donaldson, S; Feeley, M; et al. (2005) Human health implications of environmental contaminants in arctic canada: A review. Sci Total Environ 351-352165-246. The objectives of this paper are to: assess the impact of exposure to current levels of environmental contaminants in the Canadian Arctic on human health; identify the data and knowledge gaps that need to be filled by future human health research and monitoring; examine how these issues have changed since our first assessment [Van Oostdam, J., Gilman, A., Dewailly, E., Usher, P., Wheatley, B., Kuhnlein, H. et al., 1999. Human health implications of environmental contaminants in Arctic Canada: a review. Sci Total Environ 230, 1-82]. The primary exposure pathway for contaminants for various organochlorines (OCs) and toxic metals is through the traditional northern diet. Exposures tend to be higher in the eastern than the western Canadian Arctic. In recent dietary surveys among five Inuit regions, mean intakes by 20- to 40-year-old adults in Baffin, Kivalliq and Inuvialuit communities exceeded the provisional tolerable daily intakes (pTDIs) for the OCs, chlordane and toxaphene. The most recent findings in NWT and Nunavut indicate that almost half of the blood samples from Inuit mothers exceeded the level of concern value of 5 microg/L for PCBs, but none exceeded the action level of 100 microg/L. For Dene/Metis and Caucasians of the Northwest Territories exposure to OCs are mostly below this level of concern. Based on the exceedances of the pTDI and of various blood guidelines, mercury and to a lesser extent lead (from the use of lead shot in hunting game) are also concerns among Arctic peoples. The developing foetus is likely to be more sensitive to the effects of OCs and metals than adults, and is the age groups of greatest risk in the Arctic. Studies of infant development in Nunavik have linked deficits in immune function, an increase in childhood respiratory infections and birth weight to prenatal exposure to OCs. Balancing the

risks and benefits of a diet of country foods is very difficult. The nutritional benefits of country food and its contribution to the total diet are substantial. Country food contributes significantly more protein, iron and zinc to the diets of consumers than southern/market foods. The increase in obesity, diabetes and cardiovascular disease has been linked to a shift away from a country food diet and a less active lifestyle. These foods are an integral component of good health among Aboriginal peoples. The social, cultural, spiritual, nutritional and economic benefits of these foods must be considered in concert with the risks of exposure to environmental contaminants through their exposure. Consequently, the contamination of country food raises problems which go far beyond the usual confines of public health and cannot be resolved simply by risk-based health advisories or food substitutions alone. All decisions should involve the community and consider many aspects of socio-cultural stability to arrive at a decision that will be the most protective and least detrimental to the communities. Also may be used in Section(s): 3.2 & 4.4

Warraki, S. (1963) Respiratory hazards of chlorinated camphene. Arch Environ Health 7253-256.

Wells, W; Milhorn, H, Jr. (1983) Suicide attempt by toxaphene ingestion: A case report. J Miss State Med Assoc 24(12):329-330.

Zahm, S; Ward, M; Blair, A. (1997) Pesticides and cancer. Occupational Medicine (Philadelphia) 12(2):269-289.
Literature review human agricultural worker occupational health pesticides toxicology cancer pesticide carcinogen occupational exposure toxin tumor biology carcinogenicity herbicide fungicide insecticide neoplastic disease.

Zahm, S; Blair, A; Holmes, F; et al. (1988) A case-referent study of soft-tissue sarcoma and hodgkin's disease farming and insecticide use. Scand J Work Environ Health 14(4):224-230.
Human carcinogen lymphoma myomatous sarcoma chlorinated hydrocarbon agriculture.

4.2. PRECHRONIC AND CHRONIC STUDIES AND CANCER BIOASSAYS IN ANIMALS – ORAL AND INHALATION

Association for Schools of Public Health. (1979) Common agricultural pesticide found to cause liver cancer in male and female mice. Public Health Rep 94(3):291.

American Industrial Hygiene Association (1979) Report on carcinogenesis bioassay of toxaphene. Am Ind Hyg Assoc J 40(5):A26-A32.

Anonymous (1992) Initial submission: Acute toxicity screen with gana toxaphene ec in rats & rabbits with cover letter dated 071492. EPA/OTS; Doc #88-920004474.
Also may be used in Section(s): 3.1

Arnold, D; Bryce, F; Baccanale, C; et al. (2001) Toxicological consequences of toxaphene ingestion by cynomolgus (macaca fascicularis) monkeys. Part 1: Pre-mating phase. Food Chem Toxicol 39(5):467-476.

A total of 40 menstruating cynomolgus monkeys (Macaca fascicularis) with an average age of 7.25 +/- 1.06 years (standard deviation), five male cynomolgus monkeys with an average age of 12.6 +/- 0.66 years, and five male cynomolgus males with an average age of 6.2 +/- 0.23 years were obtained from the Health Canada breeding laboratory. The females were initially randomized to the four test groups in accordance with their previous reproductive success and body weight. They were then randomly allocated between two similar environmentally-controlled rooms (20 females/room). The males were randomly assigned to one of the test rooms (six or four males/room). The female test groups self-ingested capsules containing doses of 0, 0.1, 0.4 or 0.8 mg (Groups A, B, C, D) of technical grade toxaphene/kg body weight/day (i.e. five females/dose group/room). The older males (Group E) were proven breeders and were used exclusively for mating and their capsules contained no toxaphene. The younger males (Group F) ingested capsules containing 0.8 mg of technical grade toxaphene/kg body weight/day. After 20 weeks of daily dosing, it was assumed, based on the results of a pilot study [Andrews P., Headrick K., Pilon J.-C., Bryce F., Iverson F. (1996) Capillary GC-ECD and ECNI GCMS characterization of toxaphene residues in primate tissues during a feed study. Chemosphere 32, 1043-1053], that the treated monkeys had attained a qualitative pharmacokinetic steady state regarding the concentration of toxaphene in their adipose tissue and blood. On a daily basis, each monkey's feed and water consumption as well as its health were monitored. In addition, the females were swabbed daily to determine menstrual status. On a weekly basis, each monkey's body weight was determined and its dose of toxaphene adjusted. Detailed clinical examinations were conducted at intervals of 4 weeks or less. Periodically, starting prior to the initiation of dosing, blood samples were taken for serum biochemistry, haematology and toxaphene analysis. In addition, specimens from the nuchal fat pad were also obtained for toxaphene analysis. Statistical analysis did not reveal any effect of treatment on body weight gain, feed consumption, water consumption or haematological parameters during the 75-week pre-mating phase. The only serum biochemistry parameter which was consistently affected by treatment was cholesterol, the level of which decreased in a linear fashion as a consequence of dose, and this effect increased with time on test (P = 0.037). No other biological effects of toxaphene ingestion were found during the premating phase of this toxicological-reproduction study. Also may be used in Section(s): 3.1, 3.2, 3.3, & 3.4

Besselink, H; Nixon, E; McHugh, B; et al. (2000) In vitro and in vivo tumor promoting potency of technical toxaphene, uv-irradiated toxaphene, and biotransformed toxaphene. Organohalogen Compounds 47113-116.
Also may be used in Section(s): 4.5

Bryce, F; Iverson, F; Andrews, P; et al. (2001) Effects elicited by toxaphene in the cynomolgus monkey (macaca fascicularis): A pilot study. Food Chem Toxicol 39(12):1243-1251.
Toxaphene, which was added to glycerol/corn oil, was administered at a level of 1 mg/kg body weight/day in gelatin capsules to four healthy young adult cynomolgus (Macaca fascicularis) monkeys for 52 weeks. Four control monkeys ingested capsules containing only glycerol/corn oil. Each group had two males and two females. On a daily basis, each monkey's feed and water consumption was determined, its health was monitored and the females were swabbed to evaluate menstrual status. On a weekly basis, each monkey's body weight was determined and a detailed clinical evaluation was performed. At 4-week intervals, blood samples were taken for serum biochemistry, haematology and toxaphene analysis. Also, a local anaesthetic was

administered to the nuchal fat pad area of each monkey, and adipose samples were obtained for toxaphene analysis. 1 day prior to the biopsies, a 24-h urine and faecal collection was obtained for toxaphene analysis. After 34 weeks of treatment, the immune system of the monkeys was evaluated. After 52 weeks of dosing, all treated and two control animals were necropsied. Liver samples were obtained and microsomal fractions were prepared immediately. A portion of liver and kidney was taken for toxaphene analysis. All of the major internal organs were weighed and bone marrow evaluations were conducted. Organ and tissue samples were fixed in 10% formalin and processed for light microscopy. There was no effect of treatment on body weight gain, feed consumption, water consumption or haematological parameters. Two major clinical findings were inflammation and/or enlargement of the tarsal gland and impacted diverticulae in the upper and lower eye lids. At necropsy, the relative spleen and thymus weights were greater for the treated monkeys than the controls. Toxaphene administration produced an increase in metabolism of aminopyrene, methoxyresorufin and ethoxyresorufin, three substrates that are altered specifically by cytochrome P450-based hepatic monooxygenase enzymes. Histopathological examination of tissues was unremarkable by light microscopy. Tissue analysis for toxaphene and immunology findings have been published elsewhere. Also may be used in Section(s): 3.2, 3.3, 3.4, 4.2, & 4.4

Cabral, J; Raitano, F; Mollner, T; et al. (1979) Acute toxicity of pesticides in hamsters. Toxicol Appl Pharmacol 48(1).
EIS: Epidemiology Information System.

Chu, I; Villeneuve, D; Sun, C; et al. (1986) Toxicity of toxaphene in the rat and beagle dog. Fundam Appl Toxicol 7(3):406-418.
Residues of the insecticidal mixture, toxaphene, have been found in Great Lakes fish. The purpose of the present study was to assess the subchronic toxicity of toxaphene in the rat and beagle dog. In the rat study, groups of 10 male and 10 female animals were fed diets containing 0, 4, 20, 100, or 500 ppm of the test compound for 13 weeks. No clinical signs of toxicity or spontaneous deaths were observed. Toxaphene treatment up to 500 ppm had no effects on weight gain or food consumption. The liver/body weight ratio and hepatic microsomal enzyme activities (phenobarbital type) were increased in both sexes fed 500 ppm of the test compound. Toxaphene at the highest dose also caused kidney enlargement in male but not in female rats. Dose-dependent histological changes were seen in the kidney, thyroid, and liver. Changes in the liver and thyroid were considered to be adaptative but the injury in the proximal tubules of the kidney was focally severe. Groups of six male and six female beagle dogs were fed toxaphene in gelatin capsules at 0, 0.2, 2.0, and 5.0 mg/kg body wt/kg body wt/day for 13 weeks. Food consumption and growth rate were not affected. All animals survived the entire treatment period. No clinical signs of toxicity were observed. The liver/body weight ratio and serum alkaline phosphatase were increased in dogs of both sexes fed 5.0 mg/kg. Mild to moderate dose-dependent histological changes were observed in the liver and thyroid. Toxaphene was accumulated in a dose-dependent manner in the fat and liver of dogs and rats. Based on the biochemical, histological, and residue data, it was concluded that the no-adverse-effect levels of the pesticide were 4.0 ppm (0.35 mg/kg) for the rat and 0.2 mg/kg for the dog.

Gold, LS; Slone, TH; Manley, NB; et al. (1994) Heterocyclic amines formed by cooking food: Comparison of bioassay results with other chemicals in the carcinogenic potency database.

Cancer Letters 83(1-2):21-29.
Results in the Carcinogenic Potency Database (CPDB) on 11 mutagenic heterocyclic amines (HA) tested for carcinogenicity in rats, mice and cynomolgus monkeys are compared to results for other chemicals. An analysis of strength of evidence of carcinogenicity for HA vs. other mutagenic carcinogens and vs. all rodent carcinogens, indicates strong carcinogenicity of HA in terms of positivity rates and multiplicity of target sites. The liver is the most frequent target site in each species. Despite several target sites in each species, concordance in target sites between rats and mice is restricted to the liver for each HA except one. In cynomolgus monkeys, liver tumors have been induced rapidly by 2-amino-3-methylimidazo(4,5-f)quinoline (IQ). Human exposures to HA in cooked animal foods are small, in the low ppb range. A comparison of possible carcinogenic hazards from a variety of exposures to rodent carcinogens in the American diet is presented, using an index (Human Expos Mh - Biochemistry/Methods.

Johnston, B; Eden, W. (1953) The toxicity of aldrin, dieldrin, and toxaphene to rabbits by skin absorption. J Econ Entomol 46702-703.

Keller, L; Exon, J; Norbury, K. (1983) Induction of humoral immunity to protein antigen without adjuvant in rats exposed to immunosuppressive chemicals. J Toxicol Environ Health 12173-181.

Keplinger, ML; Deichmann, WB. (1967) Acute toxicity of combinations of pesticides. Toxicol Appl Pharmacol 10(3):586-595.

Kuntz, D; Rao, N; Berg, I; et al. (1990) Toxicity of mixtures of parathion, toxaphene and/or 2,4-d in mice. J Appl Toxicol 10(4):257-266.
The toxicity of the mixtures of parathion (PA), toxaphene (TOX) and/or 2,4-dichlorophenoxyacetic acid (2,4-D) was studied in ICR male mice (21-24 g) by oral intubation, in corn oil, daily for up to 14 days. On Day 15, the exposure was discontinued, and animals were monitored for an additional period of 7 days for the possible reversibility of the toxicity. The body weight gain decreased with the mixtures, as well as with the individual agricultural chemicals (ACs), during the 14-day period. The cholinesterase (ChE) activity in the serum and brain was inhibited in the animals of the groups of PA (1-10 mg kg-1) and PA (5 mg kg-1)-containing mixtures. TOX (50-200 mg kg-1) caused initial inhibitory effects of 20-65% on the serum ChE (Day 1) before producing increases of 53-64% in the enzyme activity by Day 15, with little effects on the brain ChE levels. 2,4-D (50-200 mg kg-1) resulted in significantly elevated levels of the serum ChE, with substantial decreased in the brain ChE activity. The serum glutamic pyruvic transaminase level was up (38-630%) in TOX (50 mg kg-1), 2,4-D (50 mg kg-1) or their mixture group. No pathological changes at the light microscopic level in the brain and liver were noticed. TOX and TOX-containing mixtures significantly increased the liver/body weight ratio and decreased the pentobarbital (60 mg kg-1, i.p., in saline)-induced sleep. Also may be used in Section(s): 4.5

Lackey, R. (1949) Observation on the acute and chronic toxicity of toxaphene in the dog. J Ind Hyg Toxicol 31:117-120.

Makovskaya Ye, I; Shamray, P; Grigor'yeva, N. (1972) Structural and histochemical changes of internal secretion glands during polychloropinene poisoning. Vrach Delo 2128-131.

Structural and histochemical alterations in endocrine glands of mice, rats, and rabbits due to subchronic and chronic poisoning with daily oral polychloropinene (toxaphene) doses corresponding to one-tenth and one-fiftieth LD50 are described. Investigations of the adrenal gland revealed cells with granular cytoplasm in the cortex and reduced glycogen, succinate dehydrogenase, alkaline phosphatase, lipid, and chromaffin body levels. Pyknosis and lysis of cell nuclei, edema, focal hemorrhages, and focal necrosis in the cortex were observed after four months. Hyperfunction of the thyroid gland along with focal granular degeneration and necrotic alterations of the follicular epithelium and slightly edematous stroma were determined. The pancreas displayed disturbed hemodynamics in the form of polyemia, edematous stroma, and focal hemorrhages. Necrosis of islet cells was revealed in some cases. Dystrophy of the germinative epithelium cells of the testes after two months and frequent total absence of spermatozoa after four months were observed. Degeneration of the tubular epithelium with the presence of only Sertoli cells and single spermatogoniae were determined in some cases. Large numbers of collagen fibers, fibrocytes, and macrophages were detected in the interstitial tissue. Examinations of the hypophysis showed atrophic changes with reduced numbers of basophilic cells. Proliferation of connective tissue cells in perivascular areas was observed. The findings indicate that endocrine glands are highly sensitive to organochlorine compounds.

Matsumura, F. (1978) Mechanisms of pesticide degradation.
This research project was initiated with the overall objectives of determining the chemical structures of toxic components of toxaphene, to study anaerobic metabolism to degrade toxaphene and other pesticides, and to understand the toxic action mechanism of chlordimeform. As a result of intensive efforts the molecular structures of three of the most toxic principles of toxaphene were identified. Together these comprise at least 70% of toxaphene's toxicity toward mice. This is the first time that the structure of toxic components of toxaphene became apparent despite the widespread use of toxaphene in the last 3 decades. Toxaphene on the other hand degrades relatively faster than other chlorinated pesticides such as DDT and dieldrin. The reason for it is that toxaphene is susceptible to reductive degradative forces. Chlordimeform was found to affect amine regulatory mechanisms in animals. Such actions explain some of the subtle effects of this pesticide on animals, inasmuch as that biogenic amines are known to play may important biological roles such as controlling emotion, behavior and circulatory functions of the body.

Mehendale, H. (1978) Pesticide-induced modification of hepatobiliary function: Hexachlorobenzene, ddt, and toxaphene. Food Cosmet Toxicol 16:19-25.
Also may be used in Section(s): 3.3 & 4.5

National Toxicity Program. (1979) Bioassay of toxaphene for possible carcinogenicity cas no. 8001-35-2 nci-cg-tr-37 u. 77.

NCI. (1977) Bioassay of toxaphene for possible carcinogenicity. National Cancer Institute, Division of Cancer Cause and Prevention, Carcinogenesis Testing Program. DHEW/PUB/NIH-79-837; NCI-CG-TR-37; PB-292290., 105
Bethesda, MD.

Nelson, D; Lamb, D; Mihail, F. (1984) A study of liver microsomal enzymes in rats following

propoxur (baygon) administration. Vet Hum Toxicol 26(4):305-308.
Groups of rats were given either propoxur, were left as untreated controls, or were given phenobarbital, DDT, chlordane or toxaphene which are known to induce liver microsomal detoxification enzymes. Microsomal enzyme activity was measured by testing the ability of liver homogenates to degrade EPN (O-ethyl O-(4-nitrophenyl) phenylphosphonothioate) to p-nitrophenol. The activity of aminopyrine-N-demethylase, cytochrome P-450 and p-nitroanisole-O-demethylase in liver homogenates of rats receiving propoxur was measured. Liver microsomal detoxification enzymes were not induced by propoxur exposure. Also may be used in Section(s): 4.5

Nelson, JO; Matsumura, F. (1975) Separation and comparative toxicity of toxaphene components. J Agric Food Chem 23(5):984-990.

Ortega, P; Hayes, W; Durham, W. (1957) Pathologic changes in the liver of rats after feeding low levels of various insecticides. AMA Arch Pathol 64614-622.

Pollock, G; Kilgore, W. (1980) Toxicities and description of some toxaphene fractions: Isolation and identification of a highly toxic component. J Toxicol Environ Health 6(1):115-125.
Toxaphene was separated into 13 fractions and the toxicity of each fraction was determined. The acute toxicities (LD50) to houseflies (topical in acetone) ranged from 21 to greater than 246 mg/kg (toxaphene LD50 = 33 mg/kg) and the relative toxicities ranged from 0.6 to greater than 7.5. A similar pattern was found in mice when the toxicities of several fractions were determined. The acute toxicities (LD50, ip injection in dimethyl sulfoxide) in mice ranged from 20 to 67 mg/kg (toxaphene LD50 = 33 mg/kg) for the fractions tested. The most toxic fraction was further separated into six subfractions and their toxicities (housefly LD50) were found to range from 10 to 74 mg/kg. The most toxic subfraction appeared to be an almost pure compound and was purified for further identification. It was found to be identical to a previously reported highly toxic C10H10Cl8 mixture of predominantly two components. The components were reported to be 2,2,5-endo,6-exo, 8,8,9,10-octachlorobornane and 2,2,5-endo,6-exo,8,9,9,10-octachlorobornane. This highly toxic mixture has now been isolated independently by three research teams using different separation schemes.

Pollock, GA; Krasnec, JP; Niemann, BR. (1983) Rat hepatic microsomal enzyme induction by pretreatment with toxaphene and toxaphene fractions. J Toxicol Environ Health 11(3):355-363.
The levels of hepatic microsomal induction caused by toxaphene were determined. Young Sprague-Dawley rats (70 g) were administered toxaphene (ip injection, daily for 5 d) at 0, 5, 25, and 100 mg/kg. All doses caused increases in liver/body weight ratio, cytochrome P-450 level, aminopyrine demethylation, and aldrin epoxidation. The aldrin epoxidase activity increased almost 700% at the 100-mg/kg dose. Toxaphene was separated into nonpolar (S-A) and polar (S-B) fractions and administered as before at 25 mg/kg. All treatments caused significant increases in cytochrome P-450, aminopyrine demethylation, and aldrin epoxidation. A comparison of the treatments, however, did not reveal any significant differences between the treatments.

Reuber, M. (1979) Carcinogenicity of toxaphene: A review. J Toxicol Environ Health 5(4):729-748.
Toxaphene is highly carcinogenic in rats and mice. Toxaphene induced malignant neoplasms of

the liver in rats. Neoplasms at all sites, as well as malignant neoplasms, were increased in male and female rats ingesting toxaphene. Sarcomas were found more often in male rats and carcinomas in female rats. Neoplasms of the endocrine organs were also increased in male and female toxaphene-treated rats. The incidence of neoplasms of the reproductive system was increased in female rats, as was the incidence of mammary gland neoplasms in male rats. Toxic changes in male rats given toxaphene included interstitial fibrosis of the kidney and atrophy of the testes. Toxaphene induced malignant neoplasms of the liver in male and female mice. The incidence of malignant neoplasms at all sites was also increased. In addition to hepatic neoplasms, male mice had leukemia or lymphosarcoma and females had sarcomas of the uterus. Also may be used in Section(s): 4.5

Robens, J. (1978) Tests for possible carcinogenicity of 20 pesticides in osborne-mendel rats and b6c3f1 mice. Toxicol Appl Pharmacol 45(1).
Twenty pesticides (i.e., the chlorinated hydrocarbon insecticides, chlordane, heptachlor, aldrin, dieldrin, photodieldrin, endrin, Kepone (chlordecone), toxaphene, and lindane; the organophosphorus insecticides, tetrachlorvinphos, dimethoate, dichlorvos, malathion, phosphamidon, parathion, and azinphosmethyl; the fungicides, captan and chlorothalonil; and the herbicides chloramben and picloram) were tested for possible carcinogenicity in Osborne-Mendel rats and B6C3F1 mice. The chemicals were administered in feed at one of two concentrations for 80 wk to both species; the rats were observed for an additional 30 wk and the mice for 10 wk before termination of the studies. The highest concentration tested for each chemical was the maximum compatible with survival for the period of the studies. The second concentration tested was half of this. Restarts of specific groups and lowering of the concentrations during some studies was necessary to achieve adequate survival. Following gross necropsy, 24 tissues for each treated and control animal was examined microscopically. Signs of toxicity, dose-related decreased in survival, and/or decreased mean body weight were observed in all studies, indicating that maximum tolerated doses were used. In rats, with several of the compounds there were small increased incidences of proliferative lesions of the endocrine organs, usually in one dose group of one sex. These included increases of proliferative cells of the thyroid in animals treated with chlordane, heptachlor, photodieldrin, aldrin, tetrachlorvinphos, picloram, and captan and of adrenal cortical adenomas in animals treated with captan, aldrin, dieldrin, and tetrachlorvinphos. In mice, with several of the compounds there was an increased incidence of hepatocellular carcinoma and/or adenoma in treated groups compared with that of control animals/ these incidences were statistically significant and were considered to indicate that the compounds heptachlor, chlordane, Kepone, aldrin, and tetrachlorvinphos were carcinogenic. The only other tumor observed in a significant incidence in mice was polypoid carcinoma of the duodenum in captan.

Sosnierz, M; Szczurek; Knapek, R; et al. (1972) Morphologic studies on short-term subacute toxicity of kamfochlor. Patol Pol 23(2):199-202.
Kamfochlor (toxaphene) was administered orally as a 25% olive oil solution in 0.07, 0.22, 0.66, 2.0, and 6.0 mg/kg/day dose to groups of Wistar rats (male and female) for 90 days. Examination of liver, spleen, kidneys, lungs, and testes revealed pathomorphologic changes in animals receiving high dosages (2 and 6 mg/kg) of the compound. These included circulation disorders (mainly in lungs and spleen) and degenerative lesions (liver and kidneys). Impaired circulation caused congestion and damaged blood vessel walls resulting in hyperemia, extravasation, and

hemorrhage. The compound was also cytotoxic, progressively damaging and diminishing the activity of cell organelles and leading to death of cells. In the spleen a reduction of Malpighian follicles was noted suggesting an inhibition of lymphopoiesis. Lesions in the testes indicated a harmful effect on spermatogenesis. There was no difference in severity of changes in male as compared to female rats, but individual sensitivity to the compound differed among animals. 1972.

Studdert, V. (1985) Incidence of poisoning in dogs and cats in melbourne australia. Aust Vet J 62(4):133-135.
Pesticides heavy metals drugs household products snake venom tick toxin.

Triolo, AJ; Lang, WR; Coon, JM; et al. (1982) Effect of the insecticides toxaphene and carbaryl on induction of lung tumors by benzo[a]pyrene in the mouse. J Toxicol Environ Health 9(4):637-649.
The insecticides toxaphene and carbaryl, when fed in the diet alone for 20 wk, were not tumorigenic to female A/J mice. Dietary levels of these insecticides were investigated for their effects on the incidence of lung tumors induced by oral administration of benzo[a]pyrene (BP). A significant reduction in BP-induced lung tumors was found after feeding 100 ppm toxaphene for 12 wk or 200 ppm for 20 wk. In contrast, 1000 ppm carbaryl fed for 20 wk caused a significant enhancement of BP-induced lung tumors. Mice that received toxaphene in the diet alone, or toxaphene and BP, showed an increase in BP hydroxylase activity in the liver and a decrease in enzyme activity in the lung. Carbaryl and BP increased BP hydroxylase activity in the lung without altering enzyme activity in the liver. Inhibition of lung BP hydroxylase activity was paralleled by a reduction in BP-induced lung tumors in mice fed toxaphene. Conversely, increased lung BP hydroxylase activity was associated with an enhancement of BP-induced lung tumors in animals fed carbaryl. The metabolism of BP by organs susceptible to BP-induced tumors and possible mechanisms for interactions with the insecticides are discussed. Also may be used in Section(s): 4.5

Waritz, R; Steinberg, M; Kinoshita, F; et al. (1996) Thyroid function and thyroid tumors in toxaphene-treated rats. Regul Toxicol Pharmacol 24(2 Pt 1):184-192.
Historically, a direct and irreversible genotoxic reaction of a xenobiotic with DNA has been considered to be a universal and obligatory initiating event in the etiology of neoplasia, and it was assumed therefore that (1) there was no threshold other than zero exposure for cancer initiation, and (2) like radiation, exposure was additive over a lifetime. Human exposure to xenobiotics causing neoplasia in laboratory rodents has been regulated in many countries on that basis. In the last decade evidence has accumulated indicating that some neoplasia in laboratory rodents may not be caused by a direct and irreversible interaction of xenobiotics with DNA. In addition, it has been found that some neoplasia caused in laboratory rodents by xenobiotics may not be relevant for biochemical/physiological reasons. This has raised the question whether human exposure to these xenobiotics should be regulated by the no-threshold philosophy used for direct-acting genotoxic xenobiotics or whether they can be regulated by the threshold philosophy used for classical xenobiotic-induced toxic effects. In a bioassay carried out by the National Cancer Institute and published in 1979, toxaphene was found to cause an increase in the occurrence of two spontaneously occurring tumors in laboratory rodents that since have been found to have both genotoxic and nongenotoxic etiologies in laboratory rodents. Experiments

described in this paper are part of a program to help elucidate whether the increased incidence of these two neoplasms in laboratory rodents could have had a nongenotoxic origin, and thus whether toxaphene could be regulated by a threshold approach. Forty male rats were orally intubated with 100 mg/kg/day technical grade toxaphene in corn oil for 3 days. The dose was reduced to 75 mg/ kg/day on Day 4 due to toxicity. This lower dose was administered daily for 25 days. Another group of 40 male rats was orally gavaged daily with equivalent volumes of corn oil. After 0, 7, 14, and 28 doses, 10 test and 10 vehicle control animals were sacrificed for gross and histopathological examination of thyroid, parathyroid, and pituitary glands. Weights of these endocrine organs, body weights, and brain weights were determined. Prior to sacrifice, a blood sample was obtained from each animal for preparation of serum for analyses of thyroid stimulating hormone (TSH), thyroxine (T4), thyroid hormone (T3), and reverse T3 (rT3). Thyroid glands were evaluated microscopically for follicular cell hypertrophy, hyperplasia, and colloid storage. There were significant time-related increases in serum TSH in the test animals after 7, 14, and 28 doses of toxaphene. The serum levels of T3, T4, rT3, and corrected T3 (CrT3) in the test group were not significantly different from controls at each interval. Thyroid gland weights and thyroid to brain weight ratios were not significantly ($p > 0.05$) increased in the test group at each sacrifice interval. Pituitary weight, brain weight, and the ratios of these organ weights to body weights were similar in the test and control groups at each sacrifice interval. Thyroid follicular cell hypertrophy and intrafollicular hyperplasia increased and thyroid follicular cell colloid stores decreased with duration of treatment with toxaphene. The hormonal and histopathologic changes seen in the test group were consistent with increased excretion of T3 and/or T4 resulting from cytochrome P450 enzyme induction in the liver. This mechanism for thyroid neoplasia is not known to occur in humans. Also may be used in Section(s): 4.5

4.3. REPRODUCTIVE/DEVELOPMENTAL STUDIES – ORAL AND INHALATION

Chernoff, N; Carver, B. (1976) Fetal toxicity of toxaphene in rats and mice. Bull Environ Contam Toxicol 15(6):660-664.

Chernoff, N; Kavlock, R. (1982) An in vivo teratology screen utilizing pregnant mice. J Toxicol Environ Health 10(4-5):541-550.
Twenty-eight compounds of known teratogenic potential were assayed by an in vivo screening procedure. Postnatal growth and viability of prenatally exposed offspring was used as a measure of developmental toxicity. Gravid CD-1 mice were administered maximum tolerated doses of the compounds for up to 5 consecutive days during the period of major organogenesis. The dams were allowed to give birth, and litter size and weight on postpartum d 1 and 3 were recorded and compared with concurrent controls. All 15 compounds that were teratogenic by standard teratology test criteria exhibited some form of developmental toxicity. Four chemicals known to produce only fetal toxicity (reduced weight or supernumerary ribs) were tested and the screen successfully identified those that reduced weight. Finally, of the 9 compounds that show no effect in standard tests, 6 were also negative in the screen and 3 demonstrated either reduced viability or weight.

Chernoff, N; Setzer, R; Miller, D; et al. (1990) Effects of chemically induced maternal toxicity on prenatal development in the rat. Teratology 42(6):651-658.

The hypothesis that chemically induced overt maternal toxicity induces a characteristic syndrome of adverse developmental effects in the rat was investigated. Pregnant animals (Sprague-Dawley strain) were dosed by oral gavage with one of a series of compounds on days 6-15 of gestation. These chemicals were diquat (DIQ), ethylene-bis-isothiocyanate (EBIS), toxaphene (TOX), styrene (STY), 2,4-dichlorophenoxyacetic acid (2,4-D), 2,4,5-trichlorophenol (2,4,5-Tr), triphenyl tin hydroxide (TPTH), and cacodylic acid (CAC). The compounds were chosen because they exhibited little or no developmental toxicity in previous studies. Dosage levels producing maternal weight loss and/or lethality were determined from preliminary toxicity studies. Significant maternal weight reductions were noted during the course of treatment with all compounds except CAC and 2,4,5-Tr. Maternal lethality was produced by EBIS, TOX, 2,4,-D, and 2,4,5-Tr. The main treatment-related developmental toxicity noted in litters at term consisted of increased lethality (EBIS, TPTH) and decreased fetal weight (EBIS and CAC). Treatment-related anomalies were seen in litters treated with 2,4-D and TOX (supernumerary ribs) and with EBIS and STY (enlarged renal pelvis). No significant developmental effects were produced with DIQ, or 2,4,5-Tr. This study indicates that overt maternal toxicity as defined by weight loss or mortality is not always associated with the same defined syndrome of adverse developmental effects in the rat.

Chu, I; Secours, V; Villeneuve, D; et al. (1988) Reproduction study of toxaphene in the rat. J Environ Sci Health B 23(2):101-126.
The purpose of the present study was to investigate in rats the reproductive effects of toxaphene, an insecticidal mixture which has been identified as a pollutant in the Great Lakes ecosystem. Groups of 30 female and 15 male weanling rats were given toxaphene in the diets at 0, 4.0, 20, 100 or 500 ppm in a 1 generation 2 litter reproduction study. Toxaphene treatment at the levels studied had no effects on the litter size, pup weight, fertility, or gestation and survival indices. Toxic effects in the parental rats included depressed weight gain, elevated serum cholesterol, and increased liver and kidney weight and hepatic microsomal enzyme activities. Most of these effects were associated only with 500 ppm toxaphene treatment. Treatment-related histological changes in the liver, thyroid and kidney of adult rats were observed at levels as low as 20 ppm. Based on the data presented, the no observable adverse effect dose of toxaphene was considered to be 4.0 ppm in the diet (0.29-0.38 mg/kg b.w./day depending on the amount of dietary intake).

Kavlock, R; Chernoff, N; Rogers, E. (1985) The effect of acute maternal toxicity on fetal development in the mouse. Teratog Carcinog Mutagen 5(1):3-13.
The effects of acute alterations in maternal health status upon fetal development were assessed following exposure of pregnant CD-1 mice on day 8 of gestation to one of ten chemicals at doses calculated to exert either a low or a moderate degree of maternal lethality. The dams were killed on day 18 of gestation, and the fetuses were examined by routine teratological techniques. The chemicals were cacodylic acid, caffeine, deltamethrin, dinoseb, ethylene bisisothiocyanate sulfide (EBIS), endrin, guthion, kepone, sodium salicylate, and toxaphene. Three (cacodylic acid, EBIS, and kepone) produced dose-related increases in the incidence of dams with completely resorbed litters. Prenatal mortality in litters that contained live fetuses at term was elevated only for one chemical (cacodylic acid). Fetal weight was reduced in three instances (cacodylic acid, endrin, and guthion), while the incidence of terata was markedly elevated for two (cacodylic acid and kepone). For two other chemicals (endrin and sodium salicylate), a low incidence was found of defects that were similar to defects induced by those chemicals in other species. These effects

appear to be chemospecific in nature and not the result of some indirect maternal action. Thus, maternal health status, as measured by the incidence of lethality in the treated groups and by the magnitude of maternal weight gain in surviving females, presents no simple explanation for many manifestations of fetal toxicity. However, for seven chemicals (excluding deltamethrin, EBIS, and kepone) an increased incidence of supernumerary ribs was observed. For three of these seven chemicals (caffeine, dinoseb, and toxaphene), supernumerary ribs was the only observed fetal effect. There was a significant linear inverse relationship between maternal weight gain during gestation and the incidence of extra ribs in the treated groups compared to their respective controls. Under the experimental conditions of this study, it appears that the incidence of supernumerary ribs increased in response to a nonspecific maternal toxicity. Also may be used in Section(s): 4.5

Kavlock, R; Chernoff, N; Rogers, E; et al. (1982) An analysis of fetotoxicity using biochemical endpoints of organ differentiation. Teratology 26(2):183-194.
The biochemical differentiation of the brain, lungs, liver, and kidneys of the late gestation rat fetus was examined to characterize the immediate implications of retarded growth on fetal development. Initially, the normative profile of development of the brain (weight, DNA content, and protein content), lungs (weight and surfactant accumulation), liver (weight and glycogen deposition), and kidneys (weight, alkaline phosphatase activity, and protein content) was determined on gestation days 19, 20, 21, and 22 (day 1 = finding of sperm in the vaginal smear). Subsequently, five compounds known to induce fetotoxicity (chlorambucil, methyl salicylate, mirex, nitrofen, and toxaphene) were administered during organogenesis, and the effects on organ differentiation were determined in day 21 fetuses. The effects of fetal growth retardation resulting from exposure to exogenous agents were not equally distributed among the organs studied. The liver and kidney appeared more sensitive to insult by these agents than did the brain and lungs.

Kennedy, G, Jr.; Frawley, J; Calandra, J. (1973) Multigeneration reproductive effects of three pesticides in rats. Toxicol Appl Pharmacol 25(4):589-596.

Keplinger, M; Deichman, W; Sala, F. (1968) Effects of combinations of pesticides on reproduction in mice. Ind Med Surg 37(7):525.
Abstract of paper presented at the Sixth Inter-American Conference on Toxicology and Occupational Medicine, Miami, Florida, August 26-29, 1968. Aldrin, Dieldrin, Chlordane and DDT were incorporated into the diet of mice for three generations. The individual experiments were designed to determine the effects in the young caused by absorption of a pesticide or a mixture of pesticides, by way of the placenta, by ingestion in mother's milk, and/or by ingestion with con- taminated food. Evaluation of data suggests little or no effect was noted through five or six generations of mice fed 25 ppm toxaphene, chlordane, or DDT. Marked effects in regard to fertility, gestation, viability, lactation, or survival were noted in parent, or second generation and their offspring on a diet containing aldrin or dieldrin 25 ppm; aldrin 10 ppm plus chlordane 100 ppm; aldrin 25 ppm plus chlordane 25 ppm; aldrin 25 ppm plus DDT 25 ppm; and aldrin 25 ppm plus DDT 25 ppm plus chlordane 25 ppm. Significant but less marked effects were noted after feeding aldrin 3, 5, and 10 ppm; dieldrin 3 and 10 ppm; chlordane 50 and 100 ppm; DDT 100 and 250 ppm; aldrin 5 ppm plus chlordane 50 ppm; aldrin 5ppm plus chlordane 25 ppm; dieldrin 10 ppm plus chlordane 100 ppm; aldrin 10 ppm plus DDT 100 ppm; aldrin 5 ppm plus

DDT 25 ppm; and chlordane 15 ppm plus DDT 15 ppm. Microscopic examination of the organs and tissues revealed changes in the liver of all groups and in the kidneys, lungs, and brains of most groups. Also may be used in Section(s): 3.1

Olson, K. (1978) Effects of chronic pre- and postnatal exposure to pesticides on the behavior and learning ability in rats. Diss Abstr Int B 38(7).
Pesticides of environmental concern (dieldrin, chlordimeform, toxaphene, and two fractions of toxaphene, Toxicant A and Toxican B) were fed to two generations of albino rats. The rats received daily oral doses of either 0.35 mug/kg dieldrin, 100 mug/kg chlordimeform, 50 mug/kg toxaphene, 2 mug/kg Toxicant A, or 2 mug/kg Toxicant B. Second generation animals were tested in a variety of maturational, motivational and learning tasks. The results revealed that the rats fed toxaphene, Toxicant A, Toxicant B, and chlordimeform were significantly inferior to the controls in overall swimming ability (a maturational task). The Toxicant B group was inferior to the controls, the Toxicant A group and toxaphene group in learning ability (i.e., the number of mistakes made on the test problems). The Toxicant A fed animals were inferior to the other groups in retention testing which involved running the animals on the same problem 48 hours later. Toxicant A rats made significantly more errors and had the worst total time for the trials. Early deficits in righting reflex ability were exhibited in the toxaphene rats. The dieldrin groups were significantly superior to their control groups in the retention test, thus suggesting a stimulatory effect of low dose dieldrin. In other experiments ingestion of higher levels of dieldrin resulted in behavioral impairment. (Author abstract by permission, abridged. Copies of the thesis are available from University Microfilms, order No. 77-19,724). Also may be used in Section(s): 3.3

Olson, K; Matsumura, F; Boush, G. (1980) Behavioral effects on juvenile rats from perinatal exposure to low levels of toxaphene, and its toxic components, toxicant a, and toxicant b. Arch Environ Contam Toxicol 9(2):247-257.
Behavioral effects of toxaphene, and its toxic components, toxicant A and toxicant B, were studied by perinatally exposing juvenile rats. Toxaphene was given daily to pregnant rats (and their offspring) at 50 microgram/kg body weight via their diet. The daily dietary levels of toxicants A and B were 2.0 microgram/kg body weight. Behavioral tests were performed on the offspring. All rats fed toxaphene, as well as toxicants A and B, showed retarded maturation as judged by the swimming test during their early development. However, the treated rats eventually attained normal swimming ability. The maze retention test demonstrated significant differences between the toxicant A group and all other groups. The toxicant A animals had no difficulty in learning the test problems but were inferior to the other groups in retaining that knowledge.

Welch, R; Levin, W; Kuntzman, R; et al. (1971) Effect of halogenated hydrocarbon insecticides on the metabolism and uterotropic action of estrogens in rats and mice. Toxicol Appl Pharmacol 19(2):234-246.

4.4. OTHER ENDPOINT-SPECIFIC STUDIES

Allen, A; Koller, L; Pollock, G. (1983) Effect of toxaphene exposure on immune responses in

mice. J Toxicol Environ Health 11(1):61-69.
Toxaphene was fed to female weanling Swiss-Webster mice at dosages of 10, 100, and 200 ppm for 8 wk. Immunologic assays revealed depressed IgG antibody formation in those animals receiving 100 and 200 ppm toxaphene, as compared to controls. Cell-mediated immune responses were not affected in the toxaphene-exposed mice. In another experiment, mature female mice fed the same amounts of toxaphene were mated 3 wk after feeding began and were maintained on the diets until 3 wk after parturition, at which time the pups were weaned onto the control ration. Assays performed on the offspring 8 wk after their birth revealed suppressed antibody formation in the 100-ppm-toxaphene group and enhanced antibody formation in the 200-ppm group. The cell-mediated immune response was suppressed in the offspring from the 100-ppm group, while no change from the controls occurred in the other groups. Phagocytic ability of macrophages was significantly reduced in all toxaphene-treated groups, but to a greater extent in the offspring of the mice that consumed 100 ppm toxaphene.

Badaeva, L. (1976) The effect of polychlorocamphene on some organs and their nervous apparatus in pregnant animals. Byull Eksp Biol Med 82(8):945-847.
Polychlorocamphene (toxaphene) administered orally to pregnant albino rats producted destructive structural and enzymatic changes in the cerebral cortex, heart, uterus, and spinal cord. The number of cholinesterase (CE)-positive pericellular structures decreased markedly, although their activity continued. Thin-layer chromatography showed accumulation of polychlorocamphene in the heart, uterus, and brain of the mothers and in the organs of the fetuses. Also may be used in Section 4.3.

Badaeva, L. (1979) [effect of pesticides on cholinesterase activity in the nervous elements of the heart in pregnant animals and fetuses]. Arkh Anat Gistol Embriol 76(4):68-71.
Cholinestarase activity in the cardiac neural elements of pregnant animals and in their offspring was studied under the effect of chlororganic pesticide -- polychlorcamphen and phosphororganic pesticide -- valexone. The substances in question were demonstrated to produce variously pronounced unidirected changes in cholinesterase activity in neural structures that testifies to interconnection and dependence of the changes in the system mother -- fetus. The alterations observed in nonsynaptic (trophic) cholinesterase make it possible to speak about the disorder of cholinergic innervation and about the importance of acetilcholinesterase trophic function as a regulator of cellular processes, an inhibitory index of differentiation during embryogenesis.
Also may be used in Section(s): 4.3

Badaeva, L. (1981) Experimental study of the postnatal neurotoxic effect of chloro-organic pesticides. Folia Morphol (Praha) 29(2):113-114.
Also may be used in Section(s): 4.3

Bogachuk, G; Filenko, V. (1978) [effect of general vertical vibration and polychlorocamphene on the kidneys of inbred rats]. Arkh Anat Gistol Embriol 75(7):24-27.
During two months, effects of general vertical vibration, polychlorcamphen and combination of these two factors were studied in the kidneys of 60 immature male rats of August and Wistar strains. Twenty animals were used as controls (10 per each strain). Under experimental conditions, decrease in body weight, in kidney weight, in their volume, linear dimensions and thickness of the cortical layer were noted. The changes were mostly pronounced under combined

influence of vibration and polychlorcamphen. Interstrain differences demonstrating that renal changes, under experimental conditions, could depend on the genotype were also revealed.

Boyd, E; Taylor, F. (1971) Toxaphene toxicity in protein-deficient rats. Toxicol Appl Pharmacol 18(1):158-167.
Also may be used in Section(s): 4.2

Bozelka, B; Salvaggio, J. (1985) Immunomodulation by environmental contaminants asbestos cadmium and halogenate biphenyls a review. J Environ Sci Health Part C Environ Carcinog Rev 3(1).
Human polychlorinated biphenyl polybrominated biphenyl immunotoxicity immunosuppression metal pollution. Also may be used in Section(s): 4.4

Campbell, M; Gyorkos, J; Leece, B; et al. (1983) The effects of twenty-two organochlorine pesticides as inducers of the hepatic drug-metabolizing enzymes. Gen Pharmacol 14(4):445-454.
The effects of 22 organohalogen pesticides as inducers of hepatic drug-metabolizing enzymes in the immature male Wistar rat have been determined, this group includes four isomeric hexachlorocyclohexanes, technical chlordane, alpha-chlordane, gamma-chlordane, oxychlordane, trans-nonachlor, heptachlor, heptachlor epoxide, aldrin, dieldrin, kepone, toxaphene, mirex, hexachlorobenzene (HCB) and several DDT analogs. With the exception of HCB, all of the pesticides induced microsomal dimethylaminoantipyrine, N-demethylase and aldrin epoxidase activities and the cytochrome P-450 content of microsomes from animals pretreated with most of the compounds was also increased compared to control rats. These pesticides all resembled phenobarbitone in their mode of induction. The effects of HCB as a microsomal enzyme inducer resembled those observed after coadministration of phenobarbitone plus 3-methylcholanthrene.
Also may be used in Section(s): 4.5

Casida, J. (1992) Toxicology of neuroactive insecticides. In Crisp Data Base National Institutes Of Health, California.
3.3

Chandra, J; Durairaj, G. (1993) Effect of toxaphene toxicity on enzyme activity & residue levels in vital organs of guineapig. Indian J Med Res 98193-198.
Guineapigs exposed to acute and subacute levels of toxaphene revealed a marginal reduction in the body weight. There was a significant inhibition of acetylcholinesterase and ATPases in the brain, liver and kidney. The effect of subacute toxicity of toxaphene resulted in an enhancement of cytochrome P450 and induction of aniline hydroxylase in liver and kidney. Biochemical investigations on the backbone revealed that toxaphene toxicity caused an increase in the calcium content and a decrease in the collagen content significantly. Toxaphene was accumulated more in the liver than in the kidney as reflected by residue studies. Also may be used in Section(s): 3.3, 4.2, 4.4, & 4.5

Chandra, J; Durairaj, G. (1992) Toxicity of toxaphene on histopathology of vital organs in guinea pig, cavia porcellus. Journal of Environmental Biology 13(4):315-322.
Adult male guinea pigs administered with acute and subacute doses of toxaphene exhibited an increase in the relative weight of liver. Histological and ultrastructural studies revealed specific

pathogenesis like hypoxic and anoxic changes and disfigurement of myelin in brain, chronic venous congestion and fatty changes in the hepatocytes of liver and degeneration of glomerular cells with increase in the number of mitochondria in the tubular epithelial cells of kidney. Also may be used in Section(s): 4.4

Chandra, J; Durairaj, G. (1995) Toxicity of toxaphene on the lipid profile in the vital organs of guinea pig, cavia procellus. Journal of Environmental Biology 16(1):75-81.
The impact of acute and subacute toxicity of toxaphene on the lipid profile was studied in the vital organs to evaluate certain subtle changes. Brain and liver revealed significant reduction in the phospholipid content with a definite increase in neutral lipid in brain and liver and cholesterol in brain. No appreciable changes were noticed in the lipid components in kidney excepting a significant reduction in the phospholipid content. Regarding phosphoglycerides, brain, liver and kidney revealed an increase in phosphatidyl inositol and phosphatidic acid associated with a marginal decrease in phosphatidyl ethanolamine, phosphatidyl serine and cardiolipin. Sphingomyelin revealed a significant increase in brain with a concomitant insignificant decrease of phosphatidyl choline and vice versa in liver and kidney. Liver accumulated more amount of toxaphene than kidney during subacute treatment. Also may be used in Section(s): 4.2

Cole, L; Casida, J. (1986) Polychlorocycloalkane insecticide-induced convulsions in mice in relation to disruption of the gaba-regulated chloride ionophore. Life Sci 39(20):1855-1862.
The toxicity to mice of intraperitoneally-administered polychlorocycloalkane (PCCA) insecticides is generally correlated with their potency as in vitro inhibitors of the brain specific [35S]t-butylbicyclophosphorothionate [(35S]TBPS) binding site with correction for metabolic activation and detoxification. These findings from our earlier studies are extended here to in vivo investigations relating convulsant action to inhibition of the TBPS binding site in poisoned mice. Radioligand binding assays involved brain P2 membranes washed three times with 1 mM EDTA to remove endogenous gamma-aminobutyric acid (GABA) or other modulator(s) which otherwise serves as a noncompetitive inhibitor of [35S]TBPS binding at the GABA-regulated chloride ionophore. Examination of lindane, technical toxaphene, toxaphene toxicant A, and 10 polychlorocyclodiene insecticides revealed 62 +/- 4% binding site inhibition 30 min after their LD50 doses with 32 +/- 3% inhibition at one-half and 6 +/- 3% inhibition at one-quarter of their LD50 doses. This correlation between binding site inhibition and convulsant action is also evident in dose- and time-dependency studies with endosulfan sulfate. The brain P2 membranes of treated mice contain the parent compound with each of the PCCAs plus activation products of some of the cyclodienes, i.e. endosulfan sulfate from alpha- and beta-endosulfan and 12-ketoendrin from isodrin and endrin. The finding that the brains of treated mice contain sufficient PCCA or its activation products to achieve a magnitude of [35S]TBPS binding site inhibition correlated with the severity of the poisoning signs supports the hypothesis that the acute toxicity of PCCA insecticides to mammals is due to disruption of the GABA-regulated chloride ionophore. Also may be used in Section(s): 4.2, 4.4, & 4.5

Crowder, L; Lanzaro, G; Whitson, R. (1980) Behavioral effects of methyl parathion and toxaphene exposure in rats. J Environ Sci Health B 15(4):365-378.
The behavior of rats exposed peri- and postnatally to methyl parathion (MP) and toxaphene (T) was examined with a variety of maturational and learning tests. Females received daily oral

doses of 1.0 mg/kg MP or 1.0 mg/kg MP + 2.0 mg/kg T between Days 7-15 of pregnancy. With T alone, rats of the postnatal group were dosed daily with 6 mg/kg for 21 days, while in the perinatal study females received 6 mg/kg daily from Day 7 of pregnancy until parturition. Rat pups exposed to sublethal doses of MP and T in combination or alone demonstrated few significant changes in learning ability as measured by a simple two-choice maze, motor skills, or behavior. Also may be used in Section(s): 4.3

Evangelista De Duffard, A; Duffard, R. (1996) Behavioral toxicology, risk assessment, and chlorinated hydrocarbons. Environ Health Perspect 104(Suppl 2):353-360.
Behavioral end points are being used with greater frequency in neurotoxicology to detect and characterize the adverse effects of chemicals on the nervous system. Behavioral measures are particularly important for neurotoxicity risk assessment since many known neurotoxicants do not result in neuropathology. The chlorinated hydrocarbon class consists of a wide variety of chemicals including polychlorinated biphenyls, clioquinol, trichloroethylene, hexachlorophene, organochlorine insecticides (DDT, dicofol, chlordecone, dieldrin, and lindane), and phenoxyherbicides. Each of these chemicals has effects on motor, sensory, or cognitive function that are detectable using functional measures such as behavior. Furthermore, there is evidence that if exposure occurs during critical periods of development, many of the chlorinated hydrocarbons are developmental neurotoxicants. Developmental neurotoxicity is frequently expressed as alterations in motor function or cognitive abilities. Also may be used in Section(s): 4.2

Fattah, K; Crowder, L. (1980) Plasma membrane atpases from various tissues of the cockroach (periplaneta americana) and mouse influenced by toxaphene. Bull Environ Contam Toxicol 24(3):356-363.
The effects of toxaphene (8001352) on the plasma membrane adenosine-triphosphatases (ATPases) of mouse and cockroach were studied. Male Swiss-Webster-mice were given by gavage a median lethal dose of 112mg/kg of toxaphene. In-vitro experiments were performed by treating mouse kidney, brain, and liver tissues with 10(-4) to 10(-7) molar toxaphene in ethanol. Malpighian tubules and central nervous system (CNS) of adult male Periplaneta-americana cockroaches were treated in a similar manner. Magnesium ATPase (MATP) activity was measured in the presence of ouabain in the reaction mixture. In-vivo experiments on kidney ATPases were more sensitive to toxaphene than other ATPases. Sodium potassium ATPase (SPATP) was inhibited significantly only in the kidney, and the MATP was inhibited significantly in all three tissues. Ethanol reduced the activity of all ATPases except the SPATP of the brain in-vitro. MATP was significantly reduced by all concentrations of toxaphene in the kidney and brain tissues. In the liver homogenate, only the highest concentration exhibited a significant reduction in MATP activity. SPATP was significantly reduced by all toxaphene concentrations in the CNS. The highest inhibition of 58.9 percent was observed at 10(-4) molar concentration. MATP of the CNS was reduced by the two higher toxaphene concentrations. In Malpighian tubules, MATP showed stimulation which was significant at the lowest toxaphene concentration. The stimulation due to ethanol alone was 9.6 percent in this tissue. The linear regression indicated that there was a dose response inhibition in all ATPases of the kidney, Malpighian tubules, total and SPATP of the CNS, and SPATP of the liver.

Garcia, M; Mourelle, M. (1984) Gamma-glutamyl transpeptidase: A sensitive marker in ddt and

toxaphene exposure. J Appl Toxicol 4(5):246-248.
Gamma-glutamyl transpeptidase (GGTP) activity in rat liver plasma membrane and blood serum was investigated as an analytical marker for studying acute and sub-chronic exposure to DDT and toxaphene. Twenty-four hours after a single oral dose of DDT (200 mg per kg body weight) or toxaphene (110 mg per kg body weight), GGTP activity increased two-fold in liver plasma membranes, followed by a return to normal values 48 h post-exposure. In addition, serum GGTP activity doubled following acute exposure to DDT or toxaphene, and remained elevated for 48 and 96 h, respectively. Following 2 months continuous exposure to either insecticide, serum GGTP activity levels increased to double that of control values. GGTP activity in liver plasma membranes was elevated 2.5-fold following the initial treatment with toxaphene (16.5 mg per kg body weight per day) and the activity remained high throughout the treatment period (120 days). Prolonged exposure with DDT (30 mg per kg body weight per day) did not produce any change in liver GGTP activity. Based on these results, it appears that GGTP activity could be used as a marker for acute DDT and toxaphene exposure. Also may be used in Section(s): 4.5

Gavat, V; Alexa, L; Filipiuc, M; et al. (1978) Toxicity of pesticides on laboratory animals. Rev Med Chir 82(4):623-627.
Some immunobiological and biochemical effects of Carbetox (malathion; 5 and 50 mg/kg), Dipterex (trichlorfon; 0.5, 5, and 50 mg/kg), and toxaphene (6.2 and 15.5 mg/kg) were studied in rats and rabbits in long-term experiments. The phagocytic index was inhibited significantly by toxaphene (all doses), Dipterex (50 mg/kg) and Carbetox (50 mg/kg). The bactericidal potential of the blood serum was inhibited significantly by Dipterex (50 mg/kg) and Carbetox (50 and 5 mg/kg), and stimulated significantly by Dipterex (5 mg/kg) and toxaphene (15.5 mg/kg). The highest doses of all 3 pesticides inhibited the serum lysozyme activity. The highest doses of Carbetox and Dipterex caused significant inhibition of the erythrocyte cholinesterase activity. The tissue respiration in brain homogenates was stimulated by all doses of all pesticides compared with the controls.

Gertig, H; Nowaczyk, W. (1975) The influence of carathane and toxaphene on the activity of some enzymes in rat's tissues in the studies in vivo. Pol J Pharmacol Pharm 27(4):357-364.
Administration of pesticides to the experimental animals bring changes in the activity of enzymes: 3.1.3.1. alkaline phosphatase (AP), 3.1.3.2. acid phosphatase (AcP), 1.4.1.2. glutamin dehydrogenase (GDH), 1.1.1.27. lactate dehydrogenase (LDH), 2.6.1.1. glutamic oxalacetic transaminase (GOT), and 2.6.1.2. glutamic pyruvic transaminase (GPT), determined in blood serum, liver, and kidneys. In the majority of cases these changes are statistically significant. Also may be used in Section(s): 4.2

Kodavanti, P; Mehrotra, B; Chetty, S; et al. (1988) Effect of selected insecticides on rat brain synaptosomal adenylate cyclase and phosphodiesterase. J Toxicol Environ Health 25(2):207-215.
Previous reports from our laboratory and others clearly indicated that organochlorine insecticides such as chlordecone and DDT are potent inhibitors of ATPases involved in active ion transport. The present studies were initiated to study the effect of plictran, chlordecone, toxaphene, aldrin, dieldrin, endrin, isodrin, and telodrin on enzymes involved in cyclic AMP metabolism. Rat brain synaptosomes were prepared by Ficoll-sucrose gradient centrifugation method. Adenylate cyclase activity, which is involved in anabolism of cAMP, was determined using the radioactive

method by measuring [32P]cAMP formed during hydrolysis of [32P]ATP. Phosphodiesterase activity, which is involved in the catabolism of cAMP, was estimated by measuring [3H]adenosine formed using [3H]cAMP as a substrate. Synaptosomal adenylate cyclase activity was inhibited significantly by plictran with an IC50 of 25 microM, and a maximum inhibition of 30% was observed with 50 microM chlordecone. Toxaphene, aldrin, dieldrin, endrin, isodrin, and telodrin did not affect the adenylate cyclase activity. Similarly, none of the insecticides studied inhibit the activity levels of synaptosomal phosphodiesterase. The significant inhibition of adenylate cyclase observed with plictran might be due to the tin component, since several heavy metals affect cAMP metabolism. The lack of inhibition of adenylate cyclase and phosphodiesterase with other compounds tested clearly supports our postulation that these organochlorine insecticides exert their neurotoxic action by the selective inhibition of ATPases in synaptosomes. Also may be used in Section(s): 4.5

Koller, L; Exon, J; Norbury, K. (1983) Induction of humoral immunity to protein antigen without adjuvant in rats exposed to immunosuppressive chemicals. J Toxicol Environ Health 12(2-3):173-181.
An experimental protocol was designed to assess humoral immune responses in animals antigenically challenged without the aid of adjuvants. The antigen selected was keyhole limpet hemocyanin (KLH). An enzyme-linked immunosorbent assay (ELISA) was utilized as the technique to measure serum antibody levels. The procedure was tested for sensitivity by use of a known immunosuppressant (cyclophosphamide), two metals (lead and selenium), and three chlorinated hydrocarbons (polychlorinated biphenyls, pentachlorophenol, and toxaphene). KLH without adjuvant provoked an adequate humoral immune response when assessed by the ELISA. The antibody response was greater on d 15 than on d 8 following primary KLH challenge, while secondary challenge resulted in an additional 10-fold increase in antibody levels. Cyclophosphamide suppressed the later primary response (d 15) and the secondary response more so than the early primary response (d 8). Of the 5 chemicals tested, 4 resulted in significantly impaired antibody levels to KLH at some time during the response. The magnitude of the immune response elicited to KLH is compared to that reported for bovine serum albumin and ovalbumin administered with Freund's adjuvant.

Kuz'minskaya, U; Ivanitskii, V. (1979) Study of some biological indices of the state of the sympathoadrenaline system under the effect of polychlorocamphene. Environ Health Perspect 3091-95.
The effect of exposure to different amounts of polychlorocamphene (toxaphene) on the level of cathecholamines (noradrenalin and adrenalin), their precursors (DOPA and dophamine), and a metabolite (vanillylmandelic acid) in tissues (adrenals, brain, heart) and daily urine in white male rats has been studied. It was established that the single administration of 120 mg/kg toxaphene (half the LD50) as well as 2.4 mg/kg (1/100 of LD50) for 1 and 3 months produced a disturbance of catecholamine metabolism. The absolute level of ratio of separate components of the sympathicoadrenalic system is unequally changed in tissues, the breakdown of catecholamines is increased, and the specificity of their excretion is destroyed. Also may be used in Section(s): 4.2, 4.4, & 4.5

Kuz'minskaya, UA; Yakushenko, VE; Versan, LV. (1978) The influence of prolonged entry of some pesticides on the activity of the liver's detoxicating system. Gigiena Truda i

Professional'nye Zabolevaniia, No 7(57):19781978.
The effects of prolonged ingestion of pesticides on dimethylase activity were studied in rats. Animals received 3.5 or 0.35 milligrams per kilogram (mg/kg) DDT (50293), 1.6 or 0.16mg/kg gamma-hexachlorcyclohexane (319868) (g-HCCH), 2.4 or 0.24mg/kg polychloroamphen (8001352) (PCC), 2 mg/kg milbex (2274740), 1.32mg/kg phosalon (2310170), or 6.0 or 0.6mg/kg tetramethiuramdisulfide (137268) (TMTD). Doses were given daily by stomach tube for 1, 3 or 6 months. Amidopirin was used as the substrate in determining dimethylase activity. Prolonged ingestion of DDT, g-HCCH, PCC and milbex induced microsomal dimethylase. The higher phosalon dose also enhanced activity after 3 and 6 months, while TMTD decreased the activity after 6 months of treatment. The authors conclude that the differential actions of various pesticides on mixed function microsomal oxidases should be considered when treating patients who have been exposed to pesticides. (Russian).

Mariussen, E; Fonnum, F. (2006) Neurochemical targets and behavioral effects of organohalogen compounds: An update. Critical reviews in Toxicology 36(3):253-289.
Organohalogen compounds (OHCs) have been used and still are used extensively as pesticides, flame retardants, hydraulic fluids, and in other industrial applications. These compounds are stable, most often lipophilic, and may therefore easily biomagnify. Today these compounds are found distributed both in human tissue, including breast milk, and in wildlife animals. In the late 1960s and early 1970s, high levels of the polychlorinated biphenyls (PCBs) and the pesticide dichlorodiphenyl trichloroethane (DDT) were detected in the environment. In the 1970s it was discovered that PCBs and some chlorinated pesticides, such as lindane, have neurotoxic potentials after both acute and chronic exposure. Although the use of PCBs, DDT, and other halogenated pesticides has been reduced, and environmental levels of these compounds are slowly diminishing, other halogenated compounds with potential of toxic effects are being found in the environment. These include the brominated flame retardants, chlorinated paraffins (PCAs), and perfluorinated compounds, whose levels are increasing. It is now established that several OHCs have neurobehavioral effects, indicating adverse effects on the central nervous system (CNS). For instance, several reports have shown that OHCs alter neurotransmitter functions in CNS and Ca2+ homeostatic processes, induce protein kinase C (PKC) and phospholipase A2 (PLA2) mobilization, and induce oxidative stress. In this review we summarize the findings of the neurobehavioral and neurochemical effects of some of the major OHCs with our main focus on the PCBs. Further, we try to elucidate, on the basis of available literature, the possible implications of these findings on human health. Also may be used in Section(s): 4.3

Matsumara, F; Tanaka, K. (1984) Molecular basis of neuroexcitatory actions of cyclodiene-type insecticides. In: (Narahashi, T, ed. Cellular and molecular neurotoxicology. New York, NY: Raven Press; pp. 225-240.

Miyagi, T; Lam, K; Chuang, L; et al. (1998) Suppression of chemokine-induced chemotaxis of monkey neutrophils and monocytes by chlorinated hydrocarbon insecticides. In Vivo 12(5):441-446.
Chemokines, characterized as pro-inflammatory chemicals made by the immune system, consist of a family of low molecular weight proteins with potent in vitro chemotactic activity causing leukocyte accumulation in vivo. This study determines the effects of organochlorine pesticide exposure on the chemotactic functions of monkey neutrophils and monocytes, using a 48-well

chemotaxis chamber. Chemokines IL-8 (interleukin-8) and RANTES were used as the chemoattractants to induce chemotaxis among these monkey leukocytes. Monkey neutrophils or monocytes were first treated with heptachlor, chlordane or toxaphene for 1 hour at 37 degrees C, and the number of cells migrating toward 200 ng/ml IL-8 (for neutrophils) or 100 ng/ml RANTES (for monocytes) were scored. Inhibition of chemotaxis was seen with all samples after treatment with heptachlor, chlordane and toxaphene at concentrations from as low as 10(-14) M to 10(-5) M. Among the three compounds studied, toxaphene was the least effective in preventing monocytes from migrating toward RANTES. The ability of these pesticides to inhibit chemotaxis did not correlate directly with their potential apoptotic effects on the monkey leukocytes. These studies suggest that exposure to organochlorine pesticides may alter leukocyte-related immune functions.

Moser, G; Smart, R. (1989) Hepatic tumor-promoting chlorinated hydrocarbons stimulate protein kinase c activity. Carcinogenesis 10(5):851-886.
Various chlorinated hydrocarbons, many of which are known hepatic tumor promoters, have been evaluated for their ability to stimulate protein kinase C (PKC) activity in vitro. Chlordane, kepone, toxaphene, heptachlor, 2,2-bis(4-chlorophenyl)-1,1-dichloroethane, the polychlorinated biphenyl Aroclor 1254, aldrin, 2,2-bis(4-chlorophenyl)-1,1,1-trichloroethane (DDT) and gamma-hexachlorocyclohexane (lindane) were the most potent stimulators of PKC activity. Of these compounds, chlordane was the most potent organochlorine pesticide. Chlordane (100 microM) stimulated mouse brain PKC activity in the 10(5) g supernatant to a maximum velocity equal to that obtained when the enzyme was maximally stimulated with the skin-tumor-promoting phorbol ester, 12-O-tetradecanoylphorbol-13-acetate (TPA). Chlordane concentrations as low as 1 microM significantly stimulated PKC activity. Chlordane-stimulated PKC activity was calcium-dependent, and in the presence of exogenous calcium, chlordane-stimulated PKC activity was at least 5-fold greater than in the absence of added calcium. In contrast, the addition of calcium only minimally affected (less than 30% increase) the TPA-stimulated PKC activity. Concentrations of TPA and chlordane which maximally stimulate PKC did not produce an additive effect on PKC activity. Chlordane- and TPA- stimulated PKC activity was phospholipid-dependent and could be inhibited by quercetin, a known inhibitor of PKC activity. Chlordane in the presence of calcium also stimulated mouse epidermal and hepatic PKC as well as purified rat brain PKC. These results demonstrate that a wide variety of chlorinated hydrocarbons, which are considered hepatic tumor promoters, stimulate protein kinase C activity in vitro. Also may be used in Section(s): 4.5

Mourelle, M; Garcia, M; Aguilar, C. (1985) Atpase activities in liver plasma membranes of rats treated with ddt and toxaphene. J Appl Toxicol 5(1):39-41.
The effect of exposure to chlorinated insecticides (DDT and toxaphene) on Na+,K+-ATPase, Mg2+-ATPase and Ca2+-ATPase activities of the plasma membrane of hepatocytes was determined. Acute treatment with DDT (200 mg/kg body wt) or toxaphene (110 mg/kg body wt) produced a significant decrease in Na+,K+-ATPase activity (80 and 85%, respectively) 24 h after treatment. DDT also produced a 30% decrease in Mg2+-ATPase and Ca2+-ATPase activity, but toxaphene treatment did not modify these enzymes. The effect of exposure to daily doses of DDT (30 mg/kg body wt) or toxaphene (16.5 mg/kg body wt) for 3.5 mo. was also studied. Animals were sacrificed at 15 day intervals. Na+,K+-ATPase activity decreased 80% from the beginning of each treatment and the activity remained low throughout the treatment period.

DDT, but not toxaphene, also led to a decrease in Mg2+-ATPase (20%) and Ca2+-ATPase (35%) activity. The low values observed from the beginning remained low througout the treatment period. The general mechanism of ATPase inhibition by organochloride compounds could have been the result of its interaction with membrane lipid components, although some differences could have arisen from differences in their spatial structure. Also may be used in Section(s): 4.2 & 4.5

Palmer, C; Casida, J. (1988) Two types of cage convulsant action at the gaba-gated chloride channel. Toxicol Lett 42(2):117-122.
Mouse brain membrane tert butylbicyclophosphorothionate toxicity gamma aminobutyric acid insecticide mh - animals.

Parvu, M; Sendrea, D; Colosi, D. (1980) The estimation of the toxic action of organo chlorine insecticide toxaphene by using some biochemical indicators. Toxicol Lett 2nd International Congress on Toxicology (SPEC. ISSUE 1):39.

Peakall, D. (1979) Effect of toxaphene on pyruvic and lactic acid levels in the rat. Environ Health Perspect 30:97-98.
Rats were given a single dose of toxaphene (120 mg/kg equilavent to 1/2 LD50) and sacrificed at 1, 5, and 15 days. No alterations of levels of pyruvic or lactic acid in blood plasma were observed. In a second experiment, rats were given 2.4 mg/kg daily and sacrificed at 1, 3, and 6 months, and again no alterations of pyruvic or lactic acid levels were found. It is concluded that observed alterations of the activity of lactic acid dehydrogenase induced by toxaphene do not give rise to physiological changes in unstressed rats. Also may be used in Section(s): 4.4

Peakall, DB. (1976) Effects of toxaphene on hepatic enzyme induction and circulating steroid levels in the rat. Environ Health Perspect 13:117-120.
Rats were given a single dose of toxaphene (120 mg/kg, equivalent to 1/2 LD50) and sacrificed at 1, 5, and 15 days. Liver weight and hepatic microsomal enzyme activity were increased at day 5 and 15. The level of plasma testosterone was significantly decreased at day 15. In a second experiment rats were given 2.4 mg/kg daily and sacrificed at 1, 3 and 6 months. Liver weight and microsomal enzyme activity were significantly increased over controls; enzyme activity was, however, decreasing by the end of the experiment. Plasma testosterone levels were not affected. It is concluded that enhanced hepatic enzyme induction causes only a transient drop in circulating testosterone levels followed by a return to normal values.

Rauh, J; Benner, E; Schnee, M; et al. (1997) Effects of [3h]-bidn, a novel bicyclic dinitrile radioligand for gaba-gated chloride channels of insects and vertebrates. Br J Pharmacol 121(7):1496-1505.
1. The radiolabelled bicyclic dinitrile, [3H]-3,3-bis-trifluoromethyl-bicyclo[2.2.1]heptane-2,2-dicarbonitrile ([3H]-BIDN), exhibited, specific binding of high affinity to membranes of the southern corn rootworm (Diabrotica undecimpunctata howardi) and other insects. A variety of gamma-aminobutyric acid (GABA) receptor convulsants, including the insecticides heptachlor (IC50, 35 +/- 3 nM) and dieldrin (IC50, 93 +/- 7 nM), displaced [3H]-BIDN from rootworm membranes. When tested at 100 microM, 1-(4-ethynylphenyl)-4-n-propyl-2,6,7-trioxabicyclo[2.2.2]oct ane(EBOB), 4-t-butyl-2,6,7-trioxa-1-phosphabicy-clo[2.2.2]octane-1-thio

ne (TBPS), 1-phenyl-4-t-butyl-2,6,7-trioxabicyclo[2.2.2]octane (TBOB) and picrotoxin failed to displace 50% of [3H]-BIDN binding to rootworm membranes indicating that the bicyclic dinitrile radioligand probes a site distinct from those identified by other convulsant radioligands. 2. Dissociation studies showed that dieldrin, ketoendrin, toxaphene, heptachlor epoxide and alpha and beta endosulphan displace bound [3H]-BIDN from rootworm membranes by a competitive mechanism. 3. Rat brain membranes were also shown to possess a population of saturable, specific [3H]-BIDN binding sites, though of lower affinity than in rootworm and with a different pharmacological profile. Of the insecticidal GABAergic convulsants that displaced [3H]-BIDN from rootworm, cockroach (Periplaneta americana) and rat brain membranes, many were more effective in rootworm. 4. Functional GABA-gated chloride channels of rootworm nervous system and of cockroach nerve and muscle were blocked by BIDN, whereas cockroach neuronal GABA(B) receptors were unaffected. 5. Expression in Xenopus oocytes of either rat brain mRNA, or cDNA-derived RNA encoding a GABA receptor subunit (Rdl) that is expressed widely in the nervous system of Drosophila melanogaster resulted in functional, homo-oligomeric GABA receptors that were blocked by BIDN. Thus, BIDN probes a novel site on GABA-gated Cl- channels to which a number of insecticidally-active molecules bind.

Squires, R; Saederup, E. (1989) Polychlorinated convulsant insecticides potentiate the protective effect of nacl against heat inactivation of [3h]flunitrazepam binding sites. J Neurochem 52(2):537-543.
Six polychlorinated convulsant insecticides that potently inhibit t-[35S]butylbicyclophosphorothionate ([35S]TBPS) binding to rat brain membranes also potentiate the protective effect of NaCl (200 mM) against heat inactivation of [3H]flunitrazepam binding sites on the same membranes. Similar effects were obtained with all "cage" convulsants tested. The rank order of potencies as heat protection potentiators was similar to the rank order of potencies as inhibitors of [35S]TBPS binding (alpha-endosulfan greater than endrin greater than dieldrin greater than toxaphene greater than lindane). alpha-Endosulfan and endrin are more potent in both respects than any previously reported picrotoxin-like (cage) convulsant, but are much less toxic to mammals. The greatly reduced toxicities of alpha-endosulfan and endrin in mammals may reflect partial gamma-aminobutyric acid (GABA)-neutral properties of these compounds. Time courses of heat inactivation of [3H]flunitrazepam binding sites in the presence of 200 mM NaCl plus saturating concentrations of endrin or picrotoxin revealed monophasic components constituting about 88% of the binding sites, suggesting that virtually all [3H]flunitrazepam binding sites are coupled to picrotoxin binding sites in the GABA/benzodiazepine/picrotoxin receptor complex. Protection against heat inactivation constitutes a useful tool for characterizing the various allosterically linked binding sites in neurotransmitter receptor complexes.

Steinberg, M; Kinoshita, F; Ballantyne, M. (1998) Mutagenicity studies with toxaphene congeners: Organohalogen. Compounds 35243-246.
Also may be used in Section(s): 4.5

Stelzer, A; Chan, H. (1999) The relative estrogenic activity of technical toxaphene mixture and two individual congeners. Toxicology 138(2):69-80.
Toxaphene is the most abundant persistent organic pollutant in the Arctic and in the Great Lakes. Toxaphene technical mixture (Tox) applied as a pesticide consists of over 800 congeners.

Through processes of environmental degradation, selected metabolism, and bioaccumulation, two congeners are prominent in humans; 2-exo,3-endo,5-exo,6-endo,8,8,10,10-octachlorobornane (T2 or Parlar 26) and 2-exo,3-endo,5-exo,6-endo,8,8,9,10, 10-nonachlorocamphene (T12 or Parlar 50). The MCF7-E3 human breast cancer cell model was used to screen for the estrogenic activities of Tox, T2, and T12. A concentration of 10 microM was required by all three compounds to elicit an estrogenic response as indicated by a proliferative effect (PE) upon the cells. The congeners, however, showed significantly different PEs from Tox. Both T2 and T12 had a lower PE (16 and 30%) and than Tox, and T2 had a higher PE than T12 (19%). Results from binary combination studies showed that the effects of Tox, T2, and T12 were additive. Tox, T2, and T12 had no significant effects on estrogen receptor and progesterone receptor levels. Our results suggest that the two environmental prevalent congeners had lower estrogenic activities than Tox and there is no synergistic effect. Also may be used in Section(s): 4.5

Thunberg, T; Ahlborg, U; Wahlstrom, B. (1984) Comparison between the effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin and six other compounds on the vitamin a storage, the udp-glucuronosyltransferase and the aryl hydrocarbon hydroxylase activity in the rat liver. Arch Toxicol 55(1):16-19.
The effect of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), 2,3,7,8- tetrabromodibenzo -p-dioxin (TBrDD), 5-chloro-2-(2,4-dichlorophenoxy)phenol (3-Cl- predioxin) 4,5,6-trichloro-2-(2,4-dichlorophenoxy)phenol (5-Cl- predioxin), toxaphene, 3-methylcholanthrene (3-MC) and phenobarbital (PB) on the vitamin A storage, UDP-glucuronosyltransferase (UDPGT) and aryl hydrocarbon hydroxylase (AHH) activities in the liver of Sprague-Dawley rats was investigated. Vitamin A was determined as retinol by high pressure liquid chromatography. UDPGT was measured with p-nitrophenol as an aglycone and AHH with 3,4-benzopyrene as a substrate. Both in TCDD- and toxaphene-treated animals a reduced body weight gain was recorded, but no other overt signs of toxicity were seen in this study. Both the concentration and the total amount of hepatic retinol was significantly reduced in TCDD-, 3-MC-, PB- and TBrDD -treated animals. These compounds were also those which gave the most significant enzyme induction as regards the UDPGT and AHH activities. However, the reduction of hepatic retinol caused by these compounds did not correlate with the enzyme activities studied. When compared on a molecular basis, TCDD and TBrDD were in the order of several magnitudes more potent as reducers of hepatic retinol and likewise as enzyme inducers. Also may be used in Section(s): 4.5

Trottman, C; Desaiah, D. (1980) Induction of rat hepatic microsomal enzymes by toxaphene pretreatment. J Environ Sci Health B 15(1):121-134.
The effects of pretreatment of rats with toxaphene on hepatic drug metabolizing enzymes and several other parameters of the mixed function oxidase system were investigated. Adult male Sprague-Dawley rats were fed diets containing 0, 50, 100, 150 and 200 ppm of toxaphene for 14 days. The body weight gain was unaltered as well as the food consumption in all the toxaphene fed groups. There was no change in the weights of brain, kidney, heart, and testes but the liver weight was significantly increased. The thymus weight in all the toxaphene fed grups was decreased. Hydroxylation of pentobarbital and aniline was significantly enhanced in rats exposed to toxaphene. Ethylmorphine-N-demethylase activity in the toxaphene treated rats was also elevated. Enhanced hydroxylation of pentobarbital was also evident from the decreased sleeping time following pentobarbital administration. Exposure to toxaphene increased cytochrome P-

450, NADPH-cytochrome c-reductase and dehydrogenase in hepatic microsomal fractions. The binding of aniline and hexobarbital to microsomes was also enhanced, suggesting that the intermediate steps in the electron-transfer system were increased. In conclusion, pretreatment of rats with toxaphene for fourteen days resulted in the induction of the hepatic mixed function oxidase system. Also may be used in Section(s): 3.3, 4.2, & 4.5

Tryphonas, H; Bryce, F; Huang, J; et al. (2000) Effects of toxaphene on the immune system of cynomolgus (macaca fascicularis) monkeys. A pilot study. Food Chem Toxicol 38(1):25-33. Toxaphene in glycerol/corn oil was administered at 1mg/kg body weight/day, 7 days/week in gelatin capsules to four healthy young adult cynomolgus (Macaca fascicularis) (two male and two female) monkeys for 52 weeks. Control monkeys ingested glycerol/corn oil only. Testing for immune effects was initiated at 34 weeks of treatment. Results included: reduced anti-sheep red blood cell (SRBC) titres for immunoglobulins (Ig) M and G; increased IgG titres to pneumococcal antigens, but not to the tetanus toxoid antigen; reduced T-helper/inducer mean lymphocyte numbers and the mean T-helper/inducer:T-suppressor/cytotoxic cell ratio and reduced respiratory burst activity in peripheral blood monocytes and granulocytes, albeit no changes on the phagocytic activity of these cells were detected. The above noted effects although not statistically significant (P0.05) suggest that chronic exposure to low levels of toxaphene may be immunosuppressive in cynomolgus monkeys and may pose a hazard to human health. To advance our understanding of the degree of hazard that toxaphene may pose to human health, we have undertaken additional chronic studies with a larger number of animals. Particular attention is focused on determining the potential immunotoxic effects of toxaphene in offspring following in utero exposure.

Tryphonas, H; Arnold, D; Bryce, F; et al. (2001) Effects of toxaphene on the immune system of cynomolgus (macaca fascicularis) monkeys. Food Chem Toxicol 39(9):947-958. Toxaphene, dissolved in glycerol/corn oil, was administered at 0.1, 0.4 or 0.8 mg/kg body weight/day in gelatin capsules to groups of 10 young adult female cynomolgus monkeys (Macaca fascicularis), while a group of five male monkeys (Macaca fascicularis) received 0.8 mg/kg body weight/day. Control male (a group of five) and female (a group of 10) monkeys ingested the glycerol/corn oil vehicle only. Treatment continued for 75 weeks. Testing for immune effects was initiated at 33 weeks of treatment. Immunization was initiated at 44 weeks of treatment. Pairwise comparisons between each of the treated female groups to the control indicated that the mean primary (post-immunization weeks 1-4) and secondary (post-immunization weeks 5-8) anti-SRBC IgM responses were significantly reduced at the 0.4 and 0.8 mg/kg body weight/day doses compared to the control (P< or =0.05). The mean primary (post-immunization weeks 1-4) anti-SRBC IgG response was significantly reduced compared to the control (P< or =0.05), while the secondary (post-immunization weeks 5-8) anti-SRBC IgG was not significantly affected by treatment (P>0.05). The mean anti-tetanus toxoid IgG response in the 0.8 mg/kg body weight/day dose group The mean primary anti-SRBC (IgM) response in the treated males was significantly different from the control (P<0.05), while the primary anti-SRBC IgG response was not affected by treatment. The mean absolute B-lymphocyte numbers in the female group administered 0.8 mg/kg of toxaphene was significantly reduced compared to the control (P< or =0.05). All other parameters including the natural killer cell activity, the delayed-type hypersensitivity response, the lymphoproliferative response of peripheral blood leukocytes to the mitogens Con A and PWM and the serum cortisol levels were not affected significantly by

treatment (P>0.05). The no-observed-adverse-effect level (NOAEL) for the female monkeys based on the toxaphene effects on humoral immunity was 0.1 mg/kg body weight/day.

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

Arcaro, K; Yang, Y; Vakharia, D; et al. (2000) Toxaphene is antiestrogenic in a human breast-cancer cell assay. J Toxicol Environ Health A 59(3):197-210.
Toxaphene is a complex mixture of chlorinated bornanes, bornenes, and bornadienes and was a heavily used insecticide in the United States until its use was restricted in 1982. There are conflicting reports regarding the potential for toxaphene to induce estrogenic responses in human and nonhuman animals. Due to the public concern over environmental estrogens, the estrogenicity of toxaphene was examined in a human breast-cancer cell assay, the MCF-7 focus assay, which is based on in vitro postconfluent cell proliferation and tissue restructuring. In this assay, 0.1-1 nM 17beta-estradiol (E2) produces maximum postconfluent proliferation and formation of multicellular nodules or foci. Toxaphene was also tested for its ability (1) to bind the estrogen receptor (ER) in a competitive binding assay using recombinant human ERalpha (rhER) and in a whole-cell competitive ER binding assay, and (2) to alter the catabolism of E2 in MCF-7 cell cultures. Results from the MCF-7 focus assay showed: (1) Toxaphene alone was not estrogenic between the concentrations of 0.5 nM and 10 microM, (2) toxaphene in binary combinations with chlordane, dieldrin, or endosulfan (alpha or beta) was not estrogenic, and (3) toxaphene was weakly antiestrogenic (it reduced the number of foci induced by 0.1 nM and 0.01 nM E2). Results from the competitive binding assays showed that (1) toxaphene alone did not bind rhER or ER in MCF-7 cells, and (2) toxaphene in binary combinations with other pesticides did not bind rhER. Results from the growth assay and radiometric analysis of E2 catabolism showed that (1) toxaphene did not alter the growth rate of MCF-7 cell cultures over 13 d, and (2) toxaphene did not alter the catabolism of E2. In conclusion, results from the MCF-7 focus assay demonstrate that toxaphene is weakly antiestrogenic rather than estrogenic.

Ariazi, E; Jordan, V. (2006) Estrogen-related receptors as emerging targets in cancer and metabolic disorders. Curr Top Med Chem 6(3):203-215.
While estrogen receptor (ER)-targeted therapeutics have clearly been a success in the treatment of breast cancer, the orphan estrogen-related receptors (ERRs) represent novel targets for future development. The ERRs, comprising ERRalpha, ERRbeta and ERRgamma, bind and regulate transcription via estrogen response elements (EREs) and extended ERE half-sites termed ERR response elements (ERREs), but do not bind endogenous estrogens. The emerging role of ERRalpha and ERRgamma in modulating estrogen responsiveness, substituting for ER activities, and serving as prognosticators in breast and other cancers is providing an impetus for the identification of compounds which target these proteins. Moreover, ERRalpha plays a role in energy homeostasis and will likely be targeted for the treatment of metabolic disorders. Multiple classes of synthetic ligands have already been identified. The phytoestrogens genistein, daidzein, biochanin A and 6,3'4'-tryhydroxyflavone have been reported as ERRalpha agonists. The phenolic acyl hydrazones GSK4716 and GSK9089 act as selective agonists of ERRbeta and ERRgamma. The organochlorine pesticides toxaphene and chlordane, and the synthetic compound XCT790 antagonize ERRalpha. The synthetic estrogen diethylstilbestrol antagonizes

all three ERRs. The selective estrogen receptor modulators 4-hydroxytamoxifen and 4-hydroxytoremifene antagonize ERRgamma. The rational development of synthetic ligands for the ERRs may soon provide new agents to supplement the repertoire of antihormonal therapies to combat breast cancer. Moreover, expression of ERRs in other cancers and metabolic disorders may provide a targeted treatment strategy for these patients as well.

Arnold, S; Klotz, D; Collins, B; et al. (1996) Synergistic activation of estrogen receptor with combinations of environmental chemicals. Science 272(5267):1489-1492.
Certain chemicals in the environment are estrogenic. The low potencies of these compounds, when studied singly, suggest that they may have little effect on biological systems. The estrogenic potencies of combinations of such chemicals were screened in a simple yeast estrogen system (YES) containing human estrogen receptor (hER). Combinations of two weak environmental estrogens, such as dieldrin, endosulfan, or toxaphene, were 1000 times as potent in hER-mediated transactivation as any chemical alone. Hydroxylated polychlorinated biphenyls shown previously to synergistically alter sexual development in turtles also synergized in the YES. The synergistic interaction of chemical mixtures with the estrogen receptor may have profound environmental implications. These results may represent a previously uncharacterized level of regulation of estrogen-associated responses.

Arnold, S; Vonier, P; Collins, B; et al. (1997) In vitro synergistic interaction of alligator and human estrogen receptors with combinations of environmental chemicals. Environ Health Perspect 105 (Suppl 3):615-618.
The effect of mixtures of environmental chemicals with hormonal activity has not been well studied. To investigate this phenomenon, the estrogen receptor (ER) from the American alligator (aER) or human (hER) was incubated with [3H]17beta-estradiol in the presence of selected environmental chemicals individually or in combination. The environmental chemicals included the insecticide chlordane, which has no estrogenic activity, and the pesticides dieldrin and toxaphene, which have very weak estrogenic activity. Chlordane, dieldrin, and toxaphene individually demonstrated no appreciable displacement of [3H]17beta-estradiol from aER and hER at the concentration tested. A combination of these chemicals inhibited the binding of [3H]17beta-estradiol by 20 to 40%. Alachlor, a chemical recently discovered to have weak estrogenic activity, also displaced [3H]17beta-estradiol more effectively in combination with dieldrin than alone. These results indicate that combinations of some environmental chemicals inhibit [3H]17beta-estradiol binding in a synergistic manner. This suggests that the ER may contain more than one site for binding environmental chemicals. The possibility that the ER binds multiple environmental chemicals adds another level of complexity to the interaction between the environment and the endocrine system. Also may be used in Section(s): 4.2

Ashby, J; Tennant, R. (1988) Chemical structure, salmonella mutagenicity and extent of carcinogenicity as indicators of genotoxic carcinogenesis among 222 chemicals tested in rodents by the u.S. Nci/ntp. Mutat Res 204(1):17-115.
A survey has been conducted of 222 chemicals evaluated for carcinogenicity in mice and rats by the United States NCI/NTP. The structure of each chemical has been assessed for potential electrophilic (DNA-reactive) sites, its mutagenicity to Salmonella recorded, and the level of its carcinogenicity to rodents tabulated. Correlations among these 3 parameters were then sought. A strong association exists among chemical structure (S/A), mutagenicity to Salmonella (Salm.)

and the extent and sites of rodent tumorigenicity among the 222 compounds. Thus, a 90% correlation exists between S/A and Salm. across the 115 carcinogens, the 24 equivocal carcinogens and the 83 non-carcinogens. This indicates the Salmonella assay to be a sensitive method of detecting intrinsic genotoxicity in a chemical. Concordance between S/A and Salm. have therefore been employed as an index of genotoxicity, and use of this index reveals two groups of carcinogens within the database, genotoxic and putatively non-genotoxic. These two broad groups are characterized by different overall carcinogenicity profiles. Thus, 16 tissues were subject to carcinogenesis only by genotoxins, chief among which were the stomach, Zymbal's glands, lung, subcutaneous tissue and circulatory system. Conclusions of carcinogenicity in these 16 tissues comprised 31% of the individual chemical/tissue reports of carcinogenicity. In contrast, both genotoxins and non-genotoxins were active in the remaining 13 tissues, chief among which was the mouse liver which accounted for 24% of all chemical/tissue reports of carcinogenicity. Further, the group of 70 carcinogens reported to be active in both species and/or in 2 or more tissues contained a higher proportion of Salmonella mutagens (70%) than observed for the group of 45 single-species/single-tissue carcinogens (39%). 30% of the 83 non-carcinogens were mutagenic to Salmonella. This confirms earlier observations that a significant proportion of in vitro genotoxins are non-carcinogenic, probably due to their non-absorption or preferential detoxification in vivo. Also, only 30% of the mouse liver-specific carcinogens were mutagenic to Salmonella. This is consistent with tumors being induced in this tissue (and to a lesser extent in other tissues of the mouse and rat) by mechanisms not dependent upon direct interaction of the test chemical with DNA. Detection of 103 of the 115 carcinogens could be achieved by use of only male rats and female mice. 11 of the 12 carcinogens that would be missed using this binary carcinogenicity bioassay protocol were carcinogenic in only a single tissue of a single sex of a single species, 4 being specific to the mouse liver. In contrast, use of only rats would fail to detect 34 mouse-specific carcinogens, 17 of which were active at sites other than the liver, 7 at multiple sites. It is concluded that screening chemicals for genotoxicity using structural analysis and a minimum number of genotoxicity assays, and use of a reduced cancer bioassay protocol, would enable the detection of trans-species/multiple-site rodent carcinogens. The detection of tissue/sex/species-specific carcinogens can only be achieved by conducting life-time carcinogenicity bioassays according to the present NTP protocol. The transition over the past decade from selecting candidate chemicals for bioassay based on consideration of chemical structure, to selection based on relative environmental importance, is sufficient to explain the apparent decreasing sensitivity of the Salmonella assay to rodent carcinogens. .

Bartos, T; Skarek, M; Cupr, P; et al. (2005) Genotoxic activity of a technical toxaphene mixture and its photodegradation products in sos genotoxicity tests. Mutat Res 565(2):113-120. Toxaphene (CAS No. 800-35-2) is a complex mixture of several hundred components that was used worldwide primarily as an agricultural pesticide with insecticide effects in the second half of the 20th century. In vitro investigations of the genotoxicity and mutagenicity of toxaphene were generally described in the literature, but they provided somewhat equivocal results. We re-evaluated the genotoxicity of technical toxaphene in two prokaryotic systems. The SOS Chromotest showed high sensitivity to toxaphene: three concentrations (40, 20 and 10 mg/l) were clearly positive and the dose-response effect was evident. In the umuC assay, a dose-dependent increase in genotoxic activity was observed at toxaphene concentrations from 2.5 to 40.0 mg/l, but these results were found to be not significant. The genotoxicity of toxaphene and its

photodegradation products after UV-irradiation (3-6-9 h) at concentrations ranging from 7.5 to 60.0 mg/l was also examined in this study. An irradiated solution of technical toxaphene after 3 h showed no significant evidence of bacterial growth inhibition. However, exposure of Salmonella to 6 h UV-irradiated toxaphene showed a toxic effect compared with the negative control. After 9 h irradiation, a decrease of bacterial growth was observed. Activity of beta-galactosidase in the presence of a toxaphene solution was significantly increased after 6 and 9 h irradiation, reaching values that were 2.4- and 3.1-fold higher, respectively, than the control, which exceeded the criteria of significant genotoxicity. These results show that while technical toxaphene is a weak, direct-acting mutagen in some bacterial tests, a dose-dependent toxicity and genotoxicity of its photoproducts could be conclusively demonstrated by the umuC test.

Battershill, J; Fielder, R. (1998) Mouse-specific carcinogens: An assessment of hazard and significance for validation of short-term carcinogenicity bioassays in transgenic mice. Hum Exp Toxicol 17(4):193-205.
1. The International Conference on the Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for human use (ICH) has agreed that bioassay data from only one species, the rat, supported by appropriate mutagenicity and pharmacokinetic data and also information from new (unvalidated) short term in vivo screening tests for potential carcinogenicity, could be used for the licensing of human medicines. This proposal has been supported by reviews of the utility of testing pharmaceuticals in the mouse which have concluded that the mouse bioassay contributes little to regulatory decisions. The current review was undertaken to identify 'genuine' mouse-specific carcinogens using the Gold Carcinogenicity Potency Database (CPD) for the initial identification of potential mouse-specific carcinogens from published literature. Hazard assessments were completed for these chemicals with particular attention focused on the 'genuine' mouse-specific carcinogens. The significance of such chemicals has been discussed together with consideration of on-going work on the validation of short-term carcinogenicity bioassays using transgenic mice. 2. Seventy-six potential mouse specific carcinogens were identified through the Gold Carcinogenicity Potency Database. Following more detailed consideration a total of ten chemicals were excluded from further consideration (three were multispecies carcinogens, five were considered to be non-carcinogenic in the mouse, and the data for two were uninterpretable). The review focused on the remaining 66 chemicals. There was equivocal evidence of carcinogenicity to the rat for 28 chemicals and inadequate data for a further 23 chemicals. Fifteen 'genuine' mouse-specific carcinogens were identified. These 15 chemicals comprise two genotoxic mouse-specific carcinogens (N-methylolacrylamide (924-42-5), 2,6-Dichloro-p-phenylenediamine (609-20-1); five non-genotoxic mouse-specific carcinogens 2-Aminobiphenyl.HCl (2185-92-4), Captan (133-06-2), Dieldrin (60-57-7), Diethylhexyladipate (103-23-1), and Probenicid (57-66-9); five mouse-specific carcinogens with equivocal evidence of mutagenicity were identified; (2,4-diaminophenol.2HCl (137-09-7), Dipyrone (68-89-3), Ozone (10028-15-6), Vinylidene chloride (75-35-4), and Zearalenone (17924-92-4)), and three mouse-specific carcinogens with inadequate mutagenicity data (Benzaldehyde (100-52-7), Piperonyl sulphoxide (120-62-7), Ripazepam (26308-28-1)). 3. It is suggested that the two genotoxic mouse carcinogens would have been considered as potential carcinogens in the absence of a mouse bioassay. Of the five non-genotoxic mouse-specific carcinogens; three induced tumours in mouse liver only and are considered as being of low potential hazard to human health. The remaining two chemicals would have been missed in the absence of a mouse bioassay (2-aminobiphenyl (2185-92-4) and

captan (133-06-2)) and thus are good candidates for evaluation in the short term bioassays in transgenic mice currently being validated. 4. The hardest group of mouse-specific carcinogens to evaluate are those for which there is equivocal or inadequate mutagenicity data. The difficulty in evaluating these particular chemicals emphasises the need for adequate mutagenicity data in addition to adequate carcinogenicity data in order to assess potential hazards to human health. Hazard assessments and a consideration of the potential role for short-term bioassays in transgenic mice for the eight chemicals in this subgroup are presented. 5. A number of general conclusions have been derived from this review. Firstly, there are insufficient published genotoxicity data to allow a full assessment fo mutagenic potential for 57/76 of the potential mouse-specific carcinogens identified from the CPD. This is surprising given the clear value of such data in interpreting bioassay results and the much greater resources required for carcinogenicity bioassays. Second, the newly proposed short-term tests in transgenic mice must be able to identify genotoxic carcinogens and this must include the very few mouse-specific genotoxic carcinogens. Third, there are relatively few non-genotoxic `genuine' mouse-specific carcinogens identifiable from the CPD, which may pose a significant human health hazard. 6 It is suggested that regulatory and industry data files for chemicals other than pharmaceuticals could be reviewed in order to ascertain the full significance of mouse only carcinogens.

Bayoumi, A; Perez-Pertejo, Y; Ordonez, C; et al. (2000) Changes in the glutathione-redox balance induced by the pesticides heptachlor, chlordane, and toxaphene in cho-k1 cells. Bull Environ Contam Toxicol 65(6):748-755.

Besselink, H; Nixon, E; McHugh, B; et al. (2000) In vitro and in vivo tumor promoting potency of technical toxaphene, uv-irradiated toxaphene, and biotransformed toxaphene. Organohalogen Compounds 47113-116.
Also may be used in Section(s): 4.2

Bogen, K. (1994) Applicability of alternative models of revertant variance to ames-test data for 121 mutagenic carcinogens. Mutat Res 322(4):265-273.
Models of sampling variance in replicate revertant scores play a role in analyses of Ames-test data on mutagenicity in Salmonella, both in modeling the dose-response relation and in estimating initial dose-response slope or 'potency', e.g., for use in correlating mutagenic and carcinogenic potencies among different chemicals. Both generalized Poisson (GP) and negative binomial (NB) models of revertant variance have been applied in this way, but their empirical applicability has only been assessed using Ames-test data on a few chemicals. The applicability of these and related variance models was therefore assessed for 1905 such data sets pertaining to 121 putatively mutagenic carcinogens. Only approximately 50% of the data sets analyzed were found to involve a significantly positively correlated dose-response, and < 50% were found to exhibit a plausibly heterogeneous response variance regardless of dose-response correlation. Among data sets with plausibly heterogeneous variance, < 60% were found to exhibit significantly extra-Poisson variability. Among the significantly extra-Poisson data sets, most (> 75% among dose-response correlated data sets) were found to exhibit revertant variance consistent with both the GP and NB models; while the GP model was found to be somewhat more consistent with these data, the NB model more often gave a nominally better fit when both models were consistent. Implications of these results for the design of methods used to analyze Ames-test data are discussed.

Bonefeld Jorgensen, E; Autrup, H; Hansen, J. (1997) Effect of toxaphene on estrogen receptor functions in human breast cancer cells. Carcinogenesis 18(8):1651-1654.
Toxaphene (polychlorinated camphenes) is an insecticidal mixture of >670 chemicals, which was widely used until the mid 1980s. Due to their lipophilic and volatile nature, these chemicals accumulate in animal and human tissues and continue to be a major contaminant in marine and freshwater biota. Cytotoxic and genotoxic effects in mammalian test systems suggest that toxaphene is a carcinogen and reports support the hypothesis that toxaphene could have tumor-promoting potential in human breast tissue. In order to examine the potential of toxaphene as an environmental endocrine disrupter, we investigated its effect on the estrogen receptor (ER) function in human breast cancer MCF-7 cells. Using transient gene expression experiments, we observed approximately 60% and 80% inhibition of the constitutive and 17beta-estradiol induced ER-dependent transactivation, respectively. The involvement of the ER in the ability of toxaphene to block the estrogen action was verified by cotransfection studies in ER-negative MDA-MB-231 cells. The interference of toxaphene with the ER mediated responses was supported by a significant suppression of endogenously expressed pS2 RNA and decreased levels of secreted pS2 protein. These reproducible results indicate that toxaphene can disturb hormonal signals mediated by the ER and suggest that these environmental chemicals have potential endocrine disrupting activities which may affect the reproductive health and increase the risk of carcinogenesis.

Brockman, H; De Serres, F; Hung, C; et al. (1983) Mutagenicity of toxaphene in the ad-3 forward-mutation test in nucleotide excision repair-deficient and -proficient dikaryons of neurospora crassa. Environ Mutagen 5(3):502.

Cabrera, G. (2000) Effect of five dietary antimutagens on the genotoxicity of six mutagens in the microscreen prophage-induction assay. Environ Mol Mutagen 36(3):206-220.
Dietary antimutagens have been studied extensively in the last two decades, using mainly bacterial and mammalian cells. These studies have shown that certain dietary antimutagens, acting individually or as mixtures, are useful in counteracting the effects of certain mutagens and/or carcinogens to which humans are commonly exposed. However, there are some inconsistencies among publications using different bioassays. The general purpose of the research presented here was to conduct a comparative study of the antigenotoxic activity of five dietary antimutagens against six mutagens, using three rather different short-term tests: the Microscreen prophage-induction assay, the Tradescantia micronucleus test, and the Salmonella/mammalian microsome test. In this study I report the results with the Microscreen prophage-induction assay. The antimutagens selected were chlorophyllin, beta-carotene, and vitamins A, C, and E. The mutagens selected were 2-aminoanthracene, benzo[a]pyrene, 2-nitrofluorene, toxaphene, dichlorvos, and nitrofen. The results show that chlorophyllin and beta-carotene inhibited the genotoxicity of all six mutagens; vitamin E inhibited all except dichlorvos; and vitamins C and A inhibited 2-aminoanthracene, benzo[a]pyrene, 2-nitrofluorene, and nitrofen.

Calciu, C; Chan, H; Kubow, S. (1997) Toxaphene congeners differ from toxaphene mixtures in their dysmorphogenic effects on cultured rat embryos. Toxicology 124(2):153-162.
The presence of persistent organic pollutants, including the pesticide toxaphene has been

reported even in remote regions such as the Arctic and is becoming a health concern. The technical mixture of toxaphene contains over 800 different congeners. The numbers of prevalent congeners, however, decrease along the food chain. About 20 major congeners are found in fish, eight in marine mammals and only two major ones in human, 2-exo,3-endo,5-exo,6-endo,8,8,10,10-octachlorobornane (T2) and 2-exo,3-endo,5-exo,6-endo,8,8,9,10,10-nonachlorobornane (T12). Embryotoxicity of these individual congeners is not known, as previous studies focused on the toxaphene technical mixture. We studied the relative dysmorphogenic activity of toxaphene technical mixture and individual congeners (T2 and T12) using rat embryo culture. Explanted embryos (0-2 somites) were treated for 48 h with concentrations of 0 (DMSO 0.01%), 100, 1000 and 5000 ng/ml of either (a) toxaphene technical mixture; (b) T2; (c) T12; or (d) a 50:50 mixture of T2 and T12. The treatment period corresponds to gestational days (GD) 10-12, a period within the critical time of morphogenesis and organogenesis. Both the technical mixture and the two individual congeners had a significant adverse effects on the total morphological score, somite number, head and crown rump length and the central nervous system scores of embryos. All treatments caused a high incidence of central nervous system defects. The T2 and T12 congeners differed in their spectrum of abnormalities as exposure to T2 caused limb and flexion defects which were not observed with the T12 congener. Differences were also observed in the type of toxicity and the target sites between the technical mixture and the congeners. T2 showed a more potent adverse effect on the morphological score as compared to the technical mixture. Both T2 and T12 were less inhibitory on growth than the technical mixture as indicated by crown-rump length but they showed a stronger inhibitory effect on otic system development. The mixture of T2 + T12 showed a synergistic effect on decreasing crown-rump and head length. Conversely, the combination of T2 and T12 inhibited the strong adverse effect of the individual congeners on otic development. The results suggest environmentally predominant toxaphene congeners can have organ specific embryotoxic effects not predicted by the toxaphene technical mixture. Also may be used in Section(s): 3.3

Calciu, C; Kubow, S; Chan, H. (2002) Interactive dysmorphogenic effects of toxaphene or toxaphene congeners and hyperglycemia on cultured whole rat embryos during organogenesis. Toxicology 175(1-3):153-165.
Both diabetes mellitus and exposure to environmental contaminants are becoming health hazards to many indigenous populations in the world. In earlier work, we established the embryopathy of the chlorinated pesticide, toxaphene technical mixture (TOX) and its two physiologically most important congeners, T(2) (2-exo,3-endo,5-exo,6-endo,8,8,10,10-octachlorobornane) and T(12) (2-exo,3-endo,5-exo,6-endo,8,8,9,10,10-nonachlorobornane). In this study, the combined effects of toxaphene or its two congeners and high glucose concentrations were studied using rat embryo culture in order to investigate the potential interactions between hyperglycemia and toxaphene exposure. Whole rat embryos (0-2 somite) were explanted and cultured into a normal (8 mM) or hyperglycemic 12.5 mM (12.5 G) or 18.75 mM (18.75 G) culture medium containing TOX, T(2), or T(12) at various concentrations (0, 100, 1000, 5000 ng/ml) for 48 h at 37 degrees C. All treatments, except mild hyperglycemic exposure (12.5 G), had significant adverse effects on the total morphological score, head and crown-rump length, yolk sac diameter and yolk sac circulation. Embryos exposed to 18.75 G did not show malformations but when hyperglycemia at 18.75 G was combined with higher doses of TOX or T(2) synergistic effects on the incidence of neural tube defects were observed. The embryos cultured with T(12) under severe

hyperglycemic conditions of 18.75 G showed an inhibition of T(12)-induced neural tube defects, but there was a concurrent underdevelopment of forelimbs or hindlimbs at the highest T(12) dose. The results suggest that there is a site-specific and dose-related interactive dysmorphogenesis elicited by TOX or its congeners with high levels of glucose on rat embryonic development. Because of the relatively high TOX doses used in this study, the drastic growth retardation and malformation observed are unlikely to be observed in human populations. More subtle effects, however, may not be ruled out.

Campbell, M; Gyorkos, J; Leece, B; et al. (1983) The effects of twenty-two organochlorine pesticides as inducers of the hepatic drug-metabolizing enzymes. Gen Pharmacol 14(4):445-454.
The effects of 22 organohalogen pesticides as inducers of hepatic drug-metabolizing enzymes in the immature male Wistar rat have been determined, this group includes four isomeric hexachlorocyclohexanes, technical chlordane, alpha-chlordane, gamma-chlordane, oxychlordane, trans-nonachlor, heptachlor, heptachlor epoxide, aldrin, dieldrin, kepone, toxaphene, mirex, hexachlorobenzene (HCB) and several DDT analogs. With the exception of HCB, all of the pesticides induced microsomal dimethylaminoantipyrine, N-demethylase and aldrin epoxidase activities and the cytochrome P-450 content of microsomes from animals pretreated with most of the compounds was also increased compared to control rats. These pesticides all resembled phenobarbitone in their mode of induction. The effects of HCB as a microsomal enzyme inducer resembled those observed after coadministration of phenobarbitone plus 3-methylcholanthrene.
Also may be used in Section(s): 4.4

Chen, S; Zhou, D; Yang, C; et al. (2001) Molecular basis for the constitutive activity of estrogen-related receptor alpha-1. J Biol Chem 276(30):28465-28470.
Some orphan nuclear receptors, including estrogen-related receptor alpha-1 (ERRalpha-1), can activate gene transcription in a constitutive manner. Little is known about the molecular basis of the constitutive activity of these receptors. Our results from site-directed mutagenesis experiments have revealed that Phe-329 (analogous to Ala-350 in estrogen receptor alpha (ERalpha)) is responsible for the constitutive activity of ERRalpha-1. The ERRalpha-1 mutant F329A lost the transactivation activity and acted as a dominant negative mutant. The mammalian cell transfection experiments revealed that the ERRalpha-1 mutant F329A, like wild-type ERalpha, recognized toxaphene (an organochlorine pesticide) as an agonist. This compound was previously shown to be an antagonist of wild-type ERRalpha-1. On the other hand, like wild-type ERRalpha-1, the ERalpha mutant A350F was found to be constitutively active (as demonstrated by mammalian cell transfection and yeast two-hybrid assays). These results indicate that Phe-329 in ERRalpha-1 and Ala-350 in ERalpha play important roles in both ligand binding and transactivation function.

Chuang, AJ; Yau, P; Killam, KF; et al. (1993) Analysis by polymerase chain reaction of c-myc expression in human leukemia cells induced to differentiate by heptachlor and 12-O-tetradecanoylphorbol-13-acetate. Pest Biochem Physiol 46(3): 219-227.
Heptachlor, a chlorinated hydrocarbon insecticide, was previously demonstrated to be able to induce differentiation of human myeloblastic leukemia ML-1 cells into monocyte- or macrophage-like cells, a phenomenon similar to that caused by the known tumor promoter 12-O-tetradecanoylphorbol-13-acetate (TPA). Studies have also shown that chemically induced myeloid differentiation of human promyelocytic leukemia HL-60 cells is associated with a

decline in the steady-state c-myc proto-oncogene expression. In this study, the polymerase chain reaction (PCR) was combined with primer-extension reverse transcription for the detection of subtle changes in the level of myc mRNA transcription in ML-I cells exposed to either heptachlor or TPA. Three sets of 5' primers (S1, S2, and S3) within the region bordered by two promoter sequences (P1 and P2) and a fourth 5' sequence (S4) downstream of P2 were individually paired with a 3' primer sequence (S5) for the synthesis of portions of the first exon of the c-myc oncogene. The results indicated that when S2, S3, and S4 5' primers were used, an initial increase of myc gene expression was detected and was followed by a rapid decline of myc transcripts in cells which had been exposed to TPA. However, when the S1 5' primer was used in the PCR assay, RNA transcription was shown to be less efficient. Heptachlor, under the same assay conditions, decreased the expression of the myc oncogene, but did not cause an initial stimulation. Marked depression in c-myc expression was further detected in ML-1 cells exposed to chlordane, a heptachlor-related, chlorinated hydrocarbon insecticide, but not to toxaphene, another chlorinated hydrocarbon insecticide. In addition, heptachlor was shown to stimulate the in vitro protein kinase C (PKC) activity and the binding of (3H)PDBu to ML-1, indicating a dissociation of PKC activation and myc expression in ML-1 induced to differentiate by heptachlor.

Crain, D; Noriega, N; Vonier, P; et al. (1998) Cellular bioavailability of natural hormones and environmental contaminants as a function of serum and cytosolic binding factors. Toxicol Ind Health 14(1-2):261-273.
Environmental contaminants have been reported to function as hormone mimics in various wildlife species. To investigate a potential mechanism for the interaction of contaminants with the endocrine system, we evaluated the cellular bioavailability of numerous chemicals. Hormone binding proteins from oviductal cytosol of the American alligator (Alligator mississippiensis) and yellow-bellied turtle (Trachemys scripta) were used in competitive binding assays with [3H] 17 beta-estradiol. Most of the environmental contaminants, and the potent, synthetic estrogen diethylstilbestrol (DES), did not interact with the cytosolic binding proteins. Among the compounds tested, o,p'-DDT and toxaphene exhibited the greatest affinity for the binding proteins. The functional consequence of the apparent lack of interaction of most contaminants with binding proteins was studied in a strain of yeast containing the human estrogen receptor (YES assay). The activation of YES with estradiol was reduced 30% in the presence of a physiological concentration (0.01 mg/mL) of human sex hormone binding globulin (SHBG), a hormone binding protein found in the blood. In contrast, the activity of DES was not inhibited by 0.01 mg/mL SHBG. Interestingly, ethinyl estradiol, a major component of contraceptives, did not appear to appreciably interact with SHBG in the YES system. Together, these data suggest that cytosolic and circulating binding proteins bind many environmental contaminants with much less affinity than native steroids. Therefore, such contaminants may be more hormonally active than previously hypothesized. Also may be used in Section(s): 3.2

Crisp, T; Clegg, E; Cooper, R; et al. (1998) Environmental endocrine disruption: An effects assessment and analysis. Environ Health Perspect 106(Suppl 1):11-56.
This report is an overview of the current state of the science relative to environmental endocrine disruption in humans, laboratory testing, and wildlife species. Background information is presented on the field of endocrinology, the nature of hormones, and potential sites for endocrine disruption, with specific examples of chemicals affecting these sites. An attempt is made to

present objectively the issue of endocrine disruption, consider working hypotheses, offer opposing viewpoints, analyze the available information, and provide a reasonable assessment of the problem. Emphasis is placed on disruption of central nervous system--pituitary integration of hormonal and sexual behavioral activity, female and male reproductive system development and function, and thyroid function. In addition, the potential role of environmental endocrine disruption in the induction of breast, testicular, and prostate cancers, as well as endometriosis, is evaluated. The interrelationship of the endocrine and immune system is documented. With respect to endocrine-related ecological effects, specific case examples from the peer-reviewed literature of marine invertebrates and representatives of the five classes of vertebrates are presented and discussed. The report identifies some data gaps in our understanding of the environmental endocrine disruption issue and recommends a few research needs. Finally, the report states the U.S. Environmental Protection Agency Science Policy Council's interim position on endocrine disruption and lists some of the ongoing activities to deal with this matter.

Crowder, L. (1976) Mode of action of cyclodiene insectidies. Natl Tech Inform Serv PB 251(670).
The report contains information concerning the mode of action, excretion, and metabolism of the cyclodiene insecticides. Toxaphene was the primary candidate for investigation with major emphasis on the mammalian system. Excretion of 36Cl-toxaphene was studied in the laboratory rat. Upon extraction, most of the radioactivity occurred in the water fractions of urine and feces as ionic chloride, indicating considerable metabolism of toxaphene. Occurrence of radioactivity in several tissues of Leucophaea maderae was determined after injections of 36Cl-toxaphene. Uptake of .00001M 36Cl-toxaphene in subcellular particles of ventral nerve cord and brain was studied and showed significant levels in the larger cell fragments. The toxicity syndrome of toxaphene to Gambusia affinis was divided into five stages, and the residue level at each stage was determined. Excretion was not observed. Metabolic alteration of toxaphene appeared to be minimal. Ventral nerve cords of Periplaneta americana and L. maderae showed increased nerve activity as viewed electrophysiologically when exposed to toxaphene. Toxaphene appeared to be a neurotoxicant. Also may be used in Section(s): 3.3

Dehn, P; Allen-Mocherie, S; Karek, J; et al. (2005) Organochlorine insecticides: Impacts on human hepg2 cytochrome p4501a, 2b activities and glutathione levels. Toxicol In Vitro 19(2):261-273.
This study examined the effects of the organochlorine (OC) insecticides chlordane, o,p'-DDT, dieldrin, endosulfan, kepone, methoxychlor, and toxaphene on human HepG2 cytochrome P450 (1A-EROD and 2B-PROD) activities and glutathione (GSH) levels. Cells were exposed for 24 h at high concentrations (1, 5 or 10 mM) and for 48 h at lower concentrations ranging from 0.01 to 1 mM to evaluate dose responses. Our results show that after 48 h all but dieldrin significantly induced both P4501A and 2B. P4502B responses were greater at all exposure concentrations and times. Mixed responses in GSH levels were observed. All OCs except dieldrin and MXC significantly depleted GSH after 24 h. At 48 h, chlordane, endosulfan and toxaphene significantly increased GSH at low levels and decreased GSH at high levels, while kepone and methoxychlor produced significant declines in GSH at all concentrations. These results support findings of OC insecticides inducing CYP1A, 2B in rats, with CYP2B responses more important. GSH levels declined when P4502B activity was significantly elevated and were significantly increased in the absence of significant P450 activity, suggesting that GSH levels influence the

catalytic activity of the cytochrome P450s and the cytochrome P450s influence the cell's ability to regulate GSH. Also may be used in Section(s): 3.3

Doroshchuk, VP. (1977) The effect of organo chlorine pesticides on the function of n cholino receptors. Vrach Delo 2:143-146.
Rat tubocurarine paralysis atropine autonomic-drug antidote-drug anti cholin esterase agents narcotics poly chloro pinene poly chloro camphene toxaphene lindane acetyl choline descriptors. major concepts: cell biology; membranes--cell biology; muscular system--movement and support; nervous system--neural coordination; pest assessment control and management; pharmacology; toxicology.

Drenth, H; Bouwman, C; Seinen, W; et al. (1998) Effects of some persistent halogenated environmental contaminants on aromatase (cyp19) activity in the human choriocarcinoma cell line jeg-3. Toxicol Appl Pharmacol 148(1):50-55.
Effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), 3,3',4,4',5-pentachlorobiphenyl (PCB126), a technical PCB mixture (Aroclor 1016), and a technical toxaphene mixture (Camphechlor) on aromatase (CYP19) activity were investigated in human choriocarcinoma JEG-3 cells. After 18 h incubation with TCDD, PCB126, Aroclor 1016 or toxaphene, ethoxyresorufin-O-deethylase (EROD), and aromatase activity were determined. To exclude serum effects, incubations were carried out with or without fetal calf serum in the medium. EROD activity was induced by both TCDD and PCB126 in the presence or absence of serum, which indicates that JEG-3 cells are responsive toward dioxin-like chemicals. Neither Aroclor 1016 nor toxaphene affected EROD activity in these cells. Calculated EC50 values for induction of EROD activity were 0.71 and 0.40 nM for TCDD, and 48 and 20 nM for PCB126 in presence or absence of serum, respectively. Incubation with TCDD or PCB126 with or without serum caused a concentration-dependent decrease in the aromatase activity of up to 4.9-fold. Calculated EC50 values for this effect were 52 pM and 13 nM for TCDD, and 75 and 48 nM for PCB126 in the presence and absence of serum, respectively. Aroclor 1016 and toxaphene had no effect on aromatase activity at concentrations up to 1.0 microM for Aroclor 1016 or 3.0 microM for toxaphene. These results show that aromatase activity can be decreased in a concentration dependent way within the same range where EROD activity is increased. In view of these results, possible effects of dioxin-like compounds on estrogen producing and androgen target cells should be studied in more detail. Also may be used in Section(s): 4.1

Drenth, H; Van Oevelen, C; Buitenhuis, C; et al. (2000) Induction of hepatic cytochrome p450 activities by toxaphene in rat and japanese quail. Environ Toxicol Chem 19(11):2806-2811.

Eldefrawi, A; Eldefrawi, M. (1987) Receptors for gamma-aminobutyric acid and voltage-dependent chloride channels as targets for drugs and toxicants. Faseb J 1(4):262-271.
The function of chloride (Cl-) channel proteins is to regulate the transport of Cl- across membranes. There are two major kinds of Cl- channels: 1) those activated by binding of a transmitter such as gamma-aminobutyric acid (GABA), glycine, or glutamate, and thus are receptors; and 2) those activated by membrane depolarization or by calcium. There are two kinds of GABA receptors: GABAA is the major inhibitory receptor of vertebrate brain and the one that operates a Cl- channel, and the GABAB receptor, which is proposed to regulate cAMP production that is stimulated by other receptors. Except for binding of GABA, these two GABA

receptors differ completely in their drug specificities. However, there are many similarities among the GABAA receptor, the glycine receptor, and the voltage-dependent Cl- channel. The two receptors and Cl- channels bind avermectin, whereas bicuculline binds only to mammalian GABAA and glycine receptors, not to the insect brain GABAA receptor. Barbiturates bind to GABAA and voltage-dependent Cl- channels, possibly directly activating them. Benzodiazepines potentiate both the glycine and GABAA receptors. Several insecticides act on the GABAA receptor and voltage-dependent Cl- channel. It is suggested that the GABAA receptor is the primary target for the action of toxaphene and cyclodiene insecticides but a secondary target for lindane and type II pyrethroids. On the other hand, the Cl- channel may be a primary target for avermectin and lindane but a secondary one for cyclodienes. The similarity in certain drug specificities and the operation of Cl- channels suggest a degree of homology between the subunits of GABAA and glycine receptors and the voltage-dependent Cl- channels.
Epstein, SS; Arnold, E; Andrea, J; et al. (1972) Detection of chemical mutagens by the dominant lethal assay in the mouse. Toxicology and applied pharmacology 23(2):288-325.
Also may be used in Section(s): 4.2

Epstein, SS; Arnold, E; Andrea, J; et al. (1972) Detection of chemical mutagens by the dominant lethal assay in the mouse. Toxicol Appl Pharmacol 23(2):288-325.
Also may be used in Section(s): 4.3

Gaido, K; Dohme, L; Wang, F; et al. (1998) Comparative estrogenic activity of wine extracts and organochlorine pesticide residues in food. Environ Health Perspect 106 Suppl 61347-1351.
The human diet contains industrial-derived, endocrine-active chemicals and higher levels of naturally occurring compounds that modulate multiple endocrine pathways. Hazard and risk assessment of these mixtures is complicated by noadditive interactions between different endocrine-mediated responses. This study focused on estrogenic chemicals in the diet and compared the relative potencies or estrogen equivalents (EQs) of the daily consumption of xenoestrogenic organochlorine pesticides in food (2.44 micrograms/day) with the EQs in a single 200-ml glass of red cabernet wine. The reconstituted organochlorine mixture contained 1,1,1-trichloro-2-(p-chlorophenyl)-2-(o-chlorophenyl)ethane, 1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane, 1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene, endosulfan-1, endosulfan-2, p,p'-methoxychlor, and toxaphene; the relative proportion of each chemical in the mixture resembled the composition reported in a recent U.S. Food and Drug Administration market basket survey. The following battery of in vitro 17 beta-estradiol (E2)-responsive bioassays were utilized in this study: competitive binding to mouse uterine estrogen receptor (ER); proliferation in T47D human breast cancer cells; luciferase (Luc) induction in human HepG2 cells transiently cotransfected with C3-Luc and the human ER, rat ER-alpha, or rat ER-beta; induction of chloramphenicol acetyltransferase (CAT) activity in MCF-7 human breast cancer cells transfected with E2-responsive cathepsin D-CAT or creatine kinase B-CAT plasmids. For these seven in vitro assays, the calculated EQs in extracts from 200 ml of red cabernet wine varied from 0.15 to 3.68 micrograms/day. In contrast, EQs for consumption of organochlorine pesticides (2.44 micrograms/day) varied from nondetectable to 1.24 ng/day. Based on results of the in vitro bioassays, organochlorine pesticides in food contribute minimally to dietary EQ intake.

Garcia, M; Mourelle, M. (1984) Gamma-glutamyl transpeptidase: A sensitive marker in ddt and

toxaphene exposure. J Appl Toxicol 4(5):246-248.
Gamma-glutamyl transpeptidase (GGTP) activity in rat liver plasma membrane and blood serum was investigated as an analytical marker for studying acute and sub-chronic exposure to DDT and toxaphene. Twenty-four hours after a single oral dose of DDT (200 mg per kg body weight) or toxaphene (110 mg per kg body weight), GGTP activity increased two-fold in liver plasma membranes, followed by a return to normal values 48 h post-exposure. In addition, serum GGTP activity doubled following acute exposure to DDT or toxaphene, and remained elevated for 48 and 96 h, respectively. Following 2 months continuous exposure to either insecticide, serum GGTP activity levels increased to double that of control values. GGTP activity in liver plasma membranes was elevated 2.5-fold following the initial treatment with toxaphene (16.5 mg per kg body weight per day) and the activity remained high throughout the treatment period (120 days). Prolonged exposure with DDT (30 mg per kg body weight per day) did not produce any change in liver GGTP activity. Based on these results, it appears that GGTP activity could be used as a marker for acute DDT and toxaphene exposure. Also may be used in Section(s): 3.3 & 4.2

Gauthier, M; Roberge, C; Pelletier, M; et al. (2001) Activation of human neutrophils by technical toxaphene. Clin Immunol 98(1):46-53.
Toxaphene is a persistent organic pollutant (POP) known to be composed of numerous congeners. Toxaphene technical mixture applied as a pesticide consists of over 800 congeners. Among these, T(2) and T(12) are the two environmentally prevalent forms found in humans. Although toxaphene is known to exert some toxic effects, including potential proinflammatory properties, little is known concerning its action on cells of the human immune system, especially neutrophils. In the present study, we found that toxaphene was not necrotic for human neutrophils incubated for up to 24 h with concentrations ranging from 0.1 to 50 microg/ml. Toxaphene was found to induce neutrophil superoxide production (O(-)(2)) in a concentration-dependent manner. The potency and the kinetics of toxaphene-induced O(-)(2) by neutrophils were found to be similar to that of the classical neutrophil agonists phorbol 12-myristate 13-acetate (PMA). Furthermore, the use of various transduction signal inhibitors (genistein, pertussis toxin, staurosporine, H-7, and HA-1077), suggests that, as for PMA, toxaphene mediates its effect primarily via PKCs and, to a lesser extend, via tyrosine kinases. In this respect, staurosporine, H-7, and genistein were found to inhibit toxaphene- and PMA-induced O(-)(2) production by 52, 72, and 31% and by 63, 62, and 23%, respectively. Toxaphene was also found to significantly enhance neutrophil phagocytosis of opsonized sheep red blood cells and to induce neutrophil apoptosis. The induction of neutrophil apoptosis was paralleled with a decrease in CD16 expression. T(2) and T(12), the two prevalent congeners found in humans, were also found to significantly increase the O(-)(2) production in neutrophils at a concentration of 5 microg/ml. We conclude that neutrophils are important targets for toxaphene, as this POP can activate O(-)(2) production by a PKC- and tyrosine kinase-dependent mechanism, induce phagocytosis, and accelerate the apoptotic rate. This is the first study that focuses on toxaphene/human neutrophil interactions.

Gauthier, J; Dubeau, H; Rassart, E. (1999) Induction of micronuclei in vitro by organochlorine compounds in beluga whale skin fibroblasts. Mutat Res 439(1):87-95.
Beluga whales (Delphinapterus leucas) inhabiting the St. Lawrence estuary are highly contaminated with environmental pollutants and have a high incidence of cancer. Environmental contaminants may be partly responsible for the high cancer incidence observed in this

population. DNA damage plays an important role in the development of cancer. The micronuclei (MN) assay was used to test the genotoxic potential of organochlorine (OC) pesticides with and without external metabolic factor in skin fibroblasts of an Arctic beluga whale. Toxaphene, chlordane and p,p'-DDT induced significant (p<0. 05) concentration-response increases of micronucleated cells (MNCs). Statistically significant increases in MNCs, ranging from 1.7- to 5-folds when compared to control cultures, were observed for 0.05, 0. 5, 5 and 10 microg/ml toxaphene, 2, 5 and 10 microg/ml chlordane and 10 and 15 microg/ml p,p'-DDT. Presence of exogeneous metabolic factor (S9) completely abolished the MN induction potency of chlordane and p,p'-DDT, and toxaphene induced MN formation at higher concentrations (0.5 microg/ml) than without S9 mix. The ecotoxicological significance of MN induction by low concentrations of toxaphene is unknown and do not imply that toxaphene is involved in the etiology of cancer in St. Lawrence beluga whales. However, because of the known genotoxicity of toxaphene and the long lifespan of beluga whales, it cannot be excluded that toxaphene may pose a long-term genetic hazard to the more contaminated whales of this population.

Graham, M; Cossette, L; Gelinas, S; et al. (2003) In vitro modulation of prolactin mrna by toxaphene and 3,3',4,4'-tetrachlorobiphenyl. Environmental Research 92(3):207-212.

Griffin, DE, 3rd; Hill, WE. (1978) In vitro breakage of plasmid DNA by mutagens and pesticides. Mutat Res 52(2):161-169.
Covalently closed circular molecules of the colicinogenic plasmid E1 can serve as sensitive indicators for detecting in vitro breakage of DNA. After these molecules are radioactively labeled and purified by cesium chloride density-gradient centrifugation, they are incubated with the compounds to be tested. Samples are analyzed on alkaline sucrose gradients to determine the fraction of unbroken molecules and a breakage rate is calculated. Positive results were obtained for all three mutagenic alkylating agents (MMS, EMS, and MNNG) and of the 11 pesticides tested, dexon, dichlorvos, malathion, and methyl parathion induced breaks in molecules at a rate significantly greater than the controls.

Heufelder, A; Hofbauer, L. (1996) Environmental endocrinology hidden but potent ways of activating the estrogen receptor. European Journal of Endocrinology 135(6):653-654.
Biosis copyright: biol abs. rrm note human bird fish turtle female male endocrine system estrogen receptor environmental pollution environmental sciences ddt heavy metals breast cancer 17beta-estradiol dieldrin toxaphene endosulfan chlordane transcription reproductive system disease-female neoplastic disease.

Hodges, L; Bergerson, J; Hunter, D; et al. (2000) Estrogenic effects of organochlorine pesticides on uterine leiomyoma cells in vitro. Toxicol Sci 54(2):355-364.
Although benign, uterine leiomyomas occur with high frequency and significant morbidity in reproductive-age women, and they present a significant health problem. Leiomyomas develop in the uterine myometrium and are sensitive to ovarian hormones, making them potential target sites for endocrine disruptors. Here we utilize cell lines derived from rat uterine leiomyomas to determine if a panel of 7 organochlorine pesticides have potential agonist activity in myometrial cells using cellular and molecular in vitro assays. The organochlorine pesticides investigated have been previously characterized as having agonist activity in other hormonally responsive tissues, but their effects have not been studied in uterine myometrial cells. In Eker rat

leiomyoma-derived cells, HPTE, kepone, and the alpha isomer of endosulfan stimulated proliferation, an effect dampened by the antiestrogen ICI 182,780. In addition, these compounds stimulated transcription of the vitellogenin estrogen-response element via the ER in a transcriptional reporter gene assay and induced the expression of an endogenous estrogen-responsive gene, the progesterone receptor (PR). This contrasted with the agonist profile of methoxychlor, dieldrin, toxaphene, and endosulfan-beta. These compounds, unable to stimulate proliferation of uterine leiomyoma cells, did exhibit agonistic activity in these cells at the transcriptional level in the estrogen-sensitive reporter gene assay, and they were also able to upregulate PR message. These data demonstrate that organochlorine pesticides act as estrogen receptor agonists in Eker rat uterine myometrial cells, and they indicate a need for further investigation of the potential tissue-specific agonist activity of these pesticides and their role in the pathogenesis of uterine leiomyoma. Also may be used in Section(s): 4.3

Holme, J; Dybing, E. (1997) Environmental chemicals with hormone-like properties: A human health problem? Tidsskrift for Den Norske Laegeforening 117(1):70-73.
Biosis Copyright: Biol Abs. Lately, a hypothesis linking higher frequency of testicular cancer, reduced semen quality and malformation of the male sexual organs with increased embryonic/foetal exposure to oestrogenic chemicals has received wide attention in the media. There are several examples where point-source chemical pollution has been convincingly associated with endocrine-related changes in wildlife. Such changes have also been reproduced in experimental studies. There is very little evidence, however, of such an association in humans. Nevertheless, the findings provide a clear challenge to toxicologists and epidemiologists in order to elucidate possible public health risks from environmental exposure to chemicals with hormone-like effects. Better test strategies and reproductive toxicity test guidelines are needed in order to assess any such risks, and to provide a basis for possible regulatory action.

Hooper, N; Ames, B; Saleh, M; et al. (1979) Toxaphene, a complex mixture of polychloroterpenes and a major insecticide, is mutagenic Science 205(4406):591-593.
Toxaphene, the most widely used chlorinated insecticide, is mutagenic in the Salmonella test without requiring liver homogenate for activity. This insecticide is a complex mixture (more than 177 polychloroterpenes) with carcinogenic activity in rodents. Some but not all of the mutagenic components are easily separated from the insecticidal ingredients. Also may be used in Section(s): 3.2 & 4.4

Houk, V; Demarini, D. (1986) Use of the microscreen phage-induction assay to assess the genotoxicity of selected pesticides and hazardous wastes. Environ Mutagen 8(SUPPL 6):37-38.

Houk, V; DeMarini, D. (1987) Induction of prophage lambda by chlorinated pesticides. Mutat Res 182(4):193-201.
Chlorinated organics represent an important class of environmental carcinogens. However, only a small percentage of the carcinogens of this chemical class are genotoxic in prokaryotic bioassays such as the Salmonella assay. In an effort to identify a short-term assay sensitive to chlorinated carcinogens, we have tested a group of chlorinated pesticides, most of which are carcinogenic in rodents, in a prophage-induction assay developed by Rossman et al. (1984). The Microscreen phage-induction assay is a rapid, inexpensive, miniaturized system that uses the induction of prophage lambda in Escherichia coli as an indicator of genetic damage. It has been

used successfully to screen complex environmental samples for genotoxicants and has detected carcinogenic metals that are refractory in the Salmonella assay. The pesticides tested were malathion, monuron, p,p'-DDT, mirex, lindane, nitrofen, chlordane, toxaphene, captan, and dichlorvos. All but the first 4 induced prophage. The remaining pesticides were ranked as follows according to induction potency in the presence of S9: captan greater than dichlorvos greater than toxaphene greater than lindane greater than nitrofen greater than chlordane. Rankings were similar in the absence of S9. Of these 6 pesticides, only nitrofen required S9 to induce prophage. Comparisons with mutagenesis data in Salmonella indicated that the Microscreen assay detected as genotoxic each of the pesticides that were mutagenic in Salmonella; moreover, it detected 2 additional carcinogens (chlordane and lindane) that were not mutagenic in the Salmonella assay. The possible use of the Microscreen phage-induction assay to detect chlorinated organics is discussed.

Ishikawa, TT; McNeely, S; Steiner, PM; et al. (1978) Effects of chlorinated hydrocarbons on plasma alpha-lipoprotein cholesterol in rats. Metabolism 27(1):89-96.
The effects of chlorinated hydrocarbons on plasma alpha-lipoprotein cholesterol were studied in rats. Ten chlorinated hydrocarbons were tested: p-chlorophenyl-2,4,5-trichlorophenylsulfone, ethyl-4,4'-dichlorobenzilate, decachlorooctahydro-1,3,4-methano-2H-cyclobuta(cd)pentalen-2-one (143500) (kepone), 1,2,3,4,5,6-hexachloro-cyclohexane, 4,4'-dichloro-alpha-(trichloromethyl)benzhydrol, toxaphene (8001352), dieldrin (60571), hexachlorobenzene (118741), decachloro-bis-(2,4-cyclopentadiene-1-yl)(2,4-cyclopentadiene-1-yl), and pentachlorobiphenyl (11097691) (Aroclor-1254). Male albino-rats were administered with chlorinated hydrocarbons in water at various concentrations. Blood was sampled on days 0, 7, 21, and 60 from all rats, including unexposed control rats. Concentrations of total plasma cholesterol, plasma alpha-lipoprotein cholesterol, and plasma triglycerides were determined. Statistical significance of the data was evaluated. Aroclor-1254, dieldrin, and kepone significantly increased high density lipoprotein cholesterol on day 7 after exposure, whereas on days 21 and 60, there was no further change in the Aroclor group and values returned to basal for kepone and dieldrin. None of the other chemicals had a significant effect on any of the test days after exposure. No significant effects were seen on concentrations of plasma triglycerides. The authors conclude that certain chlorinated hydrocarbons alter plasma alpha-lipoprotein concentrations. Also may be used in Section(s): 3.2 & 4.2

Janik, F; Wolf, H. (1992) The ca2+transport-atpase of human erythrocytes as an in vitro toxicity test system: Acute effects of some chlorinated compounds. J Appl Toxicol 12351-358.

Jeffery, W; Ahlin, T; Goren, C; et al. (1976) Loss of warfarin effect after occupational insecticide exposure. The Journal of the American Medical Association 236(25):2881-2882.
Also may be used in Section(s): 4.1

Joy, R. (1982) Mode of action of lindane dieldrin and related insecticides in the central nervous system. Proceedings of a Conference on Neurotoxicity of Pesticides, Raleigh, NC, USA, June 25-26, 1982 Neurobehav Toxicol Teratol 4(6):1983).
Heep copyright: biol abs. rrm review insects mammals synapse intensified activity neuro transmitters release brain plasticity seizure model.

Kao, CY; Nomata, K; Oakley, CS; et al. (1995) Two types of normal human breast epithelial cells derived from reduction mammoplasty: Phenotypic characterization and response to sv40 transfection. Carcinogenesis 16(3):531-538.
A culture method to grow two morphologically distinguishable normal human breast epithelial cell types derived from reduction mammoplasty has been developed. Type I cells were characterized by a more variable cell shape, smooth cell colony boundaries, the expression of epithelial membrane antigen (EMA) and keratin 18 and the non-expression of keratin 14 and alpha 6 integrin. In addition, the Type I cells were growth stimulated by fetal bovine serum (FBS) and were deficient in gap junctional intercellular communication (GJIC). In contrast, Type II cells were characterized by a uniform cell shape, expression of keratin 14 and alpha 6 integrin and the non-expression of EMA and keratin 18. In addition, Type II cells were growth inhibited by FBS and were proficient in GJIC. Type I cells can be induced by cholera toxin to change their morphology to a Type II cell morphology. Hence, Type I cells antigenically resemble luminal epithelial cells, while the Type II cells more closely resemble basal epithelial cells. Type I and Type II cells were transfected with SV40 DNA. Clones with extended lifespans were obtained from both Type I and Type II cells by SV40 transfection. Some (2/9) of the SV40-transfected Type I cell clones became immortal (> 100 cumulative population doubling level), whereas none (0/8) of the SV40-transfected Type II cell clones became immortal. The SV-40-transfected Type I and Type II cell-derived extended life clones and immortal cell lines phenotypically resembled their parental cells with respect to EMA, keratin 14 and keratin 18 expression and GJIC. Each (9/9) of the SV40 transfected Type I cell clones grew in soft agar; none (0/8) of the SV40-transfected Type II cell clones were capable of growing in soft agar. These results provide evidence that normal human breast epithelial cells, derived from reduction mammoplasty, can be separated into two morphologically and antigenically different cell types and that these two different cell types significantly differ in their response to an oncogenic (SV40) stimulus.

Khaykina, B; Yakushko, V; Novikova, N. (1975) Effect of some organochlorine pesticides on glucose-6-phosphate dehydrogenase activity in erythrocytes. Gig Sanit 11117-118.
PESTAB. The effect of different doses of DDT, lindane, and polychlorocamphene (toxaphene) on the glucose-6-phosphate dehydrogenase activity of the erythrocytes was studied in male white rats in acute and chronic experiments by oral administration. Lindane, administered in a daily dose of 34 mg/kg for 3 days, or in a daily dose of 1.7 mg/kg for 10, 30, or 120 days, reduced the glucose-6-phosphate dehydrogenase activity by 16-25%. Similar findings were obtained for DDT. Administered in a single dose of 120 mg/kg (50% LD50), polychlorocamphene inhibited the glucose-6-phosphate dehydrogenase activity by 18% on the first day, and by 15% on the 5th day. The enzyme activity was normal 15 days after poisoning. Administered in a daily dose of 2.4 mg/kg (1% of LD50) for 30 or 90 days, polychlorocamphene did not cause any change in the enzyme activity, but it caused a 24% reduction after the administration of this dose for 120 days. The reduction of the glucose-6-phosphate dehydrogenase activity during the prolonged administration of these organochlorine pesticides is assumed to be due to the accumulation of these substances in the organism. The aplastic anemia caused by DDT may be related to its inhibition of the glucose-6-phosphate dehydrogenase activity. The changes also indicate an effect of DDT, lindane, and polychlorocamphene on the pentose phosphate metabolism in the erythrocytes. Also may be used in Section(s): 3.1 & 4.2

Khaykina, B; Ivan'tskiy, V; Shilina, V. (1977) Metabolism of biogenic amines in rats under the

effect of dichlorodiphenyl trichloroethane and polychlorocamphene. Ukr Biokhem Zh 49(5):46-49.
After animals were affected by dichlorodiphenyl trichloroethane and polychlorocamphene, some indices of serotonin and catecholamine metabolism were investigated. An increase in serotonin metabolism and the sympatho-adrenal system activity was observed. Also, due to the administration of polychlorocamphene, the shifts in the catecholamine metabolism are more pronounced.

Kitchin, K; Brown, J. (1989) Biochemical studies of promoters of carcinogenesis in rat liver. Teratog Carcinog Mutagen 9(5):273-285.
Adult female rats were orally dosed with 1/5 to 3/5 the published LD50 of either promoters or putative promoters of carcinogenesis [hexachlorobenzene (HCB), alpha-hexachlorocyclohexane (alpha-HCH), kepone and toxaphene] or noncarcinogens [coumaphos, EDTA, caprolactam, 8-hydroxyquinoline, titanium (IV) oxide, sodium diethyldithiocarbamate (DEDTC), and sucrose] at 21 and 4 h before sacrifice. The promoters selected in this study were all of the halogenated hydrocarbon class. At doses of 1/5 to 3/5 the LD50, all four promoters or putative promoters induced rat hepatic ODC activity. The seven noncarcinogens produced several biochemical effects at doses of 1/5 the LD50: increased serum alanine aminotransferase activity (SGPT) (caprolactam and DEDTC), decreased hepatic cytochrome P-450 content (DEDTC), and increased hepatic ODC activity (8-hydroxyquinoline and DEDTC). None of the seven noncarcinogens caused hepatic DNA damage or coordinate induction of hepatic ODC and cytochrome P-450. The results support the interpretation that several of these biochemical parameters are useful in distinguishing potential tumor promoters and noncarcinogens. Also may be used in Section(s): 4.6.

Kitchin, KT; Brown, JL. (1994) Dose-response relationship for rat liver DNA damage caused by 49 rodent carcinogens. Toxicology 88(1-3):31-49.
An experimental approach was taken to the question of dose-response curves for chemical carcinogenesis. DNA damage in female rat liver was chosen as the experimental parameter because all chemicals found to damage hepatic DNA were rodent carcinogens. The lowest dose causing DNA damage was determined for the 12 active chemicals (1,2-dibromoethane, 1,2-dibromo-3-chloropropane, 1,2-dichloroethane, 1,4-dioxane, methylene chloride, auramine O, Michler's ketone, selenium sulfide, 1,3-dichloropropene, 1,2-dimethylhydrazine, N-nitroso-piperidine and butylated hydroxytoluene). The resulting dose-response curves for rat hepatic DNA damage were plotted versus log of the molar dose (all activity was in five orders of magnitude) and versus percent of chemicals' oral rat LD50 (most of the activity was in only two orders of magnitude). Dose-response studies of the active chemicals were analyzed by regression methods. With the exception of butylated hydroxytoluene, the dose-response curves fit a linear model well ($r2 = 0.886$) and a quadratic model even better ($r2 = 0.947$). Based on experimental data from 11 DNA-damaging carcinogens (a dose range of 6 orders of magnitude), an equation and graph of the dose-response relationship of an 'average DNA-damaging carcinogen' is presented over the x-axis dose range of eight orders of magnitude. Also 4.6.

Kitchin, KT; Brown, JL; Kulkarni, AP. (1992) Predictive assay for rodent carcinogenicity using in vivo biochemical parameters: Operational characteristics and complementarity. Mutat Res 266(2):253-272.

111 chemicals of known rodent carcinogenicity (49 carcinogens, 62 noncarcinogens), including many promoters of carcinogenesis, nongenotoxic carcinogens, hepatocarcinogens, and halogenated hydrocarbons, were selected for study. The chemicals were administered by gavage in two dose levels to female Sprague-Dawley rats. The effects of these 111 chemicals on 4 biochemical assays (hepatic DNA damage by alkaline elution (DD), hepatic ornithine decarboxylase activity (ODC), serum alanine aminotransferase activity (ALT), and hepatic cytochrome P-450 content (P450)) were determined. Composite parameters are defined as follows: CP = [ODC and P450), CT = [ALT and ODC), and TS = [DD or CP or CT]. The operational characteristics of TS for predicting rodent cancer were sensitivity 55%, specificity 87%, positive predictivity 77%, negative predictivity 71%, and concordance 73%. For these chemicals, the 73% concordance of this study was superior to the concordance obtained from published data from other laboratories on the Ames test (53%), structural alerts (SA) (46%), chromosome aberrations in Chinese hamster ovary cells (ABS) (48%), cell mutation in mouse lymphoma 15178Y cells (MOLY) (52%), and sister-chromatid exchange in Chinese hamster ovary cells (SCE) (60%). The 4 in vivo biochemical assays were complementary to each other. The composite parameter TS also shows complementarity to all 5 other predictors of rodent cancer examined in this paper. For example, the Ames test alone has a concordance of only 53%. In combination with TS, the concordance is increased to 62% (Ames or TS) or to 63% (Ames and TS). For the 67 chemicals with data available for SA, the concordance for predicting rodent carcinogenicity was 47% (for SA alone), 54% (for SA or TS), and 66% (for SA and TS). These biochemical assays will be useful: (1) to predict rodent carcinogenicity per se, (2) to 'confirm' the results of short-term mutagenicity tests by the high specificity mode of the biochemical assays (the specificity and positive predictivity are both 100%), and (3) to be a component of future complementary batteries of tests for predicting rodent carcinogenicity. Also 4.6.

Kodavanti, P; Mehrotra, B; Chetty, S; et al. (1988) Effect of selected insecticides on rat brain synaptosomal adenylate cyclase and phosphodiesterase. J Toxicol Environ Health 25(2):207-215.
Previous reports from our laboratory and others clearly indicated that organochlorine insecticides such as chlordecone and DDT are potent inhibitors of ATPases involved in active ion transport. The present studies were initiated to study the effect of plictran, chlordecone, toxaphene, aldrin, dieldrin, endrin, isodrin, and telodrin on enzymes involved in cyclic AMP metabolism. Rat brain synaptosomes were prepared by Ficoll-sucrose gradient centrifugation method. Adenylate cyclase activity, which is involved in anabolism of cAMP, was determined using the radioactive method by measuring [32P]cAMP formed during hydrolysis of [32P]ATP. Phosphodiesterase activity, which is involved in the catabolism of cAMP, was estimated by measuring [3H]adenosine formed using [3H]cAMP as a substrate. Synaptosomal adenylate cyclase activity was inhibited significantly by plictran with an IC50 of 25 microM, and a maximum inhibition of 30% was observed with 50 microM chlordecone. Toxaphene, aldrin, dieldrin, endrin, isodrin, and telodrin did not affect the adenylate cyclase activity. Similarly, none of the insecticides studied inhibit the activity levels of synaptosomal phosphodiesterase. The significant inhibition of adenylate cyclase observed with plictran might be due to the tin component, since several heavy metals affect cAMP metabolism. The lack of inhibition of adenylate cyclase and phosphodiesterase with other compounds tested clearly supports our postulation that these organochlorine insecticides exert their neurotoxic action by the selective inhibition of ATPases in synaptosomes. Also may be used in Section(s): 4.4

Kodavanti, P; Mehrotra, B; Chetty, S; et al. (1989) Inhibition of calmodulin activated adenylate cyclase in rat brain by selected insecticides. Neurotoxicology 10(2):219-228.
Effect of various insecticides on basal and calmodulin (CaM) activated adenylate cyclase activity was studied in solubilized rat brain nuclear and P2 fractions. Our earlier experiments indicated that plictran, chlordecone and other insecticides affect the calcium transport across cell membranes. The present experiments were designed with the assumption that these compounds might exert their neurotoxic action by interfering with CaM (a calcium receptor protein) regulated processes. We have used detergent solubilized adenylate cyclase for our studies, since membrane bound form is not sensitive to externally added CaM. CaM significantly elevated the adenylate cyclase activity in both the fractions and a maximum stimulation of 97% in nuclear fraction and 50% in P2 fraction was observed with 1 microgram of CaM. All the insecticides studied inhibited both basal and CaM activated adenylate cyclase activity in nuclear and P2 fractions to a different extent. A significant inhibition was observed at 0.05 microM and higher concentrations of plictran. Chlordecone and toxaphene inhibited both basal and CaM activated adenylate cyclase in a concentration dependent manner. Although dieldrin and aldrin inhibited basal adenylate cyclase in a concentration dependent manner, they did not exhibit a similar pattern on CaM activated adenylate cyclase. Of all the insecticides studies, chlordecone is more potent in inhibiting both basal and CaM activated adenylate cyclase which is in agreement with the greater neurotoxic action of this compound. These results indicate that all the insecticides studied are potent inhibitors of detergent solubilized adenylate cyclase, and might exert their neurotoxic differential action by interfering with CaM regulated events in central nervous system. Also may be used in Section(s): 4.2 & 4.4

Lawrence, L; Casida, J. (1984) Interactions of lindane, toxaphene and cyclodienes with brain-specific t-butylbicyclophosphorothionate receptor. Life Sci 35(2):171-178.
Three major classes of chlorinated hydrocarbon insecticides, i.e., the lindane/hexachlorocyclohexane, toxaphene and aldrin/dieldrin types, are potent, competitive, and stereospecific inhibitors of t-butylbicyclophosphorothionate (TBPS) binding to brain-specific sites, thereby indicating an action at the gamma-aminobutyric acid (GABA)-regulated chloride channel. The most inhibitory and toxic of four isomers of hexachlorocyclohexane is lindane and of greater than 188 components of toxaphene is 2,2,5-endo, 6-exo,8,9,9,10-octachlorobornane. 12-Ketoendrin (IC50 = 36 nM) is twice as active as the most potent previously known inhibitor of TBPS binding and it is also the most inhibitory and toxic of 22 cyclodienes examined. Within each of these three series of polychlorocycloalkanes the mammalian toxicity is closely related to the potency for inhibition of TBPS binding. A modified receptor assay incorporating liver microsomes and reduced nicotinamide-adenine dinucleotide phosphate compensates in part for oxidative detoxification and bioactivation. Specific TBPS binding is reduced in a dose-dependent manner in dieldrin-poisoned rats. DDT, mirex and kepone are not inhibitors of TBPS binding, even at 10 microM. Also may be used in Section(s): 3.2

Lemaire, G; Mnif, W; Pascussi, J; et al. (2006) Identification of new human pregnane x receptor ligands among pesticides using a stable reporter cell system. Toxicol Sci 91(2):501-509.
Pregnane X receptor (PXR, NR1I2) is activated by various chemically unrelated compounds, including environmental pollutants and drugs. We proceeded here to in vitro screening of 28 pesticides with a new reporter system that detects human pregnane X receptor (hPXR) activators.

The cell line was obtained by a two-step stable transfection of cervical cancer HeLa cells. The first transfected cell line, HG5LN, contained an integrated luciferase reporter gene under the control of a GAL4 yeast transcription factor-binding site. The second cell line HGPXR was derived from HG5LN and stably expressed hPXR ligand-binding domain fused to GAL4 DNA-binding domain (DBD). The HG5LN cells were used as a control to detect nonspecific activities. Pesticides from various chemical classes were demonstrated, for the first time, to be hPXR activators: (1) herbicides: pretilachlor, metolachlor, and alachlor chloracetanilides, oxadiazon oxiconazole, and isoproturon urea; (2) fungicides: bupirimate and fenarimol pyrimidines, propiconazole, fenbuconazole, prochloraz conazoles, and imazalil triazole; and (3) insecticides: toxaphene organochlorine, permethrin pyrethroid, fipronil pyrazole, and diflubenzuron urea. Pretilachlor, metolachlor, bupirimate, and oxadiazon had an affinity for hPXR equal to or greater than the positive control rifampicin. Some of the newly identified hPXR activators were also checked for their ability to induce cytochrome P450 3A4 expression in a primary culture of human hepatocytes. HGPXR, with HG5LN as a reference, was grafted onto nude mice to assess compound bioavailability through in vivo quantification of hPXR activation. Altogether, our data indicate that HGPXR cells are an efficient tool for identifying hPXR ligands and establishing pesticides as hPXR activators. Also may be used in Section(s): 3.3

Mehendale, HM. (1977) Pesticide induced impairment of hepato biliary function. J Miss Acad Sci 22(Suppl): 35.
Abstract rat kepone ddt hexa chloro benzene toxaphene insecticides fungicides ouabain.

Moorthy, K; Trottman, C; Spann, C; et al. (1987) In vivo effects of toxaphene on calmodulin-regulated calcium-pump activity in rat brain. J Toxicol Environ Health 20(3):249-259.
In vivo effect of toxaphene on calcium pump activity in rat brain P2 fraction was studied. Male Sprague-Dawley rats (200-250 g) were dosed with toxaphene at 0, 25, 50, and 100 mg/kg X d for 3 d and sacrificed 24 h after last dose. Ca2+-ATPase activity and 45Ca2+ uptake were determined in brain P2 fraction. Toxaphene decreased both Ca2+-ATPase activity and 45Ca2+ uptake, and the reduction was dose-dependent. Both substrate and Ca2+ activation kinetics of Ca2+-ATPase indicated noncompetitive type of inhibition, as evidenced by decreased catalytic velocity but not enzyme-substrate affinity. The decreased Ca2+-ATPase activity and 45Ca2+ uptake were restored to normal level by exogenously added calmodulin, which increased both velocity and affinity. The inhibition of Ca2+-ATPase activity and 45Ca2+ uptake and restoration by calmodulin suggests that toxaphene may impair active calcium transport mechanisms by decreasing levels of calmodulin. Also may be used in Section(s): 3.2, 4.2, & 4.4

Morrow, W; Trottman, C; Rao, K; et al. (1986) Effects of toxaphene and toxaphene fractions on rat brain synaptosomal atpase. Indian J Comp Anim Physiol 4(1):1-8.
Also may be used in Section(s): 4.4

Mortelmans, K; Haworth, S; Lawlor, T; et al. (1986) Salmonella mutagenicity tests. 2.Results from the testing of 270 chemicals. Environ Mutagen 8(SUPPL 7):1-119.

Mourelle, M; Garcia, M; Aguilar, C. (1985) Adenosine triphosphatase activities in plasma liver membranes of rats treated with ddt and toxaphene. J Appl Toxicol 5(1):39-41.
The effect of exposure to chlorinated insecticides (DDT and toxaphene) on Na+,K+-ATPase,

Mg2+-ATPase and Ca2+-ATPase activities of the plasma membrane of hepatocytes was determined. Acute treatment with DDT (200 mg per kg body weight) or toxaphene (110 mg per kg body weight) produced a significant decrease in Na+,K+-ATPase activity (80% and 85%, respectively) 24 h after treatment. DDT also produced a 30% decrease in Mg2+-ATPase and Ca2+-ATPase activity, but toxaphene treatment did not modify these enzymes. The effect of exposure to daily doses of DDT (30 mg per kg body weight) or toxaphene (16.5 mg per kg body weight) for a period of 3.5 months was also studied. Animals were sacrificed at 15-day intervals and results showed that Na+,K+-ATPase activity decreased 80% from the beginning of each treatment and the activity remained low throughout the treatment period. DDT, but not toxaphene, also led to a decrease in Mg2+-ATPase (20%) and Ca2+-ATPase (35%) activity. The low values observed from the beginning remained low throughout the treatment period. We believe that the general mechanism of ATPase inhibition by organochloride compounds could be the result of its interaction with membrane lipid components, although some differences could arise from differences in their spatial structure. Also may be used in Section(s): 4.2 & 4.4

Moutschen-Dahmen, J; Moutschen-Dahmen, M; Degraeve, N. (1984) Mutagenicity, carcinogenicity, and teratogenicity of insecticides. Mutagen Carcinog Teratog Ind Pollut(CASRN):60-57.

Nelson, D; Lamb, D; Mihail, F. (1984) A study of liver microsomal enzymes in rats following propoxur (baygon) administration. Vet Hum Toxicol 26(4):305-308.
Groups of rats were given either propoxur, were left as untreated controls, or were given phenobarbital, DDT, chlordane or toxaphene which are known to induce liver microsomal detoxification enzymes. Microsomal enzyme activity was measured by testing the ability of liver homogenates to degrade EPN (O-ethyl O-(4-nitrophenyl) phenylphosphonothioate) to p-nitrophenol. The activity of aminopyrine-N-demethylase, cytochrome P-450 and p-nitroanisole-O-demethylase in liver homogenates of rats receiving propoxur was measured. Liver microsomal detoxification enzymes were not induced by propoxur exposure. Also may be used in Section(s): 4.2

Pollock, GA; Krasnec, JP; Niemann, BR. (1983) Rat hepatic microsomal enzyme induction by pretreatment with toxaphene and toxaphene fractions. J Toxicol Environ Health 11(3):355-363.
The levels of hepatic microsomal induction caused by toxaphene were determined. Young Sprague-Dawley rats (70 g) were administered toxaphene (ip injection, daily for 5 d) at 0, 5, 25, and 100 mg/kg. All doses caused increases in liver/body weight ratio, cytochrome P-450 level, aminopyrine demethylation, and aldrin epoxidation. The aldrin epoxidase activity increased almost 700% at the 100-mg/kg dose. Toxaphene was separated into nonpolar (S-A) and polar (S-B) fractions and administered as before at 25 mg/kg. All treatments caused significant increases in cytochrome P-450, aminopyrine demethylation, and aldrin epoxidation. A comparison of the treatments, however, did not reveal any significant differences between the treatments.

Ramamoorthy, K; Wang, F; Chen, I; et al. (1997) Potency of combined estrogenic pesticides. Science 275(5298):405-406.

Ramamoorthy, K; Wang, F; Chen, I; et al. (1997) Estrogenic activity of a dieldrin/toxaphene mixture in the mouse uterus, mcf-7 human breast cancer cells, and yeast-based estrogen receptor

assays: No apparent synergism. Endocrinology 138(4):1520-1527.
The estrogenic activity of dieldrin, toxaphene, and an equimolar mixture of both compounds (dieldrin/toxaphene) was investigated in the 21-day-old B6C3F1 mouse uterus, MCF-7 human breast cancer cells, and in yeast-based reporter gene assays. Treatment of the animals with 17beta-estradiol (E2) (0.0053 kg/day x3) resulted in a 3.1-, 4.8-, and 7.8-fold increase in uterine wet weight, peroxidase activity, and progesterone receptor binding, respectively. In contrast, treatment with 2.5, 15 and 60 micromol/kg (x3) doses of toxaphene, dieldrin, or dieldrin/toxaphene (equimolar) did not significantly induce a dose-dependent increase in any of the E2-induced responses. The organochlorine pesticides alone and the binary mixture did not bind to the mouse uterine estrogen receptor (ER) in a competitive binding assay using [3H]E2 as the radioligand. In parallel studies, estrogenic activities were determined in MCF-7 cells by using a cell proliferation assay and by determining induction of chloramphenicol acetyl transferase (CAT) activity in MCF-7 cells transiently transfected with plasmids containing estrogen-responsive 5'-promoter regions from the rat creatine kinase B and human cathepsin D genes. E2 caused a 24-fold increase in CAT activity in MCF-7 cells transiently transfected with creatine kinase B and a 3.8-fold increase in cells transiently transfected with the human cathepsin D construct. Treatment of MCF-7 cells with dieldrin, toxaphene, or an equimolar mixture of dieldrin plus toxaphene (10(-8)-10(-5) M) did not significantly induce cell proliferation or CAT activity in the transient transfection experiment with both plasmids. The relative competitive binding of the organochlorine pesticides was determined by incubating MCF-7 cells with 10(-9) M [3H]E2 in the presence or absence of 2 x 10(-7) M unlabeled E2 (to determine nonspecific binding), toxaphene (10(-5) M), dieldrin (10(-5) M), and equimolar concentrations of the dieldrin plus toxaphene mixture (10(-5) M). The binding observed for [3H]E2 in the whole cell extracts was displaced by unlabeled E2, whereas the organochlorine pesticides and binary mixture exhibited minimal to nondetectable competitive binding activity. E2 caused a 5000-fold induction of beta-galactosidase (beta-gal) activity in yeast transformed with the human ER and a double estrogen responsive element upstream of the beta-gal reporter gene. Treatment with 10(-6)-10(-4) M chlordane, dieldrin, toxaphene, or an equimolar mixture of dieldrin/toxaphene did not induce activity, whereas 10(-4) M endosulfan caused a 2000-fold increase in beta-gal activity. Diethylstilbestrol caused a 20-fold increase in activity in yeast transformed with the mouse ER and a single estrogen responsive element upstream of the beta-gal reporter gene. Dieldrin, chlordane, toxaphene, and endosulfan induced a 1.5- to 4-fold increase in activity at a concentration of 2.5 x 10(-5) M. Synergistic transactivation was not observed for any equimolar binary mixture of the pesticides at concentrations of either 2.5 x 10(-5) M or 2.5 x 10(-4) M. The results of this study demonstrate that for several estrogen-responsive assays in the mouse uterus, MCF-7 human breast cancer cells, and yeast-based reporter gene assays, the activities of both dieldrin and toxaphene were minimal, and no synergistic interactions were observed with a binary mixture of the two compounds.

Rao, K; Trottman, C; Morrow, W; et al. (1986) Toxaphene inhibition of calmodulin-dependent calcium atpase activity in rat brain synaptosomes. Fundam Appl Toxicol 6(4):648-653.
Effect of toxaphene on Ca2+-ATPase activity in rat brain synaptosomes was studied in vitro and in vivo. Ca2+-ATPase in calmodulin-depleted synaptosomes was inhibited in vitro to a maximum of about 50% at 150 microM toxaphene. Substrate activation kinetics of Ca2+-ATPase in synaptosomes revealed that toxaphene inhibited the enzyme activity noncompetitively by decreasing Vmax values, without affecting the enzyme-substrate affinity. Toxaphene

inhibited the calmodulin activated Ca2+-ATPase activity in a concentration-dependent manner with an IC50 of 10 microM, a concentration at which no significant effect was observed on basal enzyme activity. Nuclear and P2 fraction (synaptosomes) calmodulin levels were reduced significantly in toxaphene-treated rats. The synaptosomal Ca2+-ATPase was also reduced to about 45% in toxaphene-treated rats and the activity was restored to normal levels by the exogenously added calmodulin. These results suggest that toxaphene may cause synaptic dysfunction by interfering with calmodulin and its regulation of neuronal calcium. Also may be used in Section(s): 3.2, 4.2, & 4.4

Rathasabapathy, R; Tom, M; Post, C. (1997) Modulation of the hepatic expression of the estrogen-regulated mrna stabilizing factor by estrogenic and antiestrogenic nonsteroidal xenobiotics. Biochemical Pharmacology 53(10):1425-1434.
Estrogen-mediated accumulation of apolipoprotein II (apoll) mRNA in the avian liver is due, in part, to its stabilization. This stabilization appears to he due to the estrogen-regulated mRNA stabilizing factor (E-RmRNASF) that is expressed in response to estrogen. The E-RmRNASF protects the mRNA from targeted endonucleolytic degradation (Ratnasabapathy, Cell Mol Biol Res 41: 583-594, 1995). To determine whether certain environmental xenobiotics altered the expression of the gene encoding E-RmRNASF by mimicking estrogen, roosters were given estrogen, tamoxifen, clomiphene, hexachlorophene, lindane, rotenone, chlordecone, dichlorodiphenyltrichloroethane (DDT), Araclor, methoxychlor, dieldrin, toxaphene, or bisphenol-A parenterally. Uniformly radiolabeled, capped, and polyadenylated apoll mRNA, incubated in vitro in the presence of liver cytosolic extracts from birds that received estrogen, tamoxifen, hexachlorophene, chlordecone, or Araclor, remained stable, indicating that these agents were estrogenic and stimulated the expression of E-RmRNASF. However, the same mRNA was degraded in similar extracts from control roosters and those treated with clomiphene, DDT, methoxychlor, dieldrin, rotenone, toxaphene, lindane, or bisphenol-A. To determine whether the latter agents were antiestrogenic, roosters were given a 1:5 molar combination of estrogen and each of the xenobiotics. Apoll mRNA showed degradation in liver extracts from roosters that received clomiphene, toxaphene, or bisphenol-A, indicating that these agents prevented estrogenic stimulation of expression of the E-RmRNASF and were antiestrogenic. However, the rest of the xenobiotics failed to antagonize estrogenic stimulation of E-RmRNASF gene expression. These results set a precedent in showing the estrogenic and antiestrogenic effects in vivo of environmental xenobiotics on the expression of a regulatory protein involved in estrogen-mediated mRNA stabilization.

Rosenkranz, H; Klopman, G. (1990) Structural alerts to genotoxicity: The interaction of human and artificial intelligence. Mutagenesis 5333-361.

Rosenkranz, H; Klopman, G. (1990) The structural basis of the mutagenicity of chemicals in salmonella typhimurium: The national toxicology program data base. Mutat Res 228(1):51-80. Biosis Copyright: Biol Abs. A Portion of the U.S. National Toxicology Program (NTP) Salmonella typhimurium mutagenicity data base was analyzed by CASE, an artificial intelligence SAR system. CASE identified 13 structural determinants which, with a high probability (p | 0.05) predicted the likelihood of mutagenicity of the 243 chemicals in the data base (sensitivity = 0.989; specificity = 0.950) as well as of chemicals not included in the data base. CASE also identified an additional set of structures which were highly predictive of

mutagenic potency (sensitivity = 0.949; specificity = 1.00). Even though there is little among the chemicals included in the NTP and Gene-Tox Salmonella data bases, CASE found significant similarities between the structural determinants of the mutagenicity in the two data bases, thereby validating the analyses and indicating a commonality in the structural basis of mutagenicity.

Rosenkranz, HS; Klopman, G. (1993) Structural relationships between mutagenicity, maximum tolerated dose, and carcinogenicity in rodents. Environ Mol Mutagen 21(2):193-206.
BIOSIS COPYRIGHT: BIOL ABS. The CASE structure-activity relational system was applied to a study of the structural bases of toxicity as expressed in the maximum tolerated dose (MTD) of a group of chemicals for which rodent carcinogenicity and mutagenicity data were also available. All of the results were obtained under the aegis of the U.S. National Toxicology Program. The analyses revealed that there was a structural basis for the MTD in mice and in rats and that these overlapped considerably. There was also some overlap between structural determinants of the MTD and of carcinogenicity in rodents but there was also a significant "antagonism" between such fragments; i.e., fragments associated with high toxicity (low MTD) were associated with lack of carcinogenicity and vice versa. The highest overlaps observed were between the structural determinant for a low MTD (i.e., high toxicity) and mutagenicity in Salmonella. Also may be used in Section(s): 4.2

Rosenkranz, M; Rosenkranz, H; Klopman, G. (1997) Intercellular communication, tumor promotion and non-genotoxic carcinogenesis: Relationships based upon structural considerations. Mutat Res 381(2):171-188.
An SAR model for inhibition of metabolic cooperation (iMC) was developed. The structural and physicochemical features associated with the ability to cause iMC are primarily lipophilic moieties consistent with the possibility that they represent receptor-binding ligands. There are also significant parallels between the structural descriptors associated with iMC and those associated with tumor promotion and with carcinogenesis in rodents. Overall, the present study provides structural evidence that iMC is a feature associated with the carcinogenic process.

Samosh, L. (1974) Chromosome aberrations and character of satellite associations after accidental exposure of the human body to polychlorocamphene. Cytol Genet 8(1):23-27.

Samosh, L. (1974) Chromosome aberration and character of satellite associations under casual action of polychlorocamphene on the human organism. TSitologiia i genetika 8(1):24-27.
The frequency of chromosomal aberrations and satellite associations in a culture of peripheral leukocytes in 8 women exposed to polychlorocamphene was studied. An increased number (13.1%) of aberrated cells (control, 1.6%) and a rise in the average number (92.8%) of cells with satellite associations (control, 84.5%) were found. A tendency for enhancement of associations with D chromosomes was found.

Sandal, S; Yilmaz, B; Chen, C; et al. (2004) Comparative effects of technical toxaphene, 2,5-dichloro-3-biphenylol and octabromodiphenylether on cell viability, [ca2+]i levels and membrane fluidity in mouse thymocytes. Toxicol Sci 151(3):417-428.
Flow cytometric studies of mouse thymocytes show that technical toxaphene (10-20 ppm) and 2,5-dichloro-3-biphenylol (PCB 9-OH) (5-10 ppm) kill cells and cause an increase in

intracellular calcium concentration, [Ca2+]i, whereas commercial octabromodiphenylether (OBDE) has no effect. The cell death is not a result of the rise of [Ca2+]i, since the divalent cation ionophore, ionomycin, causes a large elevation in [Ca2+]i without cell death. We have studied effects of these compounds on membrane fluorescence polarization, a measure of membrane fluidity, using 1,6-diphenyl-1,3,5-hexatriene (DPH). We find that toxaphene causes a decrease in membrane fluidity in the concentration range associated with cell death, whereas PCB 9-OH causes an increase in fluidity and OBDE has no effect. These observations suggest that alterations of membrane fluidity of thymocytes, whether it be an increase or decrease, can cause cytotoxicity. Also may be used in Section(s): 4.2

Schaefer, W; Zahradnik, H. (1997) Studies on the effect of environmental pollutants on reproduction. Bayerisches Landesamt Fuer Wasserwirtschaft, Institut Fuer Wasserforschung (Ed) Muenchener Beitraege Zur Abwasser- Fischerei- Und Flussbiologie, Band 50 Stoffe Mit Endokriner Wirkung Im Wasser (Munich Contributions To Wastewater Fishery And River Biology, Vol. 50. Endocrine Disrupting Chemicals In Water). 203p. R. Oldenbourg Verlag Gmbh: Munich, Germany; Munich, Germany. Isbn 3-486-26375-7.; 50(0):20-30.
Biosis copyright: biol abs. rrm book chapter human child female toxicology endocrine disrupting chemicals ecotoxicity infertility cancer diethylstilbestrol endocrine disrupter toxin des estrogen-mimetic effects hormonal disorder reproductive system disease-female neoplastic disease endocrine disease germany europe.

Schrader, T; Boyes, B; Matula, T; et al. (1998) In vitro investigation of toxaphene genotoxicity in s. Typhimurium and chinese hamster v79 lung fibroblasts. Mutat Res 413(2):159-168.
The polychlorinated pesticide toxaphene has been identified as a persistent environmental contaminant and is of particular concern in the Great Lakes and Arctic regions of Canada. Inconsistencies in published in vitro genotoxicology studies have hindered risk assessments of toxaphene exposure. When toxaphene mutagenicity was re-evaluated in the Ames Salmonella/microsome assay at 10-10,000 microg/plate, a dose-dependent increase in His revertants occurred in all five strains of S. typhimurium tested (TA97, TA98, TA100, TA102 and TA104) with higher mutation frequencies observed in the absence of S9 metabolic activation. However, the mutagenic potential of toxaphene was relatively low with concentrations greater than 500 microg/plate required to induce mutation. Toxaphene genotoxicity was also examined in a mammalian system using Chinese hamster V79 lung fibroblasts with metabolic activation provided by human HepG2 hepatoma cells. Genotoxicity of 1-10 microg/ml toxaphene was examined by measuring the frequency of sister chromatid exchange (SCE) and mutation induction at the hypoxanthine guanine phosphoribosyl transferase (HGPRT) gene locus. Although small increases in SCE were observed at toxic concentrations of toxaphene approaching the LD50 (10 microg/ml), they were not found to be statistically significant relative to control. Toxaphene was also unable to induce HGPRT mutagenesis at the concentrations tested. These results show that while toxaphene is a weak, direct-acting mutagen in the Ames Salmonella Test, convincing evidence of dose-dependent SCE induction and mutagenicity at the HGPRT gene locus could not be demonstrated in V79 cells.

Scippo, M; Argiris, C; Van De Weerdt, C; et al. (2004) Recombinant human estrogen, androgen and progesterone receptors for detection of potential endocrine disruptors. Analytical and Bioanalytical Chemistry 378(3):664-669.

Sobti, R; Krishan, A; Davies, J. (1983) Cytokinetic and cytogenetic effect of agricultural chemicals on human lymphoid cells in vitro. Ii. Organochlorine pesticides. Arch Toxicol 52(3):221-231.
Human lymphoid cells of LAZ-007 cell line, incubated with 10(-4) to 10(-6) molar of eight different organochlorine pesticides had dose related cytotoxicity, mitotic depression and cell cycle traverse inhibition. In cultures incubated with 10(-4) M concentrations, M1 metaphases were as high as 13% (Dicofol) as compared to less than 1% in the controls. The frequency of M3 metaphases in cultures incubated with 10(-6) M concentrations ranged from 11% (Chlordane) to 15% (Endosulfan) compared to 17% in control cultures. Statistically significant increase in SCE frequency was seen in cells exposed to Chlordane, Dicofol, Endosulfan and Toxaphene. On metabolic activation with rat liver microsomal S-9 enzymes, Chlordane, Dicofol and Tetradifon induced SCE frequency was higher than that of nonactivated cultures.

Soto, A; Chung, K; Sonnenschein, C. (1994) The pesticides endosulfan, toxaphene, and dieldrin have estrogenic effects on human estrogen-sensitive cells Environ Health Perspect 102(4):380-383.
Estrogenic pesticides such as DDT and chlordecone generate deleterious reproductive effects. An "in culture" bioassay was used to assess the estrogenicity of several pesticides. The E-screen test uses human breast estrogen-sensitive MCF7 cells and compares the cell yield achieved after 6 days of culture in medium supplemented with 5% charcoal-dextran stripped human serum in the presence (positive control) or absence (negative control) of estradiol and with estrogenic properties comparable to those of DDT and chlordecone; the latter are known to be estrogenic in rodent models. The E-screen test also revealed that estrogenic chemicals may act cumulatively; when mixed together they induce estrogenic responses at concentrations lower than those required when each compound is administered alone. Also may be used in Section(s): 4.1

Soto, A; Sonnenschein, C; Chung, K; et al. (1995) The e-screen assay as a tool to identify estrogens: An update on estrogenic environmental pollutants. Environ Health Perspect 103 Suppl 7113-122.
Estrogens are defined by their ability to induce the proliferation of cells of the female genital tract. The wide chemical diversity of estrogenic compounds precludes an accurate prediction of estrogenic activity on the basis of chemical structure. Rodent bioassays are not suited for the large-scale screening of chemicals before their release into the environment because of their cost, complexity, and ethical concerns. The E-SCREEN assay was developed to assess the estrogenicity of environmental chemicals using the proliferative effect of estrogens on their target cells as an end point. This quantitative assay compares the cell number achieved by similar inocula of MCF-7 cells in the absence of estrogens (negative control) and in the presence of 17 beta-estradiol (positive control) and a range of concentrations of chemicals suspected to be estrogenic. Among the compounds tested, several "new" estrogens were found; alkylphenols, phthalates, some PCB congeners and hydroxylated PCBs, and the insecticides dieldrin, endosulfan, and toxaphene were estrogenic by the E-SCREEN assay. In addition, these compounds competed with estradiol for binding to the estrogen receptor and increased the levels of progesterone receptor and pS2 in MCF-7 cells, as expected from estrogen mimics. Recombinant human growth factors (bFGF, EGF, IGF-1) and insulin did not increase in cell yields. The aims of the work summarized in this paper were a) to validate the E-SCREEN assay;

b) to screen a variety of chemicals present in the environment to identify those that may be causing reproductive effects in wildlife and humans; c) to assess whether environmental estrogens may act cumulatively; and finally d) to discuss the reliability of this and other assays to screen chemicals for their estrogenicity before they are released into the environment.

Squires, R; Saederup, E. (1989) Polychlorinated convulsant insecticides potentiate the protective effect of nacl against heat inactivation of [3h]flunitrazepam binding sites. J Neurochem 52(2):537-543.
Six polychlorinated convulsant insecticides that potently inhibit t-[35S]butylbicyclophosphorothionate ([35S]TBPS) binding to rat brain membranes also potentiate the protective effect of NaCl (200 mM) against heat inactivation of [3H]flunitrazepam binding sites on the same membranes. Similar effects were obtained with all "cage" convulsants tested. The rank order of potencies as heat protection potentiators was similar to the rank order of potencies as inhibitors of [35S]TBPS binding (alpha-endosulfan greater than endrin greater than dieldrin greater than toxaphene greater than lindane). alpha-Endosulfan and endrin are more potent in both respects than any previously reported picrotoxin-like (cage) convulsant, but are much less toxic to mammals. The greatly reduced toxicities of alpha-endosulfan and endrin in mammals may reflect partial gamma-aminobutyric acid (GABA)-neutral properties of these compounds. Time courses of heat inactivation of [3H]flunitrazepam binding sites in the presence of 200 mM NaCl plus saturating concentrations of endrin or picrotoxin revealed monophasic components constituting about 88% of the binding sites, suggesting that virtually all [3H]flunitrazepam binding sites are coupled to picrotoxin binding sites in the GABA/benzodiazepine/picrotoxin receptor complex. Protection against heat inactivation constitutes a useful tool for characterizing the various allosterically linked binding sites in neurotransmitter receptor complexes.

Steinel, H; Arlauskas, A; Baker, R. (1990) Sce induction and cell-cycle delay by toxaphene. Mutat Res 230(1):29-33.
Toxaphene is genotoxic in mammalian cell systems and also inhibits cell replication. It was therefore used to investigate possible masking of SCE induction due to cell-cycle delay. In this study, toxaphene-treated Chinese hamster lung (Don) cells exhibited a dose-dependent decrease in cell-cycle progression compared with untreated cells. At high, nontoxic toxaphene levels (15 micrograms/ml), cell cycling also slowed as the toxaphene treatment time was increased. Toxaphene induced significantly higher numbers of SCEs in treated cells, demonstrating a dose- and treatment time-relationship. Slopes of dose-response curves were 0.29, 0.43 and 0.77 SCE/micrograms toxaphene for 20.5 h, 24.5 h and 28.5 h incubation, respectively. There were no changes in SCE values in control cultures even when slower dividing cells were sampled e.g. at longer incubation times. Thus, higher SCE values in Chinese hamster cells were not associated per se with slower or more delayed cells. The results demonstrate that longer toxaphene treatment times were not necessary for obtaining sufficient harlequin-stained cells for SCE analysis, but that higher numbers of SCEs occurred in slower dividing cells, following prolonged incubation of cultures treated with toxaphene.

Thunberg, T; Ahlborg, U; Wahlstrom, B. (1984) Comparison between the effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin and six other compounds on the vitamin a storage, the udp-glucuronosyltransferase and the aryl hydrocarbon hydroxylase activity in the rat liver. Arch

Toxicol 55(1):16-19.
The effect of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), 2,3,7,8- tetrabromodibenzo -p-dioxin (TBrDD), 5-chloro-2-(2,4-dichlorophenoxy)phenol (3-Cl- predioxin) 4,5,6-trichloro-2-(2,4-dichlorophenoxy)phenol (5-Cl- predioxin), toxaphene, 3-methylcholanthrene (3-MC) and phenobarbital (PB) on the vitamin A storage, UDP-glucuronosyltransferase (UDPGT) and aryl hydrocarbon hydroxylase (AHH) activities in the liver of Sprague-Dawley rats was investigated. Vitamin A was determined as retinol by high pressure liquid chromatography. UDPGT was measured with p-nitrophenol as an aglycone and AHH with 3,4-benzopyrene as a substrate. Both in TCDD- and toxaphene-treated animals a reduced body weight gain was recorded, but no other overt signs of toxicity were seen in this study. Both the concentration and the total amount of hepatic retinol was significantly reduced in TCDD-, 3-MC-, PB- and TBrDD -treated animals. These compounds were also those which gave the most significant enzyme induction as regards the UDPGT and AHH activities. However, the reduction of hepatic retinol caused by these compounds did not correlate with the enzyme activities studied. When compared on a molecular basis, TCDD and TBrDD were in the order of several magnitudes more potent as reducers of hepatic retinol and likewise as enzyme inducers. Also may be used in Section(s): 4.2

Trottman, CH; Desaiah, D; Ho,IK. (1978) Effect of toxaphene on rat hepatic drug metabolizing enzymes. Pharmacologist 20(3): 199.
Abstract toxicity metabolism pento barbital aniline ethyl morphine demethylase.

Trottman, CH; Desaiah, D. (1978) Effect of toxaphene on atpase activities in mouse tissues. Fed Proceed 37(3): 502.
Abstract corn oil brain pesticide hepatic renal dys function sodium ion potassium ion magnesium ion.

Trottman, CH; Desaiah, D; Ho,IK. (1978) Effect of preexposure to toxaphene on rat hepatic drug metabolizing enzymes. Pharmacologist 20(3): 279

Trottman, C; Desaiah, D. (1979) Adenosine triphosphatase activities in brain, kidney and liver of mice treated with toxaphene. J Environ Sci Health B 14(4):393-404.
The sensitivity of Na+-K+ and Mg++ Adenosine Triphosphatases (ATPases) in mouse tissues to toxaphene, a highly chlorinated camphene, was determined both in vivo and in vitro. The brain and kidney Na+-K+ ATPase activities were significantly inhibited in vitro by toxaphene. Interestingly, the inhibition was not significantly increased with an increase in the concentration of toxaphene. The oligomycin-sensitive (mitochondrial Mg++ ATPase activities in mouse brain, kidney and liver fractions were significantly inhibited by toxaphene in a concentration-dependent fashion. The oligomycin-insensitive Mg++ ATPase in all tissues examined was also inhibited but less sensitive to toxaphene than mitochondrial Mg++ ATPase. In contrast to in vitro response, the brain ATPases were not altered in mice fed toxaphene by oral intubation for three days. The renal and hepatic ATPase activities were significantly decreased in toxaphene treated mice with the oligomycin-insensitive Mg++ ATPase activity being only slightly altered. Also may be used in Section(s): 3.2, 4.2, & 4.5

Trottman, C; Desaiah, D. (1983) Effect of toxaphene on the binding of 3h-labeled ouabain and dopamine to rat brain synaptosomes. Toxicol Lett 18(3):323-330.

The effects of toxaphene, a chlorinated hydrocarbon pesticide, on the binding of ouabain and dopamine to rat brain synaptosomes enriched with Na+-K+ ATPase were investigated. For in vitro assessment of the effects of toxaphene, the synaptosomes prepared from normal rats were used. For in vivo effects the rats were fed on 0, 50, 100, 150 and 200 ppm toxaphene mixed in their daily ration for 8 weeks. At the end of treatment the rats were killed and synaptosomes were prepared. Toxaphene inhibited Na+-K+ and Mg2+ ATPases of synaptosomes in vitro and the inhibition was significant and concentration-dependent. The IC50 values were about 30 and 12 microM toxaphene for Na+-K+ and Mg2+ ATPases, respectively. However, much higher concentrations of toxaphene were required to inhibit the binding of [3H]ouabain and [3H]dopamine to synaptosomes. A 50% inhibition of ouabain and dopamine binding was obtained at 150 and 200 microM of toxaphene. The enzyme activities of synaptosomes in toxaphene-pretreated rats were decreased significantly. However, a dose-dependent decrease was not observed. The rats receiving dosages of 100 ppm and above showed a 30-40% decrease in enzyme activities. The binding of ouabain and dopamine to synaptosomes of toxaphene-pretreated rats showed no significant changes as compared to controls. The present in vitro results suggest that toxaphene may be an effective inhibitor of ATPases with substantial effects on the binding of ouabain and dopamine to rat brain synaptosomes. However, data obtained through in vivo studies do not support this contention. The reason for this discrepancy may be that the toxaphene is being rapidly metabolized or might not have reached the site of action. Also may be used in Section(s): 4.5

Trottman, C; Prasada Rao, K; Morrow, W; et al. (1985) In vitro effects of toxaphene on mitochondrial calcium atpase and calcium uptake in selected rat tissues. Life Sci 36(5):427-433. In vitro effects of toxaphene on Ca2+-ATPase activity and 45Ca2+-uptake were studied in mitochondrial fractions of heart, kidney and liver tissues of rat. Mitochondrial fractions were prepared by the conventional centrifugation method. Ca2+-ATPase activity was determined by measuring the inorganic phosphate liberated during ATP hydrolysis. Toxaphene inhibited Ca2+-ATPase in a concentration dependent manner in all the three tissues. Substrate activation kinetics, with heart, kidney and liver tissue fractions, revealed that toxaphene inhibited Ca2+-ATPase activity non-competitively by decreasing the maximum velocity of the enzyme without affecting the enzyme-substrate affinity. Toxaphene also inhibited mitochondrial 45Ca2+-uptake in the three selected tissues in a concentration dependent manner. These results indicate that toxaphene is an inhibitor of mitochondrial Ca2+-ATPase and calcium transport in heart, kidney and liver tissues of rat. Also may be used in Section(s): 3.2 & 4.4

Trottman, C; Moorthy, K; Desaiah, D. (1986) Inhibition of calmodulin-regulated calcium pump activity in rat brain by toxaphene. 70th Annual Meeting of the Federation of American Societies for Experimental Biology, St Louis, Mo, USA, Apr 13-18, 1986 Fed Proc 45(4):1051. Biosis copyright: biol abs. rrm abstract. Also may be used in Section(s): 4.5

USEPA. (1978) Occupational exposure to toxaphene. A final report by the epidemiological studies program. Oppts.

Vachkova-Petrova, R. (1978) Mutagenic activity of pesticides. Khig Zdraveopaz 21(5):496-506. PESTAB. Studies on the mutagenicity of pesticides in plants, Drosophilia, mammalian cell cultures, human cell cultures, and human lymphocytes are reiewed. Dichlorovos, 2,4,5-T, CMK,

ceresan M, and ferbam were found to be mutagenic in the Drosophilia test. Diazinon, dimethoate, dichlorvos, malathion, methyl parathion, trichlorfon, DDT and its isomers, polychlorocamphene (toxaphene), lindane, 2,4-D, 2,4,5-T, zineb, and ziram were found to be mutagenic in human cell cultures and/or lymphocytes.

Wade, M; Desaulniers, D; Leingartner, K; et al. (1997) Interactions between endosulfan and dieldrin on estrogen-mediated processes in vitro and in vivo. Reprod Toxicol 11(6):791-798.
There is growing concern that estrogenic chemicals, both natural and human-made, may be causing a variety of reproductive disorders in wildlife and human populations. Recent in vitro data suggest that the interaction between some weakly estrogenic organochlorines, dieldrin, endosulfan, toxaphene, and chlordane, causes a synergistic increase in their estrogenic potency, an effect due to joint action on estrogen receptors (ER). As these studies were conducted using models of estrogen action derived from cells that are not physiologically controlled by estrogens, the relevance of these findings to human health are not clear. The present studies were conducted to examine the interaction between endosulfan and dieldrin in the activation of ER in or extracted from mammalian cells. Endosulfan and dieldrin showed no synergism in displacing 3H-E2 from rat uterine ER or in inducing the proliferation of MCF-7 breast cancer cells, an estrogen-dependent response. Furthermore, endosulfan (0.1 mg per animal per d) or dieldrin (0.1 mg), alone or in combination, injected intraperitoneally daily for 3 d, did not stimulate any uterotrophic activity nor had any effect on pituitary prolactin or other endocrine-related endpoints in immature female rats. These studies demonstrate that these weakly estrogenic compounds do not interact in a synergistic fashion in binding to ER or in activating ER-dependent responses in mammalian tissues or cells. Thus, these results suggest that coexposure to these weakly estrogenic environmental contaminants likely will not cause human reproductive toxicity related to estrogen action.

Whitcomb, E; Santolucito, J. (1976) The action of pesticides on conduction in the rat superior cervical ganglion. Bull Environ Contam Toxicol 15(3):348-356.
The preganglionic and postganglionic transmission and the O2 consumption of the superior cervical ganglion of the adult male Holtzman rat were measured in vitro following the onset of symptoms after oral dosing with chlordane, sevin (carbaryl), DDT, lindane, toxaphene, DFP, parathion, paraoxon, and nicotine. None of the parameters measured suggested that the sodium channels in the nerve membrane were altered after chlorinated hydrocarbon treatment. There was no evidence of spontaneous firing of the preganglionic and postganglionic fibers in Ca ion-free or Ca ion-containing media from animals treated with these compounds. The only significant difference between the chlorinated hydrocarbon group and the nontreated controls was a decreased postgangloionic area for the terminal 1 Hz stimulation in the DDT-treated animals. This appeared to be a synaptic transmission effect rather than an axonal transmission effect. The addition of paraoxon in vitro significantly reduced the uptake of O2 in the superior cervical ganglion and portions of the central nervous system. The data supports the conclusion that no significant inhibition of oxygen uptake occurs in cerebral preparations from animals killed during the first excitatory period of poisoning.

Williams, G. (1981) An epigenetic mechanism of carcinogenicity of organochlorine pesticides. In: (Khan MAQ; Stanton RH, eds.) Toxicology of halogenated hydrocarbons: Health and ecological effects. New York: Pergamon Press; pp. 161-242.

Woolley, D. (1995) Organochlorine insecticides neurotoxicity and mechanisms of action. Chang, L W and R S Dyer (Ed) Neurological Disease and Therapy, Vol 36 Handbook of Neurotoxicology Xxi+1103p Marcel Dekker, Inc: New York, New York, USA BASEL, SWITZERLAND. ISBN 0-8247-8873-7.; 0(0):475-510.
Biosis copyright: biol abs. rrm book chapter human ddt lindane dieldrin polychlorocycloalkanes convulsants environmental pollution metabolism mechanisms.

Yamasaki, H. (1990) Gap junctional intercellular communication and carcinogenesis. Carcinogenesis 11(7):1051-1058.

Yang, C; Chen, S. (1999) Two organochlorine pesticides, toxaphene and chlordane, are antagonists for estrogen-related receptor alpha-1 orphan receptor. Cancer Research 59(18):4519-4524.
Estrogen-related receptor (ERR) alpha-1 shares a high amino acid sequence homology with estrogen receptor alpha. Although estrogens are not ligands of ERR alpha-1, our recent results suggest that toxaphene and chlordane, two organochlorine pesticides with estrogen-like activity, behave as antagonists for this orphan nuclear receptor. The two compounds increased ERR alpha-1-mediated expression of the reporter enzyme beta-galactosidase in a yeast-based assay. The screen was developed by expressing the hERR alpha-1-yeast Gal 4 activation domain fusion protein in yeast cells carrying the beta-galactosidase reporter plasmid, which contains an ERR alpha-1-binding element. In transfection experiments using mammalian cell lines, such as the SK-BR-3 breast cancer cell line, the compounds were found to have an antagonist activity against ERR alpha-1-mediated expression of the reporter chloramphenicol acetyltransferase. In contrast to the findings with ERR alpha-1, the two compounds were found to slightly induce the estrogen receptor a-mediated expression of chloramphenicol acetyltransferase in SK-BR-3 cells. In a ligand-independent manner, the ERR alpha-1 activity in SK-BR-3 cells was induced 3-fold by cotransfection with the GRIP1 coactivator expression plasmid. Toxaphene was found to be capable of suppressing the GRIP1 coactivator-induced ERR alpha-1 activity in SK-BR-3 cells. In addition, a stable ERR alpha-1 expressing HepG2 hepatoma cell line was generated, and the aromatase activity in the transfected cell line was found to be twice that in the untransfected cell line. The enzyme aromatase converts androgens to estrogens, and aromatase expression in HepG2 cells is regulated in part by an ERR alpha-1-modulating promoter. A 24-h incubation of an ERR alpha-1-transfected HepG2 cell line with 10 microM toxaphene reduced its aromatase activity to the level in the untransfected cell line. Because toxaphene is not an inhibitor of aromatase, it is thought that the decrease of the aromatase activity in ERR alpha-1 transfected HepG2 cells following toxaphene treatment resulted from a suppression of the aromatase expression by toxaphene acting as the antagonist of ERR alpha-1. Toxaphene and chlordane are among the 12 persistent organic pollutants identified by the United Nations Environment Programme as requiring urgent attention. Their antagonistic effects on ERR alpha-1 should not be overlooked.

Young, J; Freeman, A. (2001) Bioavailability and mutagenicity of toxaphene after aging in anoxic soil environments. Report of work conducted under agreement 9c-r570 nasa with usepa's ord.

Young, J; Freeman, A. (2004) Comparing the mutagenicity of toxaphene after aging in anoxic soils and accumulating in fish. Report of work conducted under agreement ic-r234 nasa with usepa's ord.

4.6. SYNTHESIS OF MAJOR NONCANCER EFFECTS

Bakale, G; McCreary, R. (1992) Response of the ke test to nci/ntp-screened chemicals. Ii. Genotoxic carcinogens and non-genotoxic non-carcinogens. Carcinogenesis 13(8):1437-1445.
A physico-chemical carcinogen-screening test was used to measure the rate constants of electron attachment, kes, of 105 chemicals that had been screened in long-term rodent bioassays and short-term in vitro tests by the NCI/NTP. In the ke test, a pulse-conductivity technique is used to generate and monitor the decay of excess electrons that serve as nucleophilic surrogates for the target tissue of rodents. Of the 61 chemicals that had been found to be rodent carcinogens as well as Salmonella mutagens, 36 yield kes that are equal to or greater than the diffusion-controlled ke of carbon tetrachloride and are considered to be positive ke test responses. In contrast, 29 of the remaining 44 chemicals that are putative non-carcinogens and non-mutagens yield kes that are negative ke test responses. These results are combined with the ke responses of 46 non-mutagenic carcinogens and 20 mutagenic non-carcinogens that were reported earlier and are evaluated to determine the degree to which the measure of electron-accepting capacity that ke provides complements or overlaps the electrophilicity or DNA reactivity of chemicals that is indicated by positive mutagenicity responses in the Ames Salmonella tester strains or by positive structural alerts, S/As, of the chemicals. The combined ke test results indicate that the overall predictivity of the ke test is comparable to and complements the Ames Salmonella test and S/As in identifying rodent carcinogens. Moreover, the electrons serve as non-discriminate nucleophilic targets for both genotoxic and non-genotoxic electron-accepting molecules and appear to attach with equal efficiency to carcinogens that are active in various tissues of rodents. This property of excess electrons suggests that the predictivity of the ke test could be enhanced by combining the measured ke with an appropriate lipophilicity or pharmacokinetic parameter. A pre-chemical electron-transfer step that had been proposed to precede chemical interactions between the carcinogen and target tissue is discussed in light of recent developments in electron-donor/-acceptor chemistry and in the application of structure--activity relationships to identify carcinogens.

Bayoumi, A; García Fernández, A; Ordoñez, C; et al. (1998) Cytotoxic evaluation of organochlorine insecticides and metals in vitro on cho-k1 cell lline using four different alternative methods. Rev Toxicol 15(2):73-78.
The cytotoxicity of twelve organochlorine insecticides and seven metals has been evaluated by four different in vitro alternative methods using the established CHO-K1 cell line as a mammalian model. The assessed techniques represent distant endpoints, neutral red (NR) assay, methyl tetrazolium test (MTT) assay, total cell protein content assay and lactate dehydrogenase (LDH) leakage test. Results of the first three in vitro methods showed that, the sequence of potency for the tested insecticides was p,p´-TDE > p,p´-DDT > p,p´-DDE and/or methoxychlor as a dichlorodiphenyethanes derivatives. In case of the hexachlorocyclohexane isomers and cyclodiene derivatives, the results of both NR and total cell protein content assays showed that the mix of isomers of HCH were more toxic than the gamma isomer (lindane), and the derivatives of cyclodiene, displayed the following order of toxicity ranking chlordane >

heptachlor > aldrin > endosulfan > toxaphene. The MTT test showed different results in the sequence of potency of the hexachlorocyclohexane isomers and cyclodiene derivatives. According to NR and total cell protein content assays the toxicity of the tested metals was in the following rank order: Hg2+ > Cd2+ > Cu2+ > Zn2+ > Co2+ > Ni2+ > Pb2+, while MTT test exhibited the toxicity ranking as Hg2+ > Cd2+ > Zn2+ < Cu2+ > Ni2+ > Co2+ > Pb2+. Furthermore, the total cell protein content assay had the highest sensitivity, for p,p´-TDE, p,p´-DDT, p,p´-DDE, methoxychlor, HCH, lindane and toxaphene. Conversely, MTT test was more sensitive than the other tests against aldrin, dieldrin and endosulfan, while the NR assay had higher sensitivity than the other tests against chlordane and heptachlor. In case of the tested metals, the sequence of sensitivity between the followed methods was : MTT > NR > protein content assay. According to the LDH leakage test, it could not be reach to the midpoint cytotoxicity value to the majority of the tested agents.

Beal, D. (1990) Use of mouse liver tumor data in risk assessments performed by the u.S. Environmental protection agency. Prog Clin Biol Res 3315-18.
In summary, the EPA has begun to look critically at the induction of certain types of tumors in certain species, including liver tumors in mice. The controversy over the use of such tumor data in assessing the cancer risk for humans has been going on for some time. The present agency policy is to downgrade the weight of evidence for such data under certain conditions. Review of the cancer risk assessments for the 109 chemicals that the agency has formally verified shows that a variety of chemicals yield liver tumors in mice. However, one group of substances that consistently produced such tumors was chlorinated compounds (84%). Many of these compounds not only induced liver tumors in mice but also induced liver tumors in rats and/or other types of tumors in mice and rats. However, several of the chlorinated compounds produced only mouse liver tumors. Another group of compounds that often induced liver tumors in mice was nitrogen-containing compounds (aromatic amines, hydrazines, nitrosamines). These latter substances tended to not only induce liver tumors in mice but also a variety of other tumor types in a variety of species. Mouse liver tumor data have played a major role in the classification of substances in categories B2 and C. Fifty-six percent of the chemicals in category B2 and 40% in category C were classified based at least partially on the use of mouse liver tumor data. In addition, 21 of the 29 category B2 chemicals that produced liver tumors in mice and 5 of the 8 category C chemicals are chlorinated compounds. These two results indicate the importance of chlorinated compounds to the agency, and therefore, the importance of mouse liver tumor data in agency cancer risk assessments.

Benigni, R. (1990) Rodent tumor profiles, salmonella mutagenicity and risk assessment. Mutat Res 244(1):79-92.
The tumorigenesis profiles of 116 chemicals, which proved to induce cancer in the NCI/NTP experimentation, were studied by multivariate data analysis methods. Three main patterns of tumor induction were evident. One chemical (benzene) was not classifiable in any of the 3 clusters of chemicals. The carcinogen classes based on patterns of tumor induction did not reflect a repartition between Ames-positive and Ames-negative chemicals. Therefore any classification of carcinogens as either 'primary' (genotoxic, hence assumed to pose a greater risk) or 'secondary' (presumably carcinogenic via non-genotoxic mechanisms) would seem to be a subject for research and speculation, and, for the present, an unsuitable basis for risk assessment.

Chen, S; Zhou, D; Yang, C; et al. (2001) Modulation of aromatase expression in human breast tissue. J Steroid Biochem Mol Biol 79(1-5):35-40.
Aromatase plays an important role in breast cancer development through its role in the synthesis of estrogen. Aromatase expression in breast tissue can be regulated by several mechanisms. The major promoter usage for aromatase expression in breast tumors (i.e. cAMP-stimulated promoters I.3 and II) is different from that in normal breast tissue (i.e. glucocorticoid-stimulated promoter I.4). Recent characterization of transcription factors that interact with the two important regulatory elements near promoters I.3 and II, i.e. S1 and CREaro, helps us better understand the mechanism of the switch of promoter usage between normal breast tissue and cancer tissue. It is thought that in normal breast tissue, the function of promoters I.3 and II is suppressed through the binding of EAR-2, COUP-TFI, and EARgamma to S1, and through the binding of Snail/Slug proteins to their binding site that quenchs the CREaro activity. In cancer tissue, the expression levels of EAR-2, COUP-TFI, EARgamma, Snail, and Slug decrease, and aromatase expression is then up regulated through the binding of ERRalpha-1 to S1 and the binding of CREB or related factors to CREaro. Results from this and other laboratories reveal that aromatase activity in aromatase expressing cells can also be modified by treatment with aromatase inhibitors and the antiestrogen ICI 182, 780. While aromatase inhibitors are used to treat breast cancer, the treatment has been found to increase the level of aromatase in the breast tissue of some patients. The enhancement of aromatase activity by aromatase inhibitors is thought to be due to a decrease of aromatase protein degradation by enzyme-inhibitor complex formation, up-regulation of the aromatase gene transcription through a cAMP-mediated mechanism, and an induction of aromatase expression by gonadtropins that are released from the pituitary in response to a reduction of estrogen levels in circulation in premenopausal women. Antiestrogen ICI 182, 780 has been found to suppress aromatase expression, but the mechanism has not yet been determined. In addition, aromatase activity and expression can be affected by environmental chemicals. A detailed structure-function study has revealed that flavones, but not isoflavones, are inhibitors of aromatase. It was found that flavones bind to the active site of aromatase in an orientation in which their rings-A and -C mimic rings-D and -C of the androgen substrate. The modulation of aromatase expression by endocrine disrupting chemicals is exemplified by two organochlorine pesticides (i.e. toxaphene and chlordane) that have been found to be antagonists of ERRalpha-1 orphan receptor. These compounds reduce ERRalpha-1 activity, resulting in a suppression of aromatase expression. Also may be used in Section(s): 4.2

Dybing, E; Sanner, T; Roelfzema, H; et al. (1997) T25: A simplified carcinogenic potency index: Description of the system and study of correlations between carcinogenic potency and species/site specificity and mutagenicity. Pharmacol Toxicol 80(6):272-279.
A simplified carcinogenic potency index, the T25, is proposed as a practical method for the inclusion of potency considerations in carcinogen classification systems. The T25 is the chronic daily dose in mg per kg bodyweight which will give 25% of the animals tumours at a specific tissue site, after correction for spontaneous incidence, within the standard life span of that species. Calculated T25 values of a set of 113 US National Cancer Institute/National Toxicology Program (NC/NTP) carcinogens showed excellent correlation (correlation coefficient 0.96, $P < 0.0001$) with the carcinogenic potency index TD50 of Peto et al. (1984). The mean of T25 values for 51 transspecies, multiple common site NCI/NTP carcinogens were 10-fold lower than those for 62 NCI/NTP single species, single site carcinogens. For these 113 carcinogens, the mean T25 values were approximately 3-fold lower for agents that were also mutagenic in Salmonella

compared to the non-mutagenic agents.

Hedli, C; Snyder, R; Kinoshita, F; et al. (1998) Investigation of hepatic cytochrome p-450 enzyme induction and DNA adduct formation in male cd/1 mice following oral administration of toxaphene. J Appl Toxicol 18(3):173-178.
Exposure of experimental animals to toxaphene induces hepatic cytochrome P-450 (CYP). Although chronic administration of toxaphene to mice was found to cause an increased incidence of liver tumors, a mechanism for its carcinogenicity has yet to be elucidated. We investigated two potential mechanisms of toxaphene-induced carcinogenicity: peroxisomal proliferation and DNA binding. Peroxisomal proliferation was evaluated by measuring the level of immunodetectable CYP 4A1, an isozyme of CYP that is specifically induced by peroxisomal proliferators, in hepatic microsomes from CD1 mice that were treated by oral gavage for seven consecutive days with corn oil vehicle or 10, 25, 50 or 100 mg kg(-1) toxaphene. In comparison to control mice, toxaphene-treated mice had increased liver weight, increased liver/body weight ratios and increased levels of total hepatic CYP and cytochrome b5. No increase in the level of immunodetectable levels of CYP 4A1 was found in hepatic microsomes from toxaphene-treated mice when compared to controls. In contrast, increases in immunodetectable CYP 4A1 were detected in hepatic microsomes from mice treated with the peroxisomal proliferator clofibrate. These findings suggest that toxaphene-induced induction of CYP may not involve CYP 4A1 and that peroxisomal proliferation may not be involved in toxicity. Significant increases in immunodetectable levels of CYP 2B were, however, detected in toxaphene-treated mice, and are consistent with earlier reports demonstrating that toxaphene, like many other pesticides, induces the phenobarbital-inducible subfamily of CYP. Analysis of DNA adduct levels in the livers of toxaphene-treated mice by DNA 32P-post-labeling showed no evidence of DNA adduct formation. Also may be used in Section(s): 3.1, 3.2, 4.2

Kang, K; Wilson, M; Hayashi, T; et al. (1996) Inhibition of gap junctional intercellular communication in normal human breast epithelial cells after treatment with pesticides, pcbs, and pbbs, alone or in mixtures. Environ Health Perspect 104(2):192-200.
Chemical pollutants in the Great Lakes have found their way through the food chain into humans because of their environmental persistence and lipophilicity. Some epidemiological studies have claimed an association between metabolites of 2,2-bis(p-chlorophenyl)-1,1,1-trichloroethane (DDT), polychlorinated biphenyls (PCBs), and polybrominated biphenyls (PBBs) and breast cancer, but others have reported no such association. We examined various halogenated hydrocarbons for their capacity to inhibit gap junctional intercellular communication (GJIC) in normal human breast epithelial cells (HBEC) when given as single compounds or as mixtures. The scrape-loading/dye transfer and fluorescent redistribution after photobleaching techniques were used to measure GJIC; immunostaining and Western and Northern analyses were performed on connexin 43 (Cx43) gap junction protein and message to determine how halogenated hydrocarbons might affect GJIC. DDT, dieldrin, and toxaphene inhibited GJIC in a dose-responsive manner after 90 min treatments. Dieldrin suppressed GJIC within 30 min with no recovery after 24 hr. Inhibition of GJIC by DDT and toxaphene was partially restored after 12 hr and fully restored after 24 hr. Several PCB and PBB congeners inhibited GJIC in a dose-responsive and time-dependent manner, but GJIC was almost restored to control values 24 hr after exposure. The highest concentrations of the individual chemicals that did not inhibit GJIC was determined, and mixtures containing two of these chemicals were tested for their ability to

inhibit GJIC. Significant inhibition of GJIC was observed when cells were treated with a mixture of DDT and 2,4,5-hexachlorobiphenyl (2,4,5-HCB), dieldrin and 2,4,5-HCB, or dieldrin and 2,4,5-hexabromobiphenyl (2,4,5-HBB). These results indicate that halogenated hydrocarbons, alone or in specific combinations, can alter GJIC at the post-translational level. These results are consistent with the hypothesis that DDT, dieldrin, toxaphene, 2,3,4-HCB, 2,4,5-HCB, and 2,4,5-HBB could have tumor-promoting potential in human breast tissue.

Kolaja, KL; Engelken, DT; Klaassen, CD. (2000) Inhibition of gap-junctional-intercellular communication in intact rat liver by nongenotoxic hepatocarcinogens. Toxicology 146(1):15-22.
Many nongenotoxic hepatocarcinogens can induce cell proliferation, and inhibit apoptosis and gap-junctional-intercellular communication (GJIC). GJIC, the movement of small molecules (less than 1.2 kD) through membrane channels, is important in regulating cellular homeostasis and differentiation. The inhibition of hepatic GJIC can increase cell proliferation and possibly, inhibit apoptosis. In this study, the relationship between hepatic GJIC, proliferation, and apoptosis was examined in rats treated for 7 days with tumor-promoting doses of the nongenotoxic hepatocarcinogens phenobarbital (PB; 800 ppm), pregnenolone-16alpha-carbonitrile (PCN; 1000 ppm), and Aroclor 1254 (PCB; 100 ppm). In addition, 3-methylcholanthrene (3MC) was included as a negative control. PB, PCN, and PCB increased parenchymal-cell proliferation and inhibited hepatic apoptosis, while no alteration in these growth parameters was observed in 3MC-treated rats. GJIC, as measured by fluorescent-dye transfer through intact liver, was decreased nearly 50% by PB, PCN, and PCB, yet no effect on GJIC was observed in liver from 3MC-treated rats. These data indicate that compounds that inhibit GJIC in liver may be nongenotoxic hepatocarcinogens, which occurs simultaneously during increased cell proliferation and inhibited apoptosis.

Krutovskikh, VA; Oyamada, M; Yamasaki, H. (1991) Sequential changes of gap-junctional intercellular communications during multistage rat liver carcinogenesis: Direct measurement of communication in vivo. Carcinogenesis 12(9):1701-1706.
We have developed a simple method to measure gap-junctional intercellular communication (GJIC), by means of microinjection/dye transfer assay, in liver slices freshly removed from the rat. Using this method and immunostaining of connexin 32 (cx32), the major liver gap junction protein, we studied sequential changes of GJIC during chemical hepatocarcinogenesis in male Fischer-344 rats under a modified Solt-Farber protocol (3 weeks 4 day exposure regimen). Four weeks after commencement of the protocol, there was a substantial decrease in GJIC in the liver parenchyma, which was free from focal lesions. The decrease in GJIC persisted up to at least the 15th week of treatment, while a decrease in the number of immunoreactive cx32 spots was evident only at 4 weeks of post-protocol commencement. Most enzyme-altered (GST-P-positive) focal lesions showed markedly lower GJIC and a significantly lower number of cx32-positive spots than surrounding hepatocytes. Most GST-P-positive foci showed a selective lack of GJIC with surrounding heptocytes. Hepatocellular carcinomas arising 1 year after the carcinogenic regimen had significantly reduced communicational capacity accompanied by a large decrease in cx32 expression. These results suggest that a progressive decrease in homologous as well as heterologous GJIC in preneoplastic lesions occurs during rat hepatocarcinogenesis, and that preneoplastic lesions with the most prominent disorders in GJIC may be more likely to develop into carcinomas.

McConnell, E. (1990) Mouse liver tumors the problem. Stevenson, D E, Et Al (Ed) Progress in Clinical and Biological Research, Vol 331 Mouse Liver Carcinogenesis: Mechanisms and Species Comparisons SYMPOSIUM, AUSTIN, TEXAS, USA, NOVEMBER 30-DECEMBER 3, 1988. XIX+444P. WILEY-LISS, NEW YORK, NEW YORK, USA. ILLUS. ISBN 0-471-56695-0.; 0(0):1-4.

Moser, G; Smart, R. (1989) Hepatic tumor-promoting chlorinated hydrocarbons stimulate protein kinase c activity. Carcinogenesis 10(5):851-856.
Various chlorinated hydrocarbons, many of which are known hepatic tumor promoters, have been evaluated for their ability to stimulate protein kinase C (PKC) activity in vitro. Chlordane, kepone, toxaphene, heptachlor, 2,2-bis(4-chlorophenyl)-1,1-dichloroethane, the polychlorinated biphenyl Aroclor 1254, aldrin, 2,2-bis(4-chlorophenyl)-1,1,1-trichloroethane (DDT) and gamma-hexachlorocyclohexane (lindane) were the most potent stimulators of PKC activity. Of these compounds, chlordane was the most potent organochlorine pesticide. Chlordane (100 microM) stimulated mouse brain PKC activity in the 10(5) g supernatant to a maximum velocity equal to that obtained when the enzyme was maximally stimulated with the skin-tumor-promoting phorbol ester, 12-O-tetradecanoylphorbol-13-acetate (TPA). Chlordane concentrations as low as 1 microM significantly stimulated PKC activity. Chlordane-stimulated PKC activity was calcium-dependent, and in the presence of exogenous calcium, chlordane-stimulated PKC activity was at least 5-fold greater than in the absence of added calcium. In contrast, the addition of calcium only minimally affected (less than 30% increase) the TPA-stimulated PKC activity. Concentrations of TPA and chlordane which maximally stimulate PKC did not produce an additive effect on PKC activity. Chlordane- and TPA- stimulated PKC activity was phospholipid-dependent and could be inhibited by quercetin, a known inhibitor of PKC activity. Chlordane in the presence of calcium also stimulated mouse epidermal and hepatic PKC as well as purified rat brain PKC. These results demonstrate that a wide variety of chlorinated hydrocarbons, which are considered hepatic tumor promoters, stimulate protein kinase C activity in vitro.

Rattenborg, T; Gjermandsen, I; Bonefeld-Jorgensen, E. (2002) Inhibition of e2-induced expression of brca1 by persistent organochlorines. Breast Cancer Research 4(6):R12.
BACKGROUND: Environmental persistent organochlorines (POCs) biomagnify in the food chain, and the chemicals are suspected of being involved in a broad range of human malignancies. It is speculated that some POCs that can interfere with estrogen receptor-mediated responses are involved in the initiation and progression of human breast cancer. The tumor suppressor gene BRCA1 plays a role in cell-cycle control, in DNA repair, and in genomic stability, and it is often downregulated in sporadic mammary cancers. The aim of the present study was to elucidate whether POCs have the potential to alter the expression of BRCA1. METHODS: Using human breast cancer cell lines MCF-7 and MDA-MB-231, the effect on BRCA1 expression of chemicals belonging to different classes of organochlorine chemicals (the pesticide toxaphene, 2,3,7,8-tetrachlorodibenzo-p-dioxin, and three polychlorinated biphenyls [PCB#138, PCB#153 and PCB#180]) was measured by a reporter gene construct carrying 267 bp of the BRCA1 promoter. A twofold concentration range was analyzed in MCF-7, and the results were supported by northern blot analysis of BRCA1 mRNA using the highest concentrations of the chemicals. RESULTS: All three polychlorinated biphenyls and 2,3,7,8-tetrachlorodibenzo-p-dioxin reduced 17beta-estradiol (E2)-induced expression as well as basal reporter gene

expression in both cell lines, whereas northern blot analysis only revealed a downregulation of E2-induced BRCA1 mRNA expression in MCF-7 cells. Toxaphene, like E2, induced BRCA1 expression in MCF-7. CONCLUSION: The present study shows that some POCs have the capability to alter the expression of the tumor suppressor gene BRCA1 without affecting the cell-cycle control protein p21Waf/Cip1. Some POCs therefore have the potential to affect breast cancer risk.

Rought, S; Yau, P; Chuang, L; et al. (1999) Effect of the chlorinated hydrocarbons heptachlor, chlordane, and toxaphene on retinoblastoma tumor suppressor in human lymphocytes. Toxicol Lett 104(1-2):127-135.
Organochlorine use over the past 50 years has resulted in the contamination of soil, water, plant and animal species. This contamination has created a long-lasting environmental problem, as the members of the organochlorine class of pesticides are resistant to degradation and have been labeled as persistent bioaccumulators. Studies have shown certain organochlorines to be tumor promoters, liver toxicants and to induce immune cell dysfunction in rats and mice. Our laboratory has shown that the organochlorines heptachlor and chlordane affect leukocytic gene expression and differentiation. In this study, experiments with CEM x 174 cells, a hybrid of human T and B cells, were performed to investigate the effects of the tumor promoter heptachlor and its congeners chlordane and toxaphene on retinoblastoma (Rb) gene expression. The results indicated that heptachlor, chlordane or toxaphene, in the range of 10-50 microM, were able to reduce Rb protein levels in a concentration-dependent manner. In the case of heptachlor, the reduction could be seen as early as 12 h and was time-dependent. Analysis of Rb mRNA levels revealed no detectable difference over the same concentration range. These results suggest that members of the organochlorine class are able to downregulate Rb expression at the post-transcriptional level, an effect similar to that on p53 tumor suppressor previously reported by our laboratory. Also may be used in Section(s): 4.5

Trosko, J; Jone, C; Chang, C. (1987) Inhibition of gap junctional-mediated intercellular communication in vitro by aldrin, dieldrin, and toxaphene: A possible cellular mechanism for their tumor-promoting and neurotoxic effects. Mol Toxicol 1(1):83-93.
Several mechanisms have been postulated to be responsible for the pleiotropic effects of toxic chemicals. Although the cytotoxicity and mutagenicity of chemicals are well studied and relatively easily detected, the noncytotoxic and nonmutagenic (i.e., epigenetic) mechanisms of chemical toxicity are less well understood. An in vitro assay, using cocultures of Chinese hamster cells to measure metabolic cooperation between V79 6-thioguanine-sensitive (6TGs) and resistant (6TGr) cells, has been developed to detect noncytotoxic and nonmutagenic chemicals that inhibit, quantitatively, gap junctional communication. The insecticides aldrin, dieldrin, and toxaphene, known to have pleiotropic toxic effects in animals, were shown to inhibit gap junctional communication. Interpretation of results suggests that chemical inhibition of gap junctional communication could be a possible mechanism to explain their tumor-promoting and neurotoxic effects. Also may be used in Section(s): 4.4

Wang, G. (1984) Evaluation of pesticides which pose carcinogenicity potential in animal testing. Ii. Consideration of human exposure conditions for regulatory decision making. Regul Toxicol Pharmacol 4(4):361-371.
In reaching a regulatory decision on the use of pesticides with carcinogenic potential, it is of

great importance to investigate the extent of dermal exposure and absorption of a pesticide to users and field workers. By applying this information, along with the appropriate carcinogenicity categorization of a pesticide, a reasonably sound regulatory decision can be derived. Seven pesticides were selected, based on adequacy of tumor data, and were taken through the tumor evaluation system as reported in Part I 1984, Regul. Toxicol. Pharmacol. 4, 355-360). A step-by-step analysis on how a regulatory decision is reached on each pesticide by the EPA and CDFA was discussed. Also may be used in Section(s): 4.2

Waritz, R; Steinberg, M; Kinoshita, F; et al. (1996) Thyroid function and thyroid tumors in toxaphene-treated rats. Regul Toxicol Pharmacol 24(2 Pt 1):184-192.
Historically, a direct and irreversible genotoxic reaction of a xenobiotic with DNA has been considered to be a universal and obligatory initiating event in the etiology of neoplasia, and it was assumed therefore that (1) there was no threshold other than zero exposure for cancer initiation, and (2) like radiation, exposure was additive over a lifetime. Human exposure to xenobiotics causing neoplasia in laboratory rodents has been regulated in many countries on that basis. In the last decade evidence has accumulated indicating that some neoplasia in laboratory rodents may not be caused by a direct and irreversible interaction of xenobiotics with DNA. In addition, it has been found that some neoplasia caused in laboratory rodents by xenobiotics may not be relevant for biochemical/physiological reasons. This has raised the question whether human exposure to these xenobiotics should be regulated by the no-threshold philosophy used for direct-acting genotoxic xenobiotics or whether they can be regulated by the threshold philosophy used for classical xenobiotic-induced toxic effects. In a bioassay carried out by the National Cancer Institute and published in 1979, toxaphene was found to cause an increase in the occurrence of two spontaneously occurring tumors in laboratory rodents that since have been found to have both genotoxic and nongenotoxic etiologies in laboratory rodents. Experiments described in this paper are part of a program to help elucidate whether the increased incidence of these two neoplasms in laboratory rodents could have had a nongenotoxic origin, and thus whether toxaphene could be regulated by a threshold approach. Forty male rats were orally intubated with 100 mg/kg/day technical grade toxaphene in corn oil for 3 days. The dose was reduced to 75 mg/ kg/day on Day 4 due to toxicity. This lower dose was administered daily for 25 days. Another group of 40 male rats was orally gavaged daily with equivalent volumes of corn oil. After 0, 7, 14, and 28 doses, 10 test and 10 vehicle control animals were sacrificed for gross and histopathological examination of thyroid, parathyroid, and pituitary glands. Weights of these endocrine organs, body weights, and brain weights were determined. Prior to sacrifice, a blood sample was obtained from each animal for preparation of serum for analyses of thyroid stimulating hormone (TSH), thyroxine (T4), thyroid hormone (T3), and reverse T3 (rT3). Thyroid glands were evaluated microscopically for follicular cell hypertrophy, hyperplasia, and colloid storage. There were significant time-related increases in serum TSH in the test animals after 7, 14, and 28 doses of toxaphene. The serum levels of T3, T4, rT3, and corrected T3 (CrT3) in the test group were not significantly different from controls at each interval. Thyroid gland weights and thyroid to brain weight ratios were not significantly ($p > 0.05$) increased in the test group at each sacrifice interval. Pituitary weight, brain weight, and the ratios of these organ weights to body weights were similar in the test and control groups at each sacrifice interval. Thyroid follicular cell hypertrophy and intrafollicular hyperplasia increased and thyroid follicular cell colloid stores decreased with duration of treatment with toxaphene. The hormonal and histopathologic changes seen in the test group were consistent with increased excretion of T3

and/or T4 resulting from cytochrome P450 enzyme induction in the liver. This mechanism for thyroid neoplasia is not known to occur in humans. Also may be used in Section(s): 4.2

4.7. EVALUATION OF CARCINOGENICITY

4.8. SUSCEPTIBLE POPULATIONS AND LIFE STAGES

Munn, S; Keefe, T; Savage, E. (1985) A comparative study of pesticide exposures in adults and youth migrant field workers. Arch Environ Health 40(4):215-220.
To study possible differences between pesticide exposures received by youth (subjects less than 16 yr of age) and adults (subjects greater than 16 yr of age), human exposure samples (gloves and urine) were collected during the onion harvesting season of 1982. Environmental samples (soil, foliage, and field air) were also collected during the study period. All samples were analyzed for toxaphene, ethyl parathion, methyl parathion, and malathion. Environmental samples were found to have very low levels of these insecticides. The youth cohort had lower residue values than did the adults, and these differences were statistically significant (P less than 05) for toxaphene residues on gloves on each sampling day, and for ethyl parathion residues on gloves on one sampling day only. Detectable levels of dialkyl phosphates were found in only 2 of 44 urine samples. Also may be used in Section(s): 4.1

Tryphonas, H. (1998) The impact of pcbs and dioxins on children's health: Immunological considerations. Can J Public Health 89 Suppl 1S49-52, S54-47.
Environmental contaminants include the potentially toxic metals lead, cadmium and mercury; the chlorinated pesticides mirex, toxaphene and hexachlorobenzene; chlorinated dioxins and furans; polyaromatic hydrocarbons; and polychlorinated biphenyls. While many of these chemicals are resistant to degradation in the natural environment, they dissolve readily in oils and thus accumulate in the fatty tissues of fish, birds and mammals. Human exposure is predominantly through the ingestion of contaminated food. An array of toxic effects including effects on the immune system have been described in experimental animals and in humans accidentally exposed to these chemicals. Such studies suggest that the immune system of the developing fetus and the newborn is particularly vulnerable to the toxic effects of chemicals. To fully appreciate the magnitude of risk these chemicals pose to children's health, there is a need for additional carefully focussed epidemiologic and mechanistic studies.