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VINYL CHLORIDE

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MIDLAND, MICHIGAN, 48640

1 AU - Lawther PJ
AD - M.R.C. Toxicology Unit, Clinical Section, St. Bartholomew's Hosp., London, England
TI - TOXICOLOGICAL ASPECTS OF THE AIR WE BREATHE.
SI - CARC/79/07083
SO - Proceedings of the 1st International Congress on Toxicology: Toxicology as a Predictive Science, held in Toronto, Canada, 30 March- 2 April 1977. Plaa GL, Duncan WA, ed. New York, Academic Press, Inc., 670 pp., 1978.
LA - ENG
AB - Toxicological evaluations of air pollutants, expecially in the United Kingdom, are reviewed. Since passage of the Clean Air Act (1966), a series of studies suggests that the concentration of benzo(a)pyrene (BP) in the air is 1/10 of what it was 25 yr ago. There are also signs that the urban excess of lung cancer is declining. An association has been found between occupation in or residence near asbestos works and pleural mesothelioma. There is evidence that exposure need be only minute and that the resulting tumors may not be clinically manifest for up to 40 yr. Urban air contains many metals in trace amounts, some of which have been associated with cancer among occupational groups, eg, nickels, chromium, and beryllium. Concern about pollution of the communal air by industrial carcinogens has also been stimulated by the induction of angiosarcoma in workers using vinyl chloride monomer. Carbon monoxide exerts deleterious effects on the CNS and cardiovascular system. The effects of high dose of lead in adults and children are well-known, but there is conflicting evidence about the subclinical effects of body burdens formerly thought to be insignificant. (49 Refs)

2 AU - Kline SA ; Solomon JJ ; Van Duuren BL
AD - Lab. Organic Chemistry and Carcinogenesis, Inst. Environmental Medicine, New York Univ. Medical Center, New York, NY, 10016
TI - SYNTHESIS AND REACTIONS OF CHLOROALKENE EPOXIDES.
SI - ICDB/79/29738
SO - J Org Chem; 43(18):3596-3600 1978
LA - ENG
AB - The chloroalkene epoxides, vinyl chloride oxide (1), trichloroethylene oxide (2), tetrachloroethylene oxide (3), cis- and trans-1-chloropropene oxide (4 and 5), and cis- and trans-1,3-dichloropropene oxide (6 and 7), were synthesized from their respective chloroalkenes via either autooxygenation (in the case of 2 and 3) or m-chloroperbenzoic acid oxidation (in the case of 1 and 4-7). Dichlorobenzene was a byproduct in the synthesis of both 6 and 7. In the case of 6, its formation was determined to be a result of bimolecular reaction involving an intermediate in the synthesis of 6. Kinetics of hydrolysis at pH 7.4 and 37 C were determined for compounds 2-7. Kinetics of thermal decomposition in dilute hydrocarbon soln were determined for compounds 2, 4, 5, and 7. The hydrolysis and thermolysis rates are discussed with respect to structure and mechanism of product formation. (Author abstract) (21 Refs)

3 AU - Stevenson J ; Tamburro CH
AD - Cancer Center, Univ. Louisville Sch. Medicine, Louisville, KY, 40201
TI - EDUCATIONAL PROGRAMS IN INDUSTRIAL-CANCER DETECTION AND PREVENTION.
SI - ICDB/79/29591
SO - Prevention and Detection of Cancer. Part I. Prevention. Vol. 2. Etiology-Prevention Methods. Proceedings of the Third International Symposium on Detection and Prevention of Cancer held 26 April - 1 May 1976 New York NY. Nieburgs HE, ed.New York, Marcel Dekker, Inc., 2402 pp., 1978.
LA - ENG
AB - A system of educational programs for industrial cancer detection and prevention is outlined, and the effects of these programs on vinyl chloride industrial workers is reviewed. The program should include employee education on chemicals, safety programs, medical screening programs, effects of self-destructive life styles and specific diseases, and corporate-management, industrial medical personnel and community education. In implementing the program, the level of educational needs and the ease with which the information can be comprehended should be considered. Before the program was initiated in a vinyl chloride plant, the voluntary participation was 67% in a radiological screening (done at a hospital) and 95% in a biochemical screening program (done at the plant). After the educational program, participation was over 87% for both screening programs. Participation in the history and physical examination program, for which there was no educational brochure available, rose from 58% to only 72% in the same period of time. Redesign of educational programs for small group discussions located outside the plant at more accessible locations resulted in greater attendance. (7 Refs)

4 AU - Greenberg RA ; Tamburro CH ; Kupchella CE
AD - Cancer Center, Univ. Louisville, Louisville, KY
TI - A PROSPECTIVE MEDICAL SURVEILLANCE PROGRAM FOR THE DETECTION AND PREVENTION OF INDUSTRIALLY RELATED CANCER.
SI - ICDB/79/29579
SO - Prevention and Detection of Cancer. Part I. Prevention. Vol. 2. Etiology-Prevention Methods. Proceedings of the Third International Symposium on Detection and Prevention of Cancer held 26 April - 1 May 1976 New York NY. Nieburgs HE, ed.New York, Marcel Dekker, Inc., 2402 pp., 1978.
LA - ENG
AB - A medical surveillance system under development for a chemical plant in Louisville, KY, is described. The aim of the system is to detect early occupational disease in a work force of about 1,200 employees exposed in varying degrees to a known carcinogen, vinyl chloride. The medical surveillance system is composed of four ordered levels of screening, each of which tends to improve total precision, but at an ever increasing cost and complexity. Job classification codes, employee work histories, the ranking of chemical exposure, and development of exposure indices all

contribute to this system. The health of employees is monitored through annual and semi-annual physical examinations and through semi-annual and quarterly screening tests. The screening tests will be evaluated in terms of their usefulness in detecting overt diseases and in terms of their ability to detect early abnormalities that may be indicative of future overt disease. Mortality and morbidity rates will be monitored and compared with the best estimates of expected rates. The data being collected are being coded and stored on magnetic discs. Computer programs for the rapid access and analysis of the data are being written. (1 Ref)

5 AU - Van Duuren BL
AD - Lab. Organic Chemistry, New York Univ. Medical Center, New York, NY, 10016
TI - STRUCTURAL PROGNOSTICATION OF CARCINOGENICITY AND TUMOR-ENHANCING ACTIVITY IN VARIOUS CHEMICALS.
SI - CARC/79/06422
SO - Prevention and Detection of Cancer. Part I. Prevention. Vol. 2. Etiology-Prevention Methods. Proceedings of the Third International Symposium on Detection and Prevention of Cancer held 26 April - 1 May 1976 New York NY. Nieburgs HE, ed.New York, Marcel Dekker, Inc., 2402 pp., 1979.
LA - ENG
AB - Structure-activity relationships of direct-acting alkylating agents, tumor promoters, and cocarcinogens are reviewed. Among the 100 alkylating agents examined were epoxides (mono-, bi- and polyfunctional), beta- and gamma-lactones, and a variety of chloro ethers. The beta-lactones are carcinogenic but the gamma-lactones are not. The bifunctional epoxides exhibit carcinogenicity more frequently than the monofunctional analogs. In monofunctional agents, the presence of a reactive adjacent functional group results in carcinogenic activity. Trichloroethylene (TCE) and vinyl chloride (VC) may be metabolized via an epoxide intermediate. TCE is carcinogenic in mice but not in rats, and VC is a known human carcinogen. Because of the wide differences in chemical structure, reactivity, and physical properties of tumor promoters, cocarcinogens, and tumor inhibitors, they probably exert their activities in several different ways. They may simply alter the rate of absorption and disappearance of a carcinogen, or they may alter its metabolic pathway. Tumor-promoting agents, particularly the phorbol esters, are likely to interact at the cell membrane. As a result of structure-activity studies, it has become possible to assign biological activity to certain classes of compounds that have not yet been tested. (41 Refs)

6 AU - Hoffmann D ; Schmeltz I ; Hecht SS ; Brunnemann KD ; Wynder EL
AD - Naylor Dana Inst. Disease Prevention, American Health Foundation, Valhalla, NY, 10595
TI - VOLATILE CARCINOGENS: OCCURRENCE, FORMATION AND ANALYSIS.
SI - CARC/79/06414
SO - Prevention and Detection of Cancer. Part I. Prevention. Vol. 2. Etiology-Prevention Methods. Proceedings of the Third International Symposium on Detection and Prevention of Cancer held 26 April - 1 May 1976 New York NY. Nieburgs HE, ed.New York, Marcel Dekker, Inc., 2402 pp., 1978.
LA - ENG
AB - Carcinogenicity data (humans and animals); levels in occupational environments, polluted air, and cigarette smoke; and analytical methods for several volatile chemical carcinogens, including vinyl chloride, chlorinated hydrocarbons, bis(chloromethyl)ether, N-nitrosamines, and hydrazines, are reviewed. (33 Refs)

7 AU - Kline SA ; Solomon JJ ; Van Duuren BL
AD - Lab. Organic Chemistry and Carcinogenesis, Inst. Environmental Medicine, New York Univ. Medical Center, New York, NY, 10016
TI - SYNTHESIS AND REACTIONS OF CHLOROALKENE EPOXIDES.
SI - ICOB/79/29226
SO - J Org Chem; 43(18):3596-3600 1978
LA - ENG
AB - The chloroalkene epoxides, vinyl chloride oxide (1), trichloroethylene oxide (2), tetrachloroethylene oxide (3), cis- and trans-1-chloropropene oxide (4 and 5), and cis- and trans-1,3-dichloropropene oxide (6 and 7), were synthesized from their respective chloroalkenes via either autoxygenation (in the case of 2 and 3) or m-chloroperbenzoic acid oxidation (in the case of 1 and 4-7). Dichlorobenzene was a byproduct in the synthesis of both 6 and 7. In the case of 6, its formation was determined to be a result of bimolecular reaction involving an intermediate in the synthesis of 6. Kinetics of hydrolysis at pH 7.4 and 37 C were determined for compounds 2-7. Kinetics of thermal decomposition in dilute hydrocarbon soln were determined for compounds 2, 4, 5, and 7. The hydrolysis and thermolysis rates are discussed with respect to structure and mechanism of product formation. (Author abstract) (21 Refs)

8 AU - Environmental Protection Agency
AD - Criteria and Standards Div., Environmental Protection Agency, Washington, DC
TI - AMBIENT WATER QUALITY CRITERIA: VINYL CHLORIDE.
SI - ICOB/79/25179
SO - Ambient Water Quality Criteria: Vinyl Chloride. Available Through National Technical Information Service, Springfield, Va., as PB-292 446/2GA:, 90 pp., 1979.
LA - ENG
AB - Section 304(a) of the Clean Water Act (33 US Congress 1314(a)), requires Environmental Protection Agency to publish and periodically update water quality criteria. These criteria are to

reflect the latest scientific knowledge on the identifiable effects of pollutants on public health and welfare, aquatic life, and recreation. This report presents water quality criteria for vinyl chloride. It presents concentration criteria for the protection of fresh water and saltwater aquatic life. It presents 'safe' concentrations for humans, and in the case of suspect or proven carcinogens, gives various levels of incremental cancer risk. A section 304(a) water quality criterion is a qualitative or quantitative estimate of the concentration of a water constituent or pollutant in ambient waters which, when not exceeded, will ensure a water quality sufficient to protect a specified water use. Under the Act a criterion is a scientific entity, based solely on data and scientific judgement. It does not reflect considerations of economic or technological feasibility nor is it a water quality standard and in itself has no regulatory effect. (Author abstract)

9 AU - Squirrell DC ; Thain W ; Davis W
AD - International Agency for Res. on Cancer, 150 Cours Albert Thomas, 69371 Lyon Cedex 2, France
TI - MONITORING REQUIREMENTS IN THE PVC INDUSTRY.
SI - ICOB/79/24976
SO - IARC Sci Publ; (22):15-17,47-54 1978
LA - ENG
AB - The unification of regulations for monitoring vinyl chloride in the European Community (EC) is discussed. A method for comparing concentration values measured over different time periods is explained. This technique allows the likely av over a long time to be forecast from shorter-time averages. (10l Refs)

10 AU - Squirrell DC ; Squirrell DC ; Thain W ; Davis W
AD - International Agency Res. Cancer, 150 cours Albert Thomas, 69372 Lyon Cedex 2, France
TI - ENVIRONMENTAL CARCINOGENS: SELECTED METHODS OF ANALYSIS. STANDARDS FOR CALIBRATION AND TESTING: PREPARATION OF STANDARD MIXTURES OF VINYL CHLORIDE IN NITROGEN OR AIR, PREPARATION OF STANDARD SOLUTIONS OF VINYL CHLORIDE IN ORGANIC SOLVENTS BY VOLUMETRIC AND GRAVIMETRIC METHODS, AND PREPARATION OF STANDARD AQUEOUS SOLUTIONS OF VINYL CHLORIDE.
SI - ICOB/79/24975
SO - IARC Sci Publ; (22):123-140 1978
LA - ENG
AB - Standards for calibration and testing for vinyl chloride concentrations are reviewed. Instructions are given for the preparation of standard mixtures of vinyl chloride in nitrogen or air, standard soln of vinyl chloride in organic solvents by volumetric and gravimetric methods, and standard aqueous soln of vinyl chloride. Some procedures and parts of the necessary apparatus are illustrated. (no Refs)

11 AU - Squirrell DC ; Squirrell DC ; Thain W ; Davis W
AD - International Agency for Res. on Cancer, 150 cours Albert Thomas, 69371 Lyon Cedex 2, France
TI - METHODS FOR THE MEASUREMENT OF VINYL CHLORIDE IN POLY(VINYL CHLORIDE), AIR, WATER AND FOODSTUFFS. METHOD 8-DETERMINATION OF VINYL CHLORIDE IN FOODSTUFFS BY HEAD-SPACE SAMPLING GAS CHROMATOGRAPHY.
SI - ICDB/79/24974
SO - IARC Sci Publ; (22):113-120 1978
LA - ENG
AB - A method for determing vinyl chloride (VC) in food using head-space sample gas chromatography (GC) is specified. Analysis time, under favorable conditions, is approx 10 min and detection limits are routinely 5 nanog (ng)/g, or 5 ng/ml, down to 1 ng/g, or 1 ng/ml. Five aliquots (5 ml for liquids and 5 g for solids) of food sample are sealed in separate vials. A standard soln of VC (10 mg/liter) in water, tetrahydrofuran, dimethyl acetamide or other appropriate solvent is prepared. Using a microsyringe, 1, 2.5, 5 and 20 ul of the standard soln are added to four of the five vials to serve as calibration standards. The five vials are placed in the GC thermostated bath at 40 C and equilibrated at least 2 hr. VC peak heights on each chromatogram are corrected to a common recorder attenuation and plotted on the ordinate of a graph relating them to VC plotted on the abscissa. If the sample contains VC, the line will not pass through the zero VC value. The amount of VC contained in the sample is determined from the intercept with the abscissa: VC (ng/ml or ng/g) = intercept value (ng) divided by vol (ml) or wt (g) of sample. (no Refs)

12 AU - Griciute L
AD - Unit Environmental Carcinogens, International Agency Res. Cancer, Lyon, France
TI - THE CARCINOGENICITY OF VINYL CHLORIDE.
SI - CARC/79/05455
SO - IARC Sci Publ; (22):3-11 1978
LA - ENG
AB - Data on the carcinogenicity of vinyl chloride (VC) are summarized. Chronic exposure of laboratory animals to VC produces hepatic lesions and bone changes similar to those described in humans. In the first animal study implicating VC as a carcinogen, rats were exposed to 30,000 ppm VC, 4 hr/day, 5 days/wk, for 9-12 mo. They developed auditory sebaceous gland tumors and osteochondromas. Inhalation exposure in rats, mice, hamsters, and rabbits produced angiosarcomas of the liver and other organs and malignant tumors of the lung, intestine, kidney, skin, mammary gland, and forestomach. VC is carcinogenic in rats at 25 and 50 ppm in air and in mice and hamsters at 50 ppm in air. Ingestion of VC by gavage (50.0 and 16.6 mg/kg/day for 52 wk) produced liver angiosarcomas and other tumors in rats, but 3.3 mg/kg/day produced angiosarcomas at sites other than the liver. Transplacental administration of VC to rats between days 12 and 18 of gestation produced angiosarcomas. The in vitro mutagenicity

of VC to bacteria is greatly enhanced by liver tissue homogenates from humans, mice, and rats. Chloroethylene oxide is considered to be the main active carcinogenic metabolite of VC; it is a strong alkylating agent that is responsible for mutagenesis in bacteria, yeast, and Chinese hamster cells. VC produces chromosome alterations in human lymphocytes. Primary liver angiosarcoma is the tumor observed in workers in the polyvinyl chloride (PVC) industry. This tumor is extremely rare in the general population, and those detected in PVC workers represent a 400-fold increase over the expected incidence. It is not known whether VC induces other tumors in humans. The av latent period between initial VC exposure and liver angiosarcoma diagnosis is 20 yr. (34 Refs)

13 AU - Natarajan AT ; Van Buul PP ; Raposa T
AD - Dept. Radiation Genetics and Chemical Mutagenesis, Sylvius Labs.
TI - AN EVALUATION OF THE USE OF PERIPHERAL BLOOD LYMPHOCYTE SYSTEMS FOR ASSESSING CYTOLOGICAL EFFECTS INDUCED IN VIVO BY CHEMICAL MUTAGENS.
SI - CARC/79/05452
SO - Mutagen-Induced Chromosome Damage in Man, Proceedings of a Symposium held in Edinburgh, Scotland, July 7-8, 1977. Medical Research Council Edinburgh, Scotland, 355 pp., 1978.
LA - ENG
AB - The use of peripheral blood lymphocyte systems for monitoring populations exposed to chemical mutagens and for screening chemicals for their in vivo mutagenic effects was investigated. Investigations included analyses of the frequency of chromosome aberrations in workers exposed to low levels of vinyl chloride; the frequencies of sister chromatid exchanges (SCEs) in blood lymphocytes from patients receiving cytostatic treatment, both during treatment and a few weeks after recovery; and chromosome aberrations and SCEs in lymphocytes of rats after in vivo treatment with directly and indirectly acting alkylating agents. No strongly significant difference was noted between the control and the vinyl chloride groups of workers with regard to the occurrence and frequency of chromosome aberrations. Of the six patients treated with cytostatic drugs, five received cyclophosphamide and one thiotepa. The control group had an av of 10.3 SCEs/cell, while in the treated group two patients had significantly higher frequencies of SCEs. In a 76-yr-old patient with reticular cell sarcoma, the SCE frequencies were 23.4, 15.6, 16.2, and 12.3 per cell on days 13, 16, 18 and 20 of therapy, while the frequency decreased to 6.3 25 days after therapy was terminated. In rats, despite a very high dose of diethyl nitrosamine (DEN), no effect on SCEs and chromosomal aberrations could be observed. With both dimethyl nitrosamine and methyl nitrosourea, a dose-dependant increase in chromosome aberrations and SCEs was found. It is concluded that for low chronic exposures, this system is not sensitive in detecting mutagenic effects, while for assessing the in vivo effects of chemical mutagens, particularly those that need metabolic activation, this system may have value. (10 Refs)

14 AU - Squirrell DC ; Thain W
AD - International Agency for Res. on Cancer, 150 Cours Albert Thomas, 69372 Lyon Cedex 2, France
TI - METHOD FOR THE MEASUREMENT OF VINYL CHLORIDE IN POLY(VINYL CHLORIDE), AIR, WATER AND FOODSTUFFS. REVIEW OF TECHNIQUES OF MEASUREMENT AND MONITORING OF VINYL CHLORIDE.
SI - ICDB/79/24569
SO - IARC Sci Publ; (22):19-54 1978
LA - ENG
AB - The techniques of measuring and monitoring vinyl chloride (VC) as of mid-1978 were reviewed. The limits of VC detection with a flame-ionization detector are about 1 ppm and about 0.2 ppm with a photo-ionization detector. Because of long recovery time after exposure to the VC concentrations during monitoring, a detector in which ionization occurs at high temperature in the presence of alkali metal salts is unsuitable for VC use. Electron capture detectors are affected by water vapor and are unsuitable for atmospheric measurements. The infra-red spectrum of gaseous VC shows absorption at approx 5.15, 9.8, 10.9, and 13.9 microns; the first is a region of strong absorption by water vapor and the second is comparatively weak; the stronger band of the two remaining (10.9 microns) is used to measure concentration unless it is subject to interference from other substances. VC is transparent to radiation at 4 microns and this wave-length can be used as a reference if required. The limit of detection of VC by mass spectrometry is highly dependent on the sampling technique used. Oxidation systems work efficiently only if a certain water content is maintained. Reactions other than direct oxidation can be used, however, eg, bromination with enrichment by liquid chromatography and gas chromatography (GC). The sensitivity of color detectors depends on the detailed construction of the device and sample size. Thermal conductivity measurements in air are subject to interference from atmospheric impurities. Numerous semiconductor devices show changes in electrical properties when exposed to VC, which depend on adsorption of VC on the semiconductor surface; while adsorption may be comparatively rapid, desorption is usually slow at low VC concentrations. Many of the VC measurement techniques are nonspecific and subject to interference from other substances; the error increases as VC decreases, particularly at low concentrations. When interference is significant, a separation technique that chemically removes unwanted substances should be used, eg, GC. The specific information required often determines the sampling techniques to be used. (101 Refs)

15 AU - Squirrell DC ; Thain W
AD - International Agency for Res. on Cancer, 150 cours Albert Thomas, 69372 Lyon Cedex 2, France
TI - METHODS FOR THE MEASUREMENT OF VINYL CHLORIDE IN POLY(VINYL CHLORIDE), AIR, WATER AND FOODSTUFFS. METHOD 1-DETERMINATION OF VINYL CHLORIDE IN AIR BY GAS CHROMATOGRAPHY.
SI - ICOB/79/24568
SO - IARC Sci Publ; (22):59-64 1978
LA - ENG
AB - A method for determining of vinyl chloride (VC) in air, which can also be used for ethyl chloride, 1,1-dichloroethylene (vinylidene chloride) and 1,2-dichloroethane, was presented. The limit of detection is 0.1 ppm (vol) with a precision of +-10% up to 10 ppm and +-5% at higher levels. The total time required is approx 15 min. The atmosphere is sampled by a gas syringe, or other suitable method, and an aliquot is injected via a gas sampling valve onto the column of a gas chromatograph (GC). The vinyl chloride is detected by a flame-ionization detector. For GC calibration a standard mixture of VC in air (usually 400 ppm) is prepared and an aliquot is transferred to the GC column for analysis. VC concentration (ppm) = concentration of the standard (ppm) x VC chromatogram peak in sample x its attenuation divided by standard chromatogram peak x its attenuation. (no Refs)

16 AU - Squirrell DC ; Thain W
AD - International Agency for Res. on Cancer, 150 cours Albert Thomas, 69372 Lyon Cedex 2, France
TI - METHODS FOR THE MEASUREMENT OF VINYL CHLORIDE IN POLY(VINYL CHLORIDE), AIR, WATER AND FOODSTUFFS. METHOD 2-DETERMINATION OF THE EIGHT HOUR TIME-WEIGHTED AVERAGE CONCENTRATION OF VINYL CHLORIDE IN THE ATMOSPHERE USING A PERSONAL SAMPLER PUMP AND A CARBON TRAP.
SI - ICOB/79/24567
SO - IARC Sci Publ; (22):65-74 1978
LA - ENG
AB - A method for determining of the time-weighted av concentration of vinyl chloride (VC) in air over an 8 hr sampling period, using a personal sampler pump and a carbon trap with gas chromatography, was presented. The method is applicable in the range 0.02-50 ppm for atmospheres of normal humidity, but may give low results for humid atmospheres. Manipulative time is approx 30 min, but the measurement cycle time is governed by the duration of complete solvent elution from the chromatographic column and return to a stable recorder attenuation baseline. The cycle time can be reduced by the use of back-flush facilities. With a portable pump, the atmosphere is sampled at a constant flow rate through an adsorption tube containing carbon. VC is desorbed from the carbon with dichloromethane and determined by gas chromatography (GC). Other solvents or thermal desorption can also be used. For GC calibration a standard soln of VC in the desorption solvent is prepared. The soln is analyzed by GC and a calibration curve prepared for calculating VC concentration in the sample. (no Refs)

17 AU - Squirrell DC ; Thain W
AD - International Agency for Res. on Cancer, 150 cours Albert Thomas, 69273 Lyon Cedex 2, France
TI - METHODS FOR THE MEASUREMENT OF VINYL CHLORIDE IN POLY(VINYL CHLORIDE), AIR, WATER AND FOODSTUFFS. METHOD 3-DETERMINATION OF THE EIGHT HOUR TIME-WEIGHTED AVERAGE CONCENTRATION OF VINYL CHLORIDE IN THE ATMOSPHERE USING A PERSONAL MONITOR FITTED WITH A DETECTOR TUBE.
SI - ICDB/79/24566
SO - IARC Sci Publ; (22):75-82 1978
LA - ENG
AB - A method for determining of the time-weighted av concentration (TWA) of vinyl chloride (VC) in air over an 8 hr sampling period, using a personal monitor fitted with a detector tube, was presented. The indicator tube is calibrated over the ranges 0-5 ppm and 0-10 ppm on 9.6 and 4.8 liter samples of air, respectively. The personal monitor consists of a low flow rate sampling pump and a Draeger detector tube. The tube consists of an alkali trap, to remove HCl and chlorine, and by a potassium permanganate oxidation layer, to convert vinyl chloride to chlorine. A continuous analysis is obtained during the time atmospheric sample is drawn through the tube, producing a stain whose length is proportional to the time-weighted VC. Other unsaturated chlorinated hydrocarbons interfere, eg, trichloroethylene and vinylidene chloride, producing stains indistinguishable from those produced by VC. The Draeger tube is calibrated before use using 0-50 ul VC. The TWA (ppm) of VC = VC readings from tube (ul) divided by air sample vol (liters). (no Refs)

18 AU - Squirrell DC ; Thain W
AD - International Agency for Res. on Cancer, 150 cours Albert Thomas, 69372 Lyon Cedex 2, France
TI - METHODS FOR THE MEASUREMENT OF VINYL CHLORIDE IN POLY(VINYL CHLORIDE), AIR, WATER AND FOODSTUFFS. METHOD 4-DETERMINATION OF VINYL CHLORIDE IN AQUEOUS LIQUIDS BY HEAD-SPACE SAMPLING/GAS CHROMATOGRAPHY.
SI - ICDB/79/24565
SO - IARC Sci Publ; (22):83-88 1978
LA - ENG
AB - A method for determining of vinyl chloride (VC) in aqueous liquids using head-space sampling gas chromatography was presented. It is suitable for VC concentrations 0.001-1 ug/ml but is equally applicable to liquid effluents which contain higher levels of VC when solid matter is absent. Precision is +-25% for concentrations less than 0.005 ug/ml, +-10% at 0.02 ug/ml level and +-5% greater than 0.04 ug/ml. A vial is filled with 5.0 ml of sample, sealed, placed in the thermostated gas chromatograph (GC) bath at 30.0 C, and processed by a set of calibration standards. The GC is calibrated by preparing a standard soln of VC in water (100 mg/liter). Six vials are filled with 5.0 ml distilled water and sealed. Using a microsyringe 0, 0.5, 1.5, 2.0 and 2.5 ul of

the standard VC soln are added to separate vials. The vials are placed in the GC bath, allowed to equilibrate for at least 1 hr, and are analyzed by the automatic sequence. The height of the VC peak in the sample, corrected for recorder attenuation, is converted to concentration of VC (ug/ml) by comparison with the calibration graph obtained from the standard soln. (no Refs)

19 AU - Squirrell DC ; Thain W
AD - International Agency Res. on Cancer, 150 cours Albert Thomas, 69372 Lyon Cedex 2, France
TI - METHODS FOR THE MEASUREMENT OF VINYL CHLORIDE IN POLY(VINYL CHLORIDE), AIR, WATER AND FOODSTUFFS. METHOD 5-DETERMINATION OF TRACES OF VINYL CHLORIDE IN AIR BY TRAPPING FOLLOWED BY GAS CHROMATOGRAPHY.
SI - ICDB/79/24564
SO - IARC Sci Publ; (22):89-95 1978
LA - ENG
AB - A method for determining of traces of vinyl chloride (VC) in air using gas chromatography, applicable to 0.001 ppm (vol) was presented. The gas chromatograph (GC) is calibrated daily. A standard VC in nitrogen mixture (usually 400 ppm) is prepared. A 10 ml sample is withdrawn with a syringe, a 1 ml sample loop on the GC is filled and the remainder is injected on the GC column. VC is trapped from a 1-10 liter sample of air by passing it through silica gel at-78 C which adsorbs VC (sampling period should be less than 20 min to avoid blocking the trap with ice even when a drying tube is used). The trap is connected to a GC fitted with an Apiezone L Carbopak B column and a flame-ionization detector. The trap is heated quickly to 100 C and purged with nitrogen to transfer the desorbed VC into the chromatograph. VC concentration (ppm) = sample VC peak corrected for attenuation x vol of standard in sample valve loop x concentration of standard divided by corrected peak of standard x sample vol. (no Refs)

20 AU - Squirrell DC ; Thain W
AD - International Agency for Res. on Cancer, 150 cours Albert Thomas, 69372 Lyon Cedex 2, France
TI - METHODS FOR THE MEASUREMENT OF VINYL CHLORIDE IN POLY(VINYL CHLORIDE), AIR, WATER AND FOODSTUFFS. METHOD 6-DETERMINATION OF THE 24-HOUR TIME-WEIGHTED AVERAGE CONCENTRATION OF VINYL CHLORIDE IN AIR BY TRAPPING FOLLOWED BY GAS CHROMATOGRAPHY.
SI - ICDB/79/24563
SO - IARC Sci Publ; (22):97-103 1978
LA - ENG
AB - A method for measuring the 24-hr time-weighted av concentration of vinyl chloride (VC) in air using gas chromatography was presented. The method is sensitive to VC concentrations down to 0.005 ppm (vol). Precision under laboratory conditions is +-10% from 0.1-1 ppm; in the field at flow rates of 10 and 20 ml/min the coefficient of variation is 8.5% over the range 0.05-0.5 ppm. The atmosphere is sampled over a 24-hr period by pumping through two activated-carbon adsorption tubes in series. The adsorbed

vinyl chloride is extracted from each tube with CS2 and the two soln examined separately. The gas chromatograph (GC) is calibrated by preparing VC in CS2 standard soln (2-50 ul/ml). One ml aliquots are injected onto the GC column, peak height for each concentration measured and a calibration curve drawn. One ul supernatant CS2 extract from each sample tube is analyzed in the GC and the VC concentration determined from the calibration curve. The VC concentration (ppm) in the air sample = 2 x concentration in the extract divided by vol of the air sample (liters). (no Refs)

21 AU - Squirrell DC ; Thain W
AD - International Agency for Res. on Cancer, 150 cours Albert Thomas, 69372 Lyon Cedex 2, France
TI - METHODS FOR THE MEASUREMENT OF VINYL CHLORIDE IN POLY(VINYL CHLORIDE), AIR, WATER AND FOODSTUFFS. METHOD 7-DETERMINATION OF VINYL CHLORIDE IN POLY(VINYL CHLORIDE) BY HEAD-SPACE SAMPLING GAS CHROMATOGRAPHY.
SI - ICOB/79/24562
SO - IARC Sci Publ; (22):105-111 1978
LA - ENG
AB - A method for determining of vinyl chloride (VC) in polyvinyl chloride (PVC) using head-space sampling gas chromatography (GC) was presented. Precision of the method is +-10% at concentrations up to 10 ug/g and +-5% at concentrations greater than 10 ug/g. The method is applicable to PVC in the form of polymer powder, pre-mixed powder, compound granules and fabricated articles. Concentrations less than 2 mg VC/g of PVC can be determined. The lower limit of detection depends on how much the impurities in the solvent interfere with determination of VC. If interference is sufficiently low, 0.1 ug VC/g of PVC can be detected. The analysis time is typically 30 min, but depends on the time taken by the solvent or impurity peaks to elute and the recorder trace to return to baseline. Tetrahydrofuran (5.0 ml) is rapidly added to 0.500 g sample in a 25 ml vial with a magnetic stirrer, the vial is sealed and stirring continued until complete dissolution occurs. The vial is then placed in the gas GC thermostat bath at 30 C and allowed to equilibrate for at least 1 hr. GC calibration standards are prepared similar to the sample preparation using 0.500 g monomer-free PVC for each of five vials and either 0, 1, 3, 7 or 10 ul of standard soln (40 mg VC/ml tetrahydrofuran) to the five vials using a microsyringe (0-400 ug of VC is added). The GC automatic sampling sequence is used and a graph of peak height (after correction for attenuation) is plotted against added VC. The wt of VC is obtained from the calibration curve. The VC concentration in the PVC sample (ug/g) = VC wt/PVC wt. (no Refs)

22 AU - Squirrell DC ; Thain W
AD - International Agency for Res. on Cancer, 150 cours Albert Thomas, 69372 Lyon Cedex 2, France
TI - METHODS FOR THE MEASUREMENT OF VINYL CHLORIDE IN POLY(VINYL CHLORIDE), AIR, WATER AND FOODSTUFFS.
SI - ICDB/79/24561
SO - IARC Sci Publ. Vol. 22, 142 pp., 1978.
LA - ENG
AB - A compilation of balanced and critical views of the methods available for determining the vinyl chloride (VC) monomer was presented. An introductory chapter on the carcinogenicity of VC was followed by a review of measuring and monitoring techniques. The detailed procedures have been brought up to date in light of considerable experience since the first edition of this publication and correspond closely to those used in industrial and control laboratories. They include the following determinations: VC in air by gas chromatography; 8 hr time-weighted av concentration of VC in the atmosphere using a personal sampler pump and a carbon trap, or a personal monitor fitted with a detector tube; VC in aqueous liquids by head-space sampling/gas chromatography, VC traces in air by trapping followed by gas chromatography; 24 hr time-weighted av concentration of VC in air by trapping followed by gas chromatography; and VC in poly(vinyl chloride) and food by head-space sampling gas chromatography. Also included is the preparation of standards for calibration and testing of VC mixtures in nitrogen or air, VC soln in organic solvents by volumetric and gravimetric methods, and aqueous soln of VC. (no Refs)

23 AU - Boyland E
AD - London Sch. Hygiene and Tropical Medicine, London WC1, England
TI - SIGNIFICANCE OF OCCUPATIONAL CANCER.
SI - CARC/79/04829
SO - Prog Biochem Pharmacol; 14:76-81 1978
LA - ENG
AB - The significance of studies of occupational cancer is surveyed. At least 90% of human cancers are due to chemical agents, and about 80% are due to environmental factors. Many causes of human cancer have been found by investigation of occupational disease, and this approach is still the most promising. Because chemical carcinogens are difficult to identify by examination of human populations, it is essential to carry out animal tests on chemicals in the environment to obtain indications of carcinogenic activity. Chemical carcinogens can be divided into two groups: the first group (eg, alkylating agents) does not require metabolic transformation for activity; the second group (eg, nitrosamines and polycyclic hydrocarbons) requires metabolic or chemical activation. The metabolic reactions involved in the activation of the second group are part of the normal detoxification processes. The first step in the activation of polycyclic aromatic hydrocarbons is the formation of epoxides or

arene oxides. Their action is due to the presence of an ethylene group or double bond that can be activated and to their similarity in shape to constituents of the target DNA molecule. Vinyl chloride and trichloroethylene, two other carcinogens, combine with DNA in a manner similar to that of the arene oxides of the carcinogenic hydrocarbons. Occupational cancers have special significance because they can give indications of the specific causes of cancer, and recognition of causes of cancer in workers gives indications of the causes of cancer in the general population. (no Refs)

24 AU - Fishbein L
AD - Natl. Cancer for Toxicological Res., Jefferson, AR
TI - ENVIRONMENTAL SOURCES OF CHEMICAL MUTAGENS. II. SYNTHETIC MUTAGENS.
SI - CARC/79/04818
SO - Adv Mod Toxicol; 5:257-348 1978
LA - ENG
AB - Comparative data are reviewed on the relative amounts, residues, and transport in the environment of primarily synthetic mutagenic and potentially mutagenic agents. The agents discussed include industrial mutagens (primarily the halogenated hydrocarbons, vinyl chloride, vinylidine chloride, trichloroethylene, tetrachloroethylene, chloroprene, carbon tetrachloride, fluorocarbons, polychlorinated biphenyls, chlorodioxins, haloethers, chloride, bromoalkanes, and fluorine, phthalate esters, pesticides (DDT, dichlorvos, formaldehyde, and ethylene oxide), and metals and metalloids (lead, mercury, and arsenic). Information is sparse concerning environmental reactions and interactions, transport, residence times, stability, and fates of these agents. Also, most environmental chemicals have not been adequately studied to permit evaluation of their relative mutagenicities for humans. (470 Refs)

25 AU - Maltoni C
AD - Inst. Oncology and Tumour Center, Bologna, Italy
TI - PREDICTIVE CARCINOGENICITY BIOASSAYS IN INDUSTRIAL ONCOGENESIS.
SI - CARC/79/04581
SO - Prog Biochem Pharmacol; 14:47-56 1978
LA - ENG
AB - The use of carcinogenicity bioassays to predict the oncogenic risks associated with industrial chemicals is reviewed. The goal is to avoid human exposure to carcinogenic chemicals. The four most important cases of environmental and occupational cancers discovered since 1970 were directly or indirectly predicted experimentally. The choice of agents to be tested should follow a list of priorities based on diffusion of the agent, number of people potentially exposed, and direct and/or indirect data suggesting a possible risk. Long-term carcinogenicity bioassays include first-level bioassays in which the route of administration of the agent and affected tissues are not the same as those for humans; second-level bioassays in which the route of administration of the agent is different but the affected tissue

is the same as that for humans; and third level bioassays in which both the route of administration and affected tissues are the same as those humans. Preliminary results of bioassays of several inorganic compounds and vinyl chloride in Sprague-Dawley rats are given. (9 Refs)

26 AU - Downs TD
AD - Dept. Biometry, Univ. Texas Health Science Center at Houston, Sch. Public Health, P.O. Box 20186, Houston, TX, 77025
TI - COMMUNITY RISK ASSESSMENT.
SI - ICOB/79/17813
SO - Tex Rep Biol Med; 37:118-122 1978
LA - ENG
AB - A simplified account of a statistical method used to assess community risk from environmental carcinogens is presented. The method is called the linear model and is based on the assumption that the probability, or risk, of developing cancer from exposure to a relatively small amount of carcinogen is directly proportional to that amount. The linear model is illustrated with data on vinyl chloride inhalation in rats and subsequent development of liver angiosarcoma. Results from these experiments are extrapolated to humans. Rats were intermittently exposed to vinyl chloride at different ambient air concentrations. Exposures to vinyl chloride were maintained for 4 hr/day, 5 days/wk, for a period of 1 yr. Following this, surviving rats were housed under normal conditions until death. Whenever a rat died an autopsy was performed to determine if the rat had developed liver angiosarcoma. The proportion of rats with liver angiosarcoma increased steadily as the dose concentrations of vinyl chloride increased. The proportion of rats with liver angiosarcoma seemed roughly proportional to the dose concentration. Use of the linear model was extrapolated to humans to quantify the risk of liver angiosarcoma for residents in the vicinity of a hypothetical vinyl chloride plant. (6 Refs)

27 AU - Tamburro CH
AD - Digestive Diseases and Nutrition Section, Sch. Medicine, Univ. Louisville, 511 South Floyd Street, Room 535, MDR Building, Louisville, KY, 40201
TI - HEALTH EFFECTS OF VINYL CHLORIDE.
SI - CARC/79/03744
SO - Tex Rep Biol Med; 37:126-144 1978
LA - ENG
AB - The health effects of vinyl chloride (VC) are reviewed, and a medical surveillance system for detecting and following its effects is described. An early finding in exposed human and animals is activation of morphological changes in the sinusoidal lining cells of the liver without evidence of hepatocellular toxicity. With progressive exposure to VC there is an increase in atypia of the sinusoidal lining cells, progressive worsening of the focal sinusoidal dilatation, and malignant transformation of the sinusoidal lining cells. Most data suggest that it is the endothelial lining cell that becomes malignant and forms the

angiosarcoma. Peliosis hepatis is often seen in nontumorous portions of the liver; whether this is a precarcinogenic or preangiosarcomatous lesion in VC workers is under study. Preliminary epidemiological and histological data suggest that the frequency of lung cancer is increased among VC workers. Two cases are reported in which the duration and degree of exposure to VC were almost identical, yet one man developed primary hepatocellular carcinoma and the other angiosarcoma. The man in whom hepatocellular carcinoma developed had a history of extensive alcohol consumption, which may have played a role in the inability of the hepatocytes to detoxify VC metabolites. A prospective medical surveillance system has been designed based on classification of industrial environments into three categories according to the level of possible carcinogens. (10 Refs)

28 AU - Wyatt S
AD - United States Environmental Protection Agency, Research Triangle Park, NC, 27711
TI - CONTROL STATUS OF VINYL CHLORIDE.
SI - ICDB/79/17327
SO - Tox Rep Biol Med; 37:145 1978
LA - ENG
AB - The Environmental Protection Agency (EPA) listed vinyl chloride as a hazardous air pollutant in December, 1975, and promulgated a national emission standard for it under the authority of section 112 of the Clean Air Act on October 21, 1976. On November 19, 1976, the Environmental Defense Fund (EDF) petitioned the United States Court of Appeals for review of the standard. On March 24, 1977, EDF and EPA moved to dismiss the court proceedings in view of a settlement agreement requiring EPA to propose certain amendments to the standard. These amendments to the standard were proposed on June 2, 1977. Since that time EPA has received numerous comments from the industry on the proposal. The main issue involved is how carcinogens should be regulated under section 112 of the Clean Air Act. Section 112 of the Act requires that emission standards be set 'at the level which, in the judgment of the Administrator, provides an ample margin of safety to protect the public health from such hazardous air pollutants.' It has not been possible to determine a threshold level of effects for vinyl chloride and it is not certain that such a threshold may be determined in the near future. Therefore, EPA has developed standards which require emission reduction to the lowest level achievable using technological means. (Author abstract) (no Refs)

29 AU - Heath CW
AD - Chronic Diseases Div., Bureau Epidemiology, Center Disease Control, Atlanta, GA, 30333
TI - ENVIRONMENTAL POLLUTANTS AND THE EPIDEMIOLOGY OF CANCER.
SI - CARC/79/03005
SO - Environ Health Perspect; 27:7-10 1978
LA - ENG
AB - Approaches used in epidemiologic studies of environmental carcinogenesis are reviewed briefly. Some approaches, as with kepone, a chlorinated hydrocarbon insecticide, and with polybrominated biphenyls, start with exposed populations and measure disease frequency, the so-called prospective or cohort approach. Others, illustrated by vinyl chloride monomer studies, start with cases of cancer (hepatic angiosarcoma) and measure the extent of toxic exposure; ie, the retrospective or case history (case-control) approach. Other studies describe patterns of cancer occurrence and then seek correlations with potentially related population characteristics. All of these approaches are part of epidemiologic methodology and all are predicated on the existence of prior human exposure or prior disease occurrence. In this regard, major limiting factors involve concepts of latency and exposure dose. Although in vitro and animal test systems will never fully supplant human studies, they represent the only means for detecting potential carcinogenicity before human exposure has become widespread or long-established. (17 Refs)

30 AU - Frank AL
AD - Mount Sinai Sch. Medicine, New York, NY
TI - OCCUPATIONAL LUNG CANCER.
SI - ICDB/79/13543
SO - Pathogenesis and Therapy of Lung Cancer. Harris CC, ed. New York and Basel, Marcel Dekker, Inc., Lung Biology in Health and Disease, Vol. 10, 762 pp., 1978.
LA - ENG
AB - An overview is presented of factors that contribute to lung cancers associated with working areas. Major occupational respiratory carcinogens discussed are arsenic, asbestos, chloromethyl ethers, chromium, carbon compounds including coke and tar, mustard gas, nickel and radiation. Additional agents are discussed with proven, suspected, or possible carcinogenic risk: beryllium, carbamates, chloroprene, fibrous glass, isopropyl oil, methylene-bis-ortho-chloroaniline and nitrosamines. Also discussed, in connection with lung cancer, are smelting operations, various vegetable dusts, vinyl chloride and woodworking. The review concludes with a brief consideration of directions in occupational carcinogenesis. Despite the interest of various professional and legislative groups, it is pointed out that there will still be a need for the astute clinician to note unexpected associations. (146 Refs)

31 AU - Gideon J ; Schoultz K ; Bochinski J
AD - Natl. Inst. Occupational Safety and Health, Cincinnati, OH
TI - ENGINEERING CONTROL TECHNOLOGY IN POLYVINYL CHLORIDE POLYMERIZATION PLANTS (MEETING ABSTRACT).
SI - ICOS/79/11873
SO - Proceedings of the First Annual NIOSH Scientific Symposium held in Cincinnati, OH, 17-19 April, 1978 National Institute for Occupational Safety and Health, Cincinnati, OH, 1978.
LA - ENG
AB - The National Institute for Occupational Safety and Health, Division of Physical Sciences and Engineering has initiated a research program in control technology. The objective of this program is to facilitate the implementation of effective preventative measures in order to prevent occupational illness. The objectives of the plastics and resins industry control technology assessment were to document and evaluate effective control technology for plastics and resins polymerization plants. Particular emphasis was given to polyvinyl chloride (PVC) polymerization processes, since the relatively recent lowering in the personal exposure limit for vinyl chloride monomer (VCM) to an 8-hr 1 ppm time weighted av has required the application of state-of-the art controls. The present paper contains a summary of the control technology that was found to be effective in controlling VCM in processes manufacturing PVC by suspension, bulk, and dispersion polymerization. Controls necessary for VCM include process and equipment modification, isolation, local and general ventilation, work practices, personal protective equipment, workplace monitoring systems, employee/employer education, and on-going effort by both workers and management. All of these components must function together as an integrated coordinated system in order to assure worker protection under normal operating conditions. (no Refs)

32 AU - Simmon VF ; Tardiff RG
AD - Microbial Genetics Program, Stanford Res. Inst. International, Menlo Park, CA, 94025
TI - THE MUTAGENIC ACTIVITY OF HALOGENATED COMPOUNDS FOUND IN CHLORINATED DRINKING WATER.
SI - CARC/79/02788
SO - Water Chlorination; 2:417-431 1978
LA - ENG
AB - The mutagenic activities of 22 halogenated compounds found in chlorinated drinking water were determined using the Ames Salmonella/microsome procedure with S. typhimurium strains TA1535 and TA100. Two known carcinogens, carbon tetrachloride and chloroform, were not mutagenic in this system, probably because mutagenic metabolites were formed in insufficient amounts or they were so unstable that they did not survive long enough to penetrate the bacteria and interact with the DNA. Known carcinogens that were mutagenic were vinyl chloride, vinylidine chloride, 1,2-dichloroethane, 1,1,2-trichloroethylene, bis-(2-chloroethyl)ether, methyl iodide, and bromoform. Mutagenic

activity was also observed with bromodichloromethane, chlorodibromomethane, methylene bromide, bromochloromethane, methylene chloride, methyl bromide, methyl chloride, 2-chloropropane, 1-chloropropene, bis(2-chloroisopropyl)ether, n-butyl bromide, t-butyl bromide, and s-butyl bromide. The results indicate that the number and amount of alkyl halides in potable water should be reduced to lessen possible health hazards. (20 Refs)

33 AU - Szybinski Z ; Popiela T
AD - Instytut Medycyny Wewnetrznej AM, Al. Pokoju, Boczna 9, m. 7, 31-543 Krakow, Poland
TI - MULTISTAGE STUDIES AIMED AT EARLY DETECTION OF CHRONIC EFFECTS OF VINYL CHLORIDE AND MERCURY VAPORS.
SI - ICDD/79/10703
SO - Med Pr; 29(5):371-377 1978
LA - POL
AB - A total of 168 workers occupationally exposed to vinyl chloride (VC) vapors were subjected to multistage clinical investigations. Biochemical tests were performed in 34 subjects, liver scintigraphy in 30, and liver biopsies in 11. Of the 168 workers, 66 were exposed to an av concentration of 17.9 mg/m3 (36 of them for greater than 10 yr), and 102 to an av concentration of 133 mg/m3 (49 of them for greater than 10 yr). Hepatomegaly was found in 19/102 patients exposed to high concentrations and in 7/66 workers exposed to lower concentrations. Pathological liver enzyme activities and bilirubin levels were found in 45 workers exposed to high concentrations and in 24 workers exposed to lower concentrations of VC. Angiosarcoma was not found. (no Refs)

34 AU - Lee CC ; Bhandari JC ; Winston JM ; House WB ; Dixon RL ; Woods JS
AD - Midwest Res. Inst., 425 Volker Blvd., Kansas City, MO, 64110
TI - CARCINOGENICITY OF VINYL CHLORIDE AND VINYLIDENE CHLORIDE.
SI - CARC/79/02129
SO - J Toxicol Environ Health; 4(1):15-30 1978
LA - ENG
AB - The effects of exposure to 50, 250, or 1,000 ppm vinyl chloride (VC) or 55 ppm vinylidene chloride (VDC) for 6 hr/day, 5/days/wk, were studied in albino CD-1 mice and CD rats. The animals were killed after 1, 2, 3, 6, 9, or 12 mo. Bronchioloalveolar adenomas developed in 12/63, 22/63, and 48/69 mice exposed to 50, 250, and 1,000 ppm VC, respectively. Bronchioloalveolar adenomas developed in 6/35 animals exposed to VDC. Three of 29, 23/63, and 31/69 mice exposed to 50, 250, and 1,000 ppm VC, respectively, developed hemangiosarcomas (HS) in the liver. In the mice exposed to VDC, HS developed in the livers of two males and one female. Mammary gland tumors occurred in 9/34, 3/34, and 13/36 female mice exposed to 50, 250, 1,000 ppm VC respectively, and they included ductular adenocarcinomas and squamous and anaplastic cell carcinomas with metastasis to the lung. Malignant lymphomas were found in various organs of mice exposed to VC but not in any of the mice exposed to VDC. Twelve of 70 and 21/70 rats exposed to 250 and 1,000 ppm VC, respectively, developed HS in the liver;

3/34 female rats exposed to 250 ppm VC and 13/70 rats exposed to 1,000 VC also developed HS in the lung. Two of 36 male rats exposed to VDC developed HS in the mesenteric lymph node or sc tissue. It is concluded that VC is highly carcinogenic in mice; the incidence and severity of the tumors increased with dose and length of exposure. Rats were more resistant to the carcinogenic effects of VC and VDC. (26 Refs)

35 AU - Muller G ; Norpoth K ; Owczarski W
AD - Institut fur Staublungenforschung, Westring 10, D-4400 Munster, W. Germany
TI - IN VIVO TRAPPING OF A VINYL CHLORIDE METABOLITE BY MEANS OF 3,4-DICHLOROBENZENETHIOL.
SI - CARC/79/01939
SO - Int Arch Occup Environ Health; 42(2):137-139 1978
LA - ENG
AB - A method for trapping metabolites of vinyl chloride (VC) and 2,2'-dichlorodiethylether (DDE) is reported. Rats treated with VC and 3,4-dichlorobenzenethiol excrete S-2(3,4-dichlorothiophenyl)acetic acid in the urine. The structure of the compound was confirmed by gas chromatography-mass spectrophotometry. Similar results were obtained with DDE. Thus, the formation of ultimate carcinogens from nonelectrophilic precursors can be proved by the use of nucleophilic trapping agents both in vitro and in vivo. (9 Refs)

36 AU - Matufuji H
AD - Occupational Health Service Center, Inst. Science Labor, Japan
TI - VINYL CHLORIDE POISONING IN THE USSR: LITERATURE SURVEY.
SI - ICDB/79/06137
SO - Rodo Kagaku; 54(11):585-592 1978
LA - JPN
AB - Among workers exposed to vinyl chloride in western countries about 70 cases of hepatic angiosarcoma have been reported in Western countries, while none have been reported in the Soviet Union (USSR). However, many cases of chronic vinyl chloride poisoning have been reported in the USSR, while few have been reported in Western countries. The USSR requires poisoned workers to change to work unrelated to vinyl chloride and limited exposure time on the job. Tolerated limits of vinyl chloride are set at 10.7 ppm in the USSR, while the limit has been 500 ppm (1959-1971) to 200 ppm (1971-1975) in the United States. Inspection of USSR factories between 1953 and 1969 revealed that unacceptable levels (greater than 10.7 ppm) occurred in 2-80% of cases. Exposure regulations and the low tolerance limits in the USSR may explain why patients with chronic vinyl chloride poisoning with characteristic symptoms have not progressed to the point of developing hepatic angiosarcoma. (42 Refs)

37 AU - Biran D ; Gilbert SG ; Giacin JR
AD - Bait Yizchak, Israel
TI - SORPTION OF VINYLCHLORIDE BY SELECTED FOOD CONSTITUENTS.
SI - CARC/79/01526
SO - J Food Sci; 44(1):56-58 1978
LA - ENG
AB - The sorption of vinyl chloride monomer for selected food constituents (water, corn oil, oil-in-water emulsions, casein, and sucrose) was found to be affected significantly by the chemical nature of the food constituent, the initial concentration of VCM, and temperature. (12 Refs)

38 AU - Biran D ; Giacin JR ; Hayakawa K ; Gilbert SG
AD - Bait Yizchak, Israel
TI - VINYLCHLORIDE SORPTION BY DRY CASEIN PARTICLES: MECHANISTIC CONSIDERATIONS.
SI - CARC/79/01524
SO - J Food Sci; 44(1):59-61 1978
LA - ENG
AB - The amount of vinyl chloride monomer (VCM) sorbed by dry casein particles increases with a decrease in temperature or a reduction in moisture content of the particles. Adsorption is presumed to take place on the casein surface and to involve two distinctly different modes of sorption: active site sorption in which VCM molecules are attracted to the casein surface and an intermolecular attraction of VCM molecules, in which there is clustering around initially bound VCM. (10 Refs)

39 AU - Ames BN
AD - Berkeley, CA, 94720, Univ. California
TI - SESSION II. CARCINOGEN SCREENING: OBSTACLES AND OPTIONS. IN VITRO TESTING OF ENVIRONMENTAL MUTAGENS/CARCINOGENS.
SI - CARC/79/01094
SO - Structural Correlates of Carcinogenesis and Mutagenesis A Guide to Testing Priorities? Proceedings of the Second Food and Drug Administration Office of Science Summer Symposium held in Annapolis, 31 August-2 September 1977. Office of Science, FDA, Annapolis, MD, HEW Publication No (FDA)78-1046, 241 pp., 1978.
LA - ENG
AB - The development, accuracy, and recent applications of the Ames Salmonella mutagenesis test are discussed. Chemicals tested for mutagenicity and carcinogenicity have included flame retardants in children's pajamas, pesticides, vinyl chloride, and dibromo compounds in citrus-flavored soft drinks. (9 Refs)

40 AU - Fishbein L
AD - Natl. Center Toxicological Res., Little Rock, AR, 72207
TI - STRUCTURAL PARAMETERS ASSOCIATED WITH CARCINOGENESIS (HALOGENATED OLEFINS, VINYL AND ALLYL ANALOGS AND EPOXIDES).
SI - CARC/79/01092
SO - Structural Correlates of Carcinogenesis and Mutagenesis. A Guide to Testing Priorities? Proceedings of the Second Food and Drug Administration Office of Science Summer Symposium held in Annapolis, 31 August-2 September 1977. Office of Science, FDA Annapolis, MD HEW Publication No. (FDA)78-1046, 241 pp., 1978.
LA - ENG
AB - A number of reportedly carcinogenic industrial compounds (including halogenated olefins, vinyl and allyl analogs, and epoxides) were examined to determine if their structural, biological, and metabolic similarities could help predict their carcinogenicity. The chlorinated olefinic derivatives of major concern are vinyl chloride, vinylidene chloride, trichloroethylene, chloroprene, dichlorobutene, and perchloroethylene, all of which have been proved to be carcinogenic to humans and/or laboratory animals. Evidence suggests that all chlorinated ethylenes are metabolized to oxiranes (epoxides) as a first step. The oxiranes, which are strongly electrophilic, may react directly with cell nucleophiles or they may undergo intramolecular arrangements. No such structure-activity relationship has been demonstrated for the various vinyl and allyl analogs that are carcinogenic and/or mutagenic. In the case of the epoxides, the presence of a reactive functional group (as in epichlorohydrin) or a double bond (as in glycidaldehyde) near the epoxide appears to enhance carcinogenicity by allowing the chemical to act as a difunctional alkylating agent for macromolecules. Greater reliance should be placed on mutagenicity testing and on definitive metabolic and pharmacokinetic studies to augment structure-activity predictions of carcinogenicity. (79 Refs)

41 AU - Simmon VF
AD - SRI International, Menlo Park, CA, 94025
TI - STRUCTURAL CORRELATIONS OF CARCINOGENIC AND MUTAGENIC ALKYL HALIDES.
SI - CARC/79/01073
SO - Structural Correlates of Carcinogenesis and Mutagenesis. A Guide to Testing Priorities? Proceedings of the Second Food and Drug Administration Office of Science Summer Symposium held in Annapolis, 31 August-2 September 1977. Office of Science, FDA Annapolis, MD HEW Publication No. (FDA)78-1046, 241 pp., 1978.
LA - ENG
AB - The Ames Salmonella typhimurium microsome assay, using strain TA100, was used to determine the mutagenicity of 23 alkyl halides, 10 of which were unknown carcinogens. Twenty-one of these halides were mutagenic with and without S-9 liver microsome mix. The mutagenic compounds (c denotes proven carcinogen) included methyl bromide, methyl chloride, methyl iodide (c),

methylene chloride (c), bromochloromethane, methylene bromide, bromoform (c), dibromochloromethane, bromodichloromethane, vinyl chloride (c), vinylidene chloride (c), 1,1,2-trichloroethylene (c), bis(2-chloroethyl) ether (c), bis(2-chloroisopropyl) ether, 1-chloropropene, 3-chloropropene, epichlorohydrin (c), hexachlorobutadiene, 3-bromopropionic acid, 3-iodopropionic acid, and 3-chloropropionic acid. Two known carcinogens, carbon tetrachloride and chloroform, were not mutagenic in the presence or absence of the S-9 mix. It is likely that an insufficient amount of the mutagenic form was produced or that this form was so unstable it was unavailable to interact with the bacterial DNA. In general, the mutagenicity correlated with chemical reactivity. Of interest was the mutagenicity of methylene chloride, a widely used industrial chemical with broad environmental exposure (via paint removers and aerosol spray cans). (17 Refs)

42 AU - Weisburger EK
AD - NCI, Bethesda, MD
TI - CARCINOGENIC NATURAL PRODUCTS.
SI - CARC/79/01070
SO - Structural Correlates of Carcinogenesis and Mutagenesis. A Guide to Testing Priorities? Proceedings of the Second Food and Drug Administration Office of Science Summer Symposium held in Annapolis, 31 August-2 September 1977. Office of Science, FDA Annapolis, MD NEW Publication No. (FDA)78-11046, 241 pp., 1978.
LA - ENG
AB - A review is presented of carcinogenic compounds occurring naturally in plants and fungi. Studies have shown tobacco to contain nitrosamine, hydrazine, vinyl chloride, benz(a)pyrene, and polycyclic aromatic hydrocarbons, all proven carcinogens. The nut of the cycad plant, sometimes used as a source of starch, may contain cycasin, which is known to induce carcinomas of the liver, kidney, and intestine in laboratory animals. Among fungal carcinogens, ethyl carbamate (urethane), a by-product of food and beverage fermentation, has been shown to induce lung and liver tumors when administered to mice and newborn rats, respectively. Mycotoxins, particularly aflatoxin B1 (and to a lesser extent B2, G1, and G2) produced by the fungus Aspergillus flavus is an extremely potent carcinogen and readily contaminates many types of grains and oilseeds. It is postulated that many other naturally occurring carcinogens are present in the environment but these are generally thought to be weak or adequately defended against by normal detoxification mechanisms, repair enzymes, and natural protective substances in foods (eg, indole derivatives in vegetables). (49 Refs)

43 AU - Chatterji DC ; Greene RF ; Gallelli JF
AD - Pharmaceutical Development Service, Pharmacy Dept., Clinical Center, NIH, Bethesda, MD, 20014
TI - MECHANISM OF HYDROLYSIS OF HALOGENATED NITROSOUREAS.
SI - CATH/79/00638
SO - J Pharm Sci; 67(11):1527-1532 1978
LA - ENG
AB - The hydrolysis of chlorozotocin (CZT), carmustine (BCNU), lomustine (CCNU), semustine (methyl-CCNU), 1,3-bis(2-fluoroethyl)-1-nitrosourea, and streptozotocin (SZT) were investigated using CZT as a model. The hydrolytic reactions of the nitrosoureas at pH 3-8 represented a summation of water- and hydroxide ion-catalyzed reactions. The later reaction was the sum of two parallel reactions. The relative contribution of each reaction depended upon pH, which resulted in different product distributions. Dianionic phosphate increased the production of free chloride ion without causing a significant change in the hydrolysis rate. The active alkylating intermediate of the chloroethylnitrosoureas under physiologic conditions has not yet been identified, but it may be the 2-chloroethyl cation or the corresponding diazonium hydroxide. The increased chloride ion production caused by phosphate dianion led to a proposed mechanism whereby the 2-chloroethylcarbonium ion acts as a bifunctional alkylating agent of phosphate dianion. The 2-chloroethylcarbonium ions derived from BCNU, CCNU, methyl-CCNU, and CZT may act as bifunctional alkylating agents to form inter- or intrastrand nucleic acid cross-links. The inability of the non-halogenated nitrosoureas (such as SZT) to form bifunctional reactive intermediates may account for their lower activity. The higher activity of the halogenated nitrosoureas may also be caused by significant production of acetaldehyde and vinyl cation products at physiologic pH. (11 Refs)

44 AU - Curran KL ; Kupchella CE ; Sandoz J ; Tamburro CH
AD - Cancer Center and Div. Digestive Diseases and Nutrition, Univ. Louisville Sch. Medicine, Louisville, KY
TI - URINARY GLYCOSAMINOGLYCAN PATTERNS IN HUMAN HEPATIC ANGIOSARCOMA, HEPATOMA, AND IN WORKERS AT RISK FOR ANGIOSARCOMA (MEETING ABSTRACT).
SI - ICDD/79/01166
SO - Gastroenterology; 75(5):959 1978
LA - ENG
AB - A previous study reported an aberration in glycosaminoglycans (GAGs) eluted from anion-exchange columns with 1.25 and 1.5 M NaCl in the urine of patients with hepatic angiosarcoma. A controlled pilot study examined urinary GAG patterns in workers at risk for angiosarcoma. Six individuals with a history of high vinyl chloride exposure and documented liver disease were paired with individuals with a high exposure index to vinyl chloride but no clinical liver disease. Similarly six persons with low exposure but abnormal liver function were paired with low exposure/normal liver function individuals. A 24-hr urine was

collected from each individual and the GAGs analyzed by anion-exchange chromatography. Individuals with clinically active liver disease at the time of this study were found to have urinary GAG excretion patterns which were similar to those described in angiosarcoma. No significant differences were found between high vs low vinyl chloride exposure or between those with inactive liver disease and those with normal liver function. GAG excretion was also studied in an additional hepatic angiosarcoma and human hapatoma and confirm the reported urinary changes. These findings support the concept that urinary GAGs are increased only in active hepatic disease and may be useful in evaluating the degree of activity at the various stages of liver disease in humans. (no Refs)

45 AU - Jones RN ; Weill H
AD - Tulane Medical Center, New Orleans, LA
TI - OCCUPATIONAL LUNG DISEASE.
SI - CARC/79/00464
SO - Respir Care; 23(10):989-998 1978
LA - ENG
AB - Occupational lung disorders are reviewed with regard to their causative agents and the pathologic responses evoked. Dust macules (which are caused by inhaling tin, barium, iron, or coal salts), pulmonary fibrosis, hypersensitivity pneumonia, beryllium lung disease, and obstructive airways diseases are discussed. Asbestos, arsenic, chromates, nickel radioactive inhalants, the halo ethers, and vinyl chloride monomer may induce respiratory tract tumors. Asbestos may also cause cancer of the larynx and carcinoma of the gastrointestinal tract, and brain tumors and hemangiosarcoma of the liver may result from exposure to vinyl chloride. The diagnosis of occupational lung disease is discussed, as is the setting and enforcement of permissible dust exposure levels. (10 Refs)

46 AU - Tamburro CH ; Creech JL ; Davis A ; Greenberg RA
AD - Cancer Center, Univ. Louisville Sch. Medicine, Louisville, KY
TI - INDOCYANINE GREEN CLEARANCE AS THE PROSPECTIVE INDICATOR OF HEPATOCELLULAR CHEMICAL TOXICITY (MEETING ABSTRACT).
SI - ICDB/79/00973
SO - Gastroenterology; 75(5):989 1978
LA - ENG
AB - Standard biochemical liver tests (alanine (SGPT) and aspartate aminotransferase, gamma glutamyl transpeptidase, alkaline phosphatase (AP), bilirubin, lactic acid dehydrogenase, prothrombin time, albumin, and cholesterol) are the mainstay for clinical screening of liver injury, including cancer development, in industrial environments. Twelve-hundred chemical workers were screened with physical examination, standard biochemical liver tests (SBLT), liver-spleen scans and indocyanine green (ICG) clearance (0.5, 2.5, & 5.0 mg/kg doses) over a four-year period. Individuals with persistent abnormalities received a liver biopsy. Every employee had a ranked ordered exposure work history for 22 chemicals used at 350 job classifications over the past 35

yr. The frequency with which each SBLT and ICG could identify liver injury were studied. ICG was found to be the most effective in correctly identifying the presence of liver damage. Vinyl chloride workers also showed a progressively increased frequency of abnormal ICG clearances with progressive chemical exposure. The SGPT, AP, and other studies only show increased abnormalities late in the exposure, often concomitant with clinical manifestations of overt hepatic disease. This data illustrate th inability of SBLTs to detect early latent hepatic injury and the ability of ICG clearance to identify prospectively early, developing lesions and follow their progressive course. (no Refs

47 AU - Roche J ; Fournet J ; Hostein J ; Panh M ; Bonnet-Eymard JB
AD - Clinique d'Hepatologie-Gastroenterologie, C.H.U. de Grenoble, Hopital des Sablons, F 38700 La Tronche, France
TI - HEPATIC ANGIOSARCOMA DUE TO VINYL CHLORIDE. REPORT OF 4 CASES.
SI - CARC/79/00300
SO - Gastroenterol Clin Biol; 2(8/9):669-678 1978
LA - FRE
AB - Angiosarcomas of the liver developed in four men (aged 63, 48, 38, and 42 yr) who had worked in the production of vinyl chloride (VC) for 12, 26, 10, and 12 yr, respectively. Initial symptoms were abdominal pain in three patients and back pain (due to metastases) in one. The most constant laboratory indication was elevated serum alkaline phosphatase (55-77 milli(m)IU); gamma-glutamyltranspeptidases were markedly elevated (217 and 298 mIU) in the two patients in which they were measured. alpha-Fetoprotein was normal, and SGOT and SGPT were close to normal. Two patients had hepatomegaly, which was the principal clinical finding in the literature on other VC-induced angiosarcomas. Arteriography revealed the angiosarcoma in the four patients, although liver scans with Tc99m also indicated liver pathology in two patients. Gastrointestinal tract hemorrhage occurred in two patients and hemorrhage into the peritoneum in two. Survival was 2-13 mo. Clinical, biochemical and histological features of previously reported patients with VC-induced angiosarcomas are reviewed. (50 Refs)

48 AU - Green T ; Hathway DE
AD - Imperial Chemical Industries Ltd., Central Toxicology Lab., Alderley Park, Cheshire SK10 4TJ, England
TI - INTERACTIONS OF VINYL CHLORIDE WITH RAT-LIVER DNA IN VIVO.
SI - CARC/79/00007
SO - Chem Biol Interact; 22(2/3):211-224 1978
LA - ENG
AB - The reaction of vinyl chloride (VC) with liver DNA in Wistar rats and the reaction of chloroacetaldehyde (CAA) and calf thymus DNA were investigated. 9beta-D-2'-Deoxyribofuranosylimidazo-(2,1,i)-purine (ethenodeoxyadenosine) and 1beta-D-2'-deoxyribofuranosyl-1,2-dihydro-2-oxoimidazo-(1,2-c)-pyrimidine (ethenodeoxycytidine) were identified in the enzyme hydrolysates obtained (1) from calf thymus DNA that had been

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modified by chemical reaction with CAA and (2) from liver DNA prepared from rats that had been exposed po to VC in their drinking water (250 ppm) for approx 2 yr. Thus, VC-derived chloroethylene oxide and/or CAA behaved as a bifunctional alkylating agent toward deoxyadenosine and deoxycytidine residues of DNA. It is concluded that modification of the DNA structure by VC, through imidazo-cyclization of deoxyadenosine and deoxycytidine residues and through depurination of the resulting ethanodeoxyadenosine residues, is related to the mutagenicity of VC. The carcinogenicity of VC in animals and in humans and its mutagenic properties after biotransformation (by microsomal enzymes) into the active metabolites chloroethylene oxide and CAA, which show electrophilic reactivity toward DNA, would appear to conform with the idea of a relationship between carcinogenesis and mutagenesis. (41 Refs)

49 AU - Cylwik B ; Grabowski H ; Gula-Fietkiewicz E
AD - Zaklad Anatomii Patologicznej, Instytut Biostruktury AM, ul. Kilinskiego 1, 15-230 Bialystok, Poland
TI - PRIMARY MALIGNANT HEMANGIOENDOTHELIOMA OF THE LIVER WITH METASTASES TO THE LUNGS, ADRENAL GLANDS AND LYMPH NODES.
SI - ICDB/78/30389
SO - Pol Arch Med Wewn; 60(2):183-187 1978
LA - POL
AB - Malignant hemangioendothelioma of the liver and metastases to the left lung, adrenal glands and lymph nodes were found at autopsy in a 69-yr-old man who died from bronchopneumonia with lung emphysema, circulatory insufficiency, chronic gastritis and cachexia. The patient had never been exposed to vinyl chloride, Thorotrast, or any other substance believed to induce such tumors. (11 Refs)

50 AU - Simmon VF ; Kauhanen K ; Mortelmans K ; Tardiff R
AD - Stanford Res. Inst., Menlo Park, CA
TI - MUTAGENIC ACTIVITY OF CHEMICALS IDENTIFIED IN DRINKING WATER (MEETING ABSTRACT).
SI - ICDB/78/30040
SO - Mutat Res; 53(2):262 1978
LA - ENG
AB - Approx 300 chemicals have been identified in finished drinking water in the US. Some of these chemicals are known to be carcinogens in rodents (eg, aldrin, carbon tetrachloride) and/or humans (benzopyrene). We have begun to analyze these chemicals for their mutagenic activity in microorganisms. Of 128 chemicals that we have tested, 21 were mutagenic in preliminary spot tests on Salmonella typhimurium TA100 (without metabolic activation). We have obtained dose-dependent mutagenic responses with 19 of these compounds (benzopyrene, bromochloromethane, bromodichloromethane, bromoform, bromomethane; n-butyl bromide, sec-butyl bromide, tert-butyl bromide, technical grade chlordane, chlorodibromomethane, bis(2-chloroethyl) ether, dibromomethane, 1,2-dichloroethane, 1,1-dichloroethylene, hexachloro-1,3-butadiene, iodomethane, methyl chloride, methylene

chloride and vinyl chloride) in strains of S typhimurium. Additional mutagenicity assays using Escherichia coli WP2 and Saccharomyces cerevisiae D3 are underway. (no Refs)

51 AU - Rannug U ; Ramel C
AD - Environmental Toxicology Unit, Wallenberg Lab., Univ. Stockholm, Stockholm, Sweden
TI - THE MUTAGENICITY AND METABOLISM OF 1,2-DICHLOROETHANE (MEETING ABSTRACT).
SI - ICDB/78/30026
SO - Mutat Res; 53(2):251-252 1978
LA - ENG
AB - The tar-like waste product from the vinyl chloride production has shown mutagenic properties in the Salmonella microsome test using strain TA1535. Ethylenedichloride (1,2-dichloroethane), one of the main components in the tar, was also mutagenic in the test but cannot be responsible for the mutagenicity of the total tar. In both cases an increase in the number of mutants is seen when the metabolizing system is present, but the activation of the tar is NADPH-dependent and the activation of 1,2-dichloroethane is NADPH-independent. The metabolism and mutagenicity of the latter was therefore studied in more detail with Salmonella and different metabolizing systems. From the results it can be concluded that the activation to a more potent mutagen is carried out by enzymes in the soluble fraction. This activation is further stimulated by addition of glutathione to the system, indicating a formation of a conjugate between 1,2-dichloroethane and glutathione. 1,2-Dichloroethane has also been tested on the same Salmonella strain (TA-1353) with perfused rat-liver as metabolizing system. In this test the bile produced, within half an hour after the addition of 1,2-dichloroethane, is strongly mutagenic, while no effect can be seen in the perfusate. A corresponding enhancement in the mutagenicity of 1,2-dichloroethane was seen if the bacteria were incubated in the presence of enzyme preparations of glutathione S-transferases, glutathione and 1,2-dichloroethane. It can therefore be concluded that one metabolic pathway of 1,2-dichloroethane involves direct conjugation with glutathione. This conjugate is excreted in the bile, where the mutagenicity is found. Normally the conjugation with glutathione is regarded as a detoxication, but in this case the effect is quite the contrary. The substance is activated by the conjugation. The results also illustrate the usefulness of the mutagenicity test based on Salmonella and in vitro metabolism in tracing metabolic pathways which could be more difficult to detect in vivo. (no Refs)

52 AU - Ivanetich KM ; Katz ID ; Aronson I
AD - Dept. Physiology and Medical Biochemistry, Univ. Cape Town Medical Sch., Cape Town, S. Africa
TI - THE METABOLIC ACTIVATION OF VINYL CHLORIDE IN VITRO (MEETING ABSTRACT).
SI - ICDB/78/30020
SO - Mutat Res; 53(2):204 1978
LA - ENG
AB - In the presence of hepatic microsomes, vinyl chloride produces a 'Type I' difference spectrum and stimulates carbon monoxide inhibitable NADPH consumption. Vinyl chloride, therefore, appears to bind to and to be metabolized by hepatic microsomal cytochrome P-450 in vitro. The Ks value for the binding of vinyl chloride to cytochromes P-450 in uninduced microsomes (80 mM) is decreased to approx 10 mM following phenobarbital or 3-methylcholanthrene induction. The change in Amax and max velocity values are not altered by 3-methylcholanthrene induction, but are enhanced 2-to 3-fold by phenobarbital induction. These resuts indicate that more one type P-450 cytochrome binds and metabolizes vinyl chloride, but that the cytochrome P-450 induced by phenobarbital plays a major role in these processes. In the presence of NADPH and hepatic microsomes, vinyl chloride mediates the degradation of the heme moiety of cytochrome P-450. Under these conditions, the levels of other hepatic microsomal enzymes are not affected. The effect of vinyl chloride on the levels of cytochrome P-450 is slight in uninduced or 3-methylcholanthrene microsomes but is striking in phenobarbital microsomes. The effect is abolished in the absence of NADPH or vinyl chloride and is diminished by reduced glutathione. The activated metabolite of vinyl chloride produced by cytochrome P-450 may in part mediate the mutagenic and carcinogenic effects of vinyl chloride. (no Refs)

53 AU - Dreven C ; Kuroki T ; Montesano R
AD - International Agency for Res. on Cancer, 150 cours Albert Thomas, 69008, Lyon, France
TI - MICROSOME-MEDIATED MUTAGENESIS OF A CHINESE HAMSTER CELL LINE BY VARIOUS CHEMICALS (MEETING ABSTRACT).
SI - ICDB/78/29991
SO - Mutat Res; 53(2):101-102 1978
LA - ENG
AB - A microsome-mediated mutagenesis system for mammalian cells has been established using V79 cells, a Chinese hamster cell line. The cells, grown in monolayer, were treated with the chemicals to be tested in the presence of a post-mitochondrial fraction (S15) and cofactors for 1 hr or more (depending on the chemicals), washed and incubated for 2-3 hr on fresh culture medium, and then the cells were plated for toxicity and mutagenicity assays. Mutation was determined by resistance to 20 ug/ml 8-azaguanine or 1 millM ouabain. In our assay system, S15 and cofactors were not found to be toxic to the cells. The chemicals tested included 12 nitrosamines, 3 chlorinated hydrocarbons, several polycyclic hydrocarbons and aflatoxin B1. Dose-related mutation and

cytotoxicity were induced after incubation with dimethylnitrosamine (DMN) only in the presence of both the S15 fraction of the livers of BD-V1 male rats and the cofactors. Pretreatment of rats with phenobarbital (PB) led to an approx 2-fold increase in the mutation rate over that with the untreated rats are DMN concentrations ranging from 2 to 50 milliM, while aminoacetonitrile pretreatment reduced the mutagenic effect. Methylcholanthrene pretreatment resulted in an increase in the mutation frequency with a higher concentration of DMN (50 milliM). A good correlation was found between in vivo carcinogenicity and this mutagenesis test: with the exception of N-nitrosomethylphenylamine, the carcinogenic nitrosamines (DMN, N-nitrosodiethylamine, N-nitrosodi-n-propylamine, N-nitrosodi-n-butylamine, N-nitrosodi-n-pentylamine, N-nitrosomethyl-n-propylamine, N-nitrosomorpholine, N-nitrosopyrrolidin, N-nitroso-N'-methylpiperazine, N-nitrosomethylphenylamine) were mutagenic to V79 Chinese hamster cells in the presence of the PB-pretreated S15 fraction and cofactors. The non-carcinogenic N-nitrosodiphenylamine and N-nitrosomethyl-tert-butyl-amine had no mutagenic effect. Vinyl chloride, vinylidene chloride and 2-chlorobutadiene were tested, but only vinyl chloride was mutagenic in the presence of PB-pretreated S15 and cofactors while the others were found to be toxic but not mutagenic. The mutagenicity of polycyclic hydrocarbons and aflatoxin B1 is now under investigation. (no Refs)

54 AU - Leonard A ; Decat G ; Leonard ED
AD - Mammalian Genetics Lab., C.E.N-S.C.K., B-2400 Mol, Belgium
TI - CYTOGENETIC INVESTIGATIONS ON LYMPHOCYTES FROM WORKERS EXPOSED TO VINYL CHLORIDE (MEETING ABSTRACT).
SI - ICDB/78/29965
SO - Mutat Res; 53(2):219 1978
LA - ENG
AB - Male workers from the polymerization department of a vinyl chloride (VC) factory, people employed in the laboratory of another VC plant and controls from outside the factory environment were examined for the presence of chromosome aberrations in blood lymphocytes. The incidence of chromatid aberrations (gaps and breaks) and of chromosome gaps was not significantly increased after VC exposure, but more severe chromosome anomalies such as chromosome fragments, rings and dicentrics were observed in most of the workers from the polymerization department. The medical history of the workers shows that most people from the polymerization department received several radiographies. The conclusion that the chromosome fragments and chromosome dicentics result from VC exposure remains, therefore, dubious. It is much more probable that these anomalies originate from the diagnostic exposure to ionizing radiation. (no Refs)

55 AU - Fucerova M ; Polivkova Z
AD - Pediatric Dept., Postgraduate Medical Inst., Prague, Czechoslovakia
TI - MUTAGENIC EFFECTS OF DIFFERENT MUTAGENS ON HUMAN CHROMOSOMES IN VITRO AND IN VIVO AS DETECTED BY CONVENTIONAL AND 'HARLEQUIN' METHODS (MEETING ABSTRACT).
SI - ICOB/78/29960
SO - Mutat Res; 53(2):215 1978
LA - ENG
AB - In vitro studies were performed which considered the mutagenic effects of Mitomycin C, Alexan, triethylene thiophosphoramide (TEPA), Imuran, Vincristine and Vinblastine on peripheral human lymphocytes exposed for the last 24 hr of cultivation to 10**-2, 10**-3, 10**-4, 10**-5, 10**-6 and 10**-7 mg/ml concentrations of these chemicals. The lowest concentrations were ineffective when using conventional cytogenetic technique. The possible mutagenic effect of this lowest concentration of 10**-7 mg/ml was tested also by 'harlequin' method scoring the numbers of sister chromatid exchange (SCE). Only Mitomycin C, Alexan, Imuran and TEPA were found to increase the number of SCE, while Vincristine and Vinblastine did not induce any significant changes. In vivo studies dealt with patients treated with Imuran, with children vaccinated against variola and with workers occupationally exposed to vinyl chloride. Again both conventional and 'harlequin' techniques were used, comparing the relationship between the number of gross chromosome aberrations and the number of SCE induced by in vivo exposure to these three mutagens. The results detected by conventional and 'harlequin' cytogenetic methods have revealed a highly specific susceptibility of human peripheral lymphocytes to different types of mutagens after in vitro and in vivo exposures. (no Refs)

56 AU - Barbin A ; Planche G ; Croisy A ; Malaveille C ; Bartsch H
AD - Unit Chemical Carcinogenesis, International Agency for Res. on Cancer, 150 cours Albert Thomas, 69008 Lyon, France
TI - DETECTION OF ELECTROPHILIC METABOLITES OF HALOGENATED OLEFINS WITH 4-(4-NITROBENZYL)PYRIDINE (NBP) OR WITH SALMONELLA TYPHIMURIUM (MEETING ABSTRACT).
SI - ICOB/78/29930
SO - Mutat Res; 53(2):150 1978
LA - ENG
AB - Metabolic conversion of volatile substances can be assayed by passing a gaseous mixture of the test compound and oxygen (air) through a mouse liver microsomal system and by trapping volatile alkylating metabolites by reaction with excess NBP. Using this system, epoxide formation from vinyl chloride or vinyl bromide was demonstrated; 2-chloro-1,3-butadiene (chloroprene) yielded an alkylating intermediate although, 1,1-difluoroethylene, 1,1-dichloroethylene and trichloroethylene did not. Chloroethylene oxide, perhaps the ultimate carcinogenic metabolite of vinyl chloride, showed potent biological activity in various short-term tests for the detection of potential

carcinogens. In all the in vitro assays used, the color reaction with NBP showed the highest sensitivity for detecting chloroethylene oxide at a 2 uM concentration. S typhimurium TA100, in the presence of a 9000 x g supernatant of PB-treated mice, was exposed to gaseous mixtures of the following test compounds/air. Mutation rates (his+ revertant colonies/umol/hr/plate) taken from the linear region of time and dose-dependent assays either with or without NADP+, were as follows: vinyl acetate, 1,1-difluoroethylene and trichloroethylene 0 (0); vinyl chloride 6 (2); 1,1-dichloroethylene 15 (1); vinyl bromide 26 (9); 2-chloro-1,3-butadiene 51 (9); 1-chloro-1,3-butadiene 157 (81); 3,4-dichlorobutene-1, 490 (345). 1,4-Dichlorobutene-2 (77% trans-isomer), when incorporated in the soft agar layer, showed a mutagenic effect in TA100. Microsomal fractions from mouse and human liver enhanced the mutagenicity three-fold. The putative synthetic metabolite 1,4-dichloro-2,3-epoxy butane was, however, four times less mutagenic in TA100 than in the parent olefin. (no Refs)

57 AU - Carere A ; Ortali VA ; Cardamone G ; Morpurgo G
AD - Istituto Superiore di Sanita, Universita di Roma, Rome, Italy
TI - MUTAGENICITY OF DICHLORVOS AND OTHER STRUCTURALLY RELATED PESTICIDES IN SALMONELLA AND STREPTOMYCES.
SI - ICOB/73/29748
SO - Chem Biol Interact; 22(2/3):297-308 1978
LA - ENG
AB - The following pesticides: azinphosmethyl, diallate, dichlorvos, EPTC (S-ethyldipropyl thiol + carbamate), fenchlorphos, mevinphos, monocrotophos, noruron, parathionmethyl, triallate, trichlorphon and vegadex were tested for the ability to induce his+ revertants in four histidine-requiring strains of Salmonella typhimurium, TAI 535 (missense), TAI 536, TAI 537 and TAI 538 (frame-shift), and resistance to low levels of streptomycin in Streptomyces coelicolor. Dichlorvos, which is a phosphoric ester with a dichlorovinyl group as side chain, and trichlorphon, which is known for its spontaneous conversion in dichlorvos, are both mutagenic in Salmonella (strain TAI 535) and Streptomyces. Five organophosphorus pesticides similar to dichlorvos but devoid of the vinyl group are not mutagenic. Three carbamates, diallate, triallate and vegadex, which contain a chloroallyl group similar to the vinyl group of dichlorvos are mutagenic in Streptomyces; triallate and vegadex are powerful mutagens also in Salmonella (strain TAI 535); two other carbamates devoid of the chlorinated group are not mutagenic. The results suggest that the presence of a vinyl chloride or allyl chloride group in the molecule of these pesticides is responsible for the ability to induce point mutations in Salmonella and Streptomyces. (Author abstract) (27 Refs)

58 AU - Ungvary G ; Hudak A ; Tatrai E ; Lorincz M ; Folly G
AD - Dept. Experimental Pathology, State Inst. Occupational Health Budapest, H-1450 Budapest P.O.B. 22, Hungary
TI - EFFECTS OF VINYL CHLORIDE EXPOSURE ALONE AND IN COMBINATION WITH TRYPAN BLUE--APPLIED SYSTEMATICALLY DURING ALL THIRDS OF PREGNANCY--ON THE FETUSES OF CFY RATS.
SI - CARC/78/07866
SO - Toxicology; 11(1):45-54 1978
LA - ENG
AB - The teratogenic and embryotoxic effects of vinyl chloride and/or trypan blue were investigated in CFY rats. VC was found in the fetal and maternal blood as well as in the amniotic fluid of pregnant CFY rats exposed to an atmospheric concentration of 5,500, 18,000, or 33,000 mg/m**3 VC for 2.5 hr on gestation day 18, indicating the permeability of the placenta to the agent. Investigation of the offspring of pregnant rats exposed continuously to 4,000 mg/m**3 VC during the first, second, or last trimester showed that VC has no teratological or embryotoxic effects when applied during the second or last trimester. However, exposure to VC during the first trimester resulted in an increased fetal mortality and in the manifestation of embryotoxic effects. Fetal losses and the induction of CNS malformations due to trypan blue (50 mg/kg sc on gestation days 7 and 8) were not potentiated by 4,000 mg/m**3 VC. Occupational exposure of women of childbearing age may be hazardous. (34 Refs)

59 AU - Thomassen MJ ; Buoen LC ; Brand I ; Brand KG
AD - Dept. Pediatrics, Case Western Reserve Univ., Cleveland, OH, 44106
TI - FOREIGN-BODY TUMORIGENESIS IN MICE: DNA SYNTHESIS IN SURFACE-ATTACHED CELLS DURING PRENEOPLASIA.
SI - CARC/78/07817
SO - JNCI; 61(2):359-363 1978
LA - ENG
AB - DNA synthesis throughout the stages of foreign body (FB) tumorigenesis was investigated to provide insight into the role of macrophages in the development of neoplasia. Four unplasticized vinyl chloride-vinyl acetate copolymer films (15 x 22 mm) were implanted sc into the flanks of (CBA/H x CBA/H-T6)F1 mice. The animals were pulsed with **3H-thymidine at various times during the next 15 mo. DNA synthesis occurred consistently in the film-attached cells, predominantly macrophages, throughout the preneoplastic phase in both male and female mice. The labeling rate was calculated to be 5-15 cells/1,000, the cell turnover rate to be 1.5%-4.5%/day, and the mitotic rate to be less than 3 cells/10,000. Giant cells with less than 10 nuclei were labeled synchronously and asynchronously. No DNA synthesis was detected in giant cells with greater than 10 nuclei. The results show that the macrophages were not dormant with respect to DNA synthesis. (16 Refs)

60 AU - Delorme F
AD - Centre Hospitalier Regional de la Mauricie, C.P. 1130, Shawinigan-Sud, Quebec, Canada
TI - TEN CASES OF ANGIOSARCOMA OF THE LIVER IN VINYL CHLORIDE WORKERS IN CANADA.
SI - CARC/78/07702
SO - Ann Anat Pathol (Paris); 23(2):97-104 1978
LA - FRE
AB - Ten cases of hepatic angiosarcoma were found among employees of a vinyl chloride plant in Shawinigan, Canada. All patients had been exposed to vinyl chloride vapors. The av age of the patients was 50 yr (41-61 yr); the length of occupational exposure to vinyl chloride averaged 16 yr 10 mo (ranging from 5 yr, 8 mo to 26 yr); and the time lapse between first exposure and diagnosis was 20.5 yr (11-18 yr). Survival after diagnosis averaged 4.4 mo (1-8 mo). The risk of hepatic angiosarcoma appears to be highest among vat cleaners, pipe fitters, and polymerization workers. (16 Refs)

61 AU - Delorme F
AD - Centre Hospitalier Regional de la Mauricie, C.P. 1130, Shawinigan-Sud, Quebec, Canada
TI - ASSOCIATION OF AN ANGIOSARCOMA OF THE LIVER WITH A HEPATOMA IN A VINYL CHLORIDE WORKER.
SI - CARC/78/07701
SO - Ann Anat Pathol (Paris); 23(2):105-113 1978
LA - FRE
AB - A 51-yr-old man who had been exposed occupationally to vinyl chloride vapors for 23 yr, 4 mo died in a coma with jaundice. Autopsy revealed the association of a hepatic angiosarcoma with a hepatoma. Alcohol consumption by the patient was negligible. The association of the two tumors is the first ever to be reported in the literature. This case raises doubts about the theory that suggests that vinyl chloride induces vascular tumors in humans. (22 Refs)

62 AU - Vainio H
AD - Dept. Industrial and Toxicology, Inst. Occupational Health, Haartmaninkatu 1, SF-00290 Helsinki 29, Finland
TI - VINYL CHLORIDE AND VINYL BENZENE (STYRENE)--METABOLISM, MUTAGENICITY AND CARCINOGENICITY.
SI - CARC/78/07652
SO - Chem Biol Interact; 22(1):117-124 1978
LA - ENG
AB - The metabolism, mutagenicity, and carcinogenicity of vinyl chloride, (VC) and vinyl benzene (styrene) are reviewed briefly. VC and styrene are mutagenic in bacterial test systems, Drosophila, yeast, and mammalian cells. The mutagenicity of VC in bacterial test systems depends, at least partially, on metabolic activation by microsomal enzymes. Chloroethylene oxide, the primary biotransformation product of VC, is a potent mutagenic and alkylating agent. Styrene is mutagenic to Salmonella

typhimurium, but only after metabolic activation, whereas styrene oxide, its primary biotransformation product, is mutagenic to Salmonella without activation. In several studies, an excess of chromosome aberrations (compared with controls) was found in the lymphocytes of workers exposed to VC monomer. In addition, an excess fetal loss occurred among women whose husbands are heavily exposed to VC. Workers exposed to styrene also had increased chromosome aberrations in their lymphocytes. Both chloroethylene oxide and styrene oxide bind covalently to cellular macromolecules. VC is carcinogenic in rats (skin, lung, bone, liver) and humans (liver, brain, lung, and lymphatic tissue). Styrene oxide was a weak carcinogen when applied to mouse skin. Styrene is currently being tested in animals. These findings raise concern about the possible genetic risks of VC and styrene to humans. (55 Refs)

63 AU - Neumayr A
AD - I. Medizinische Abteilung, Krankenanstalt Rudolfstiftung, Juchgasse 25, A-1030 Wien, Austria
TI - NEW DEVELOPMENTS IN HEPATOLOGY.
SI - ICDB/78/27768
SO - Therapiewoche; 28(34):5996-5998,6000,6003-6007 1978
LA - GER
AB - Recent findings in the study of liver disease are reviewed. Viral hepatitis, the hepatorenal syndrome, environmentally induced hepatic tumors, vinyl chloride and resulting hepatic angiosarcoma, recent advancements in portal vein surgery and scintisplenoportography, and new application methods of the Chiba needle in percutaneous transhepatic cholangiography are discussed. (58 Refs)

64 AU - Matos EL ; De Lustig ES
AD - Departamento de Investigaciones, Instituto de Oncologia Angel H. Roffo, Av. San Martin 5481, 1417 Buenos Aires, Argentina
TI - THE ROLE OF CHEMICAL CARCINOGENS IN ENVIRONMENTAL CONTAMINATION.
SI - ICDB/78/27724
SO - Medicina (B Aires); 38(2):200-203 1978
LA - SPA
AB - Known carcinogens present in the environment are reviewed. The principal fixed sources of carcinogens contaminating the atmosphere are domestic and industrial incinerators, in addition to petroleum refineries which emit volatile and highly carcinogenic substances. Airborne carcinogens (automobile pollutants) are considered more dangerous as they have easier access to human repiratory passages. Solid phase aerosol carcinogens include polycyclic and heterocyclic aromatic hydrocarbons, aromatic amines and inorganic substances including nickel, beryllium, arsenic and asbestos. Liquid aerosol carcinogens consist mainly of benzene compounds, bischloromethylether, halogenated compounds, nitrosamines and their precursors, sulfated compounds, and nitrogenated precursors of nitrous acid and nitrosamines. Gas phase carcinogens include anhydrous oxidants such as nitrogen dioxide and sulfurous

anhydride, formaldehyde, halogenated carbon compounds, and vinyl chloride. Benzopyrene and asbestos are considered to represent the greatest risk due to their high conentration and diffusion in the environment. An increase of 1 ug benzopyrene/1,000 meter**3 of air can result in a 5% increase in tumors. Large asbestos fibers carry a greater carcinogenic risk as their ability to absorb hydrocarbons, metal particles, viral particles and other carcinogens from the air is augmented by their size. Cancer due to asbestos inhalation is greater among smokers than non-smokers. Water contamination is principally by hydrocarbon derivatives such as 3,4-dibenzanthracene, 1,2,5,6-dibenzanthracene, 7,12-methylbenzanthracene and 20-methylcolanthrene. Alimentary contamination is mainly by nitroso compounds, natural carcinogens such as aflatoxin, cycasine, arsenic, molybdenum, and food dyes. (16 Refs)

65 AU - Rall DP
AD - Natl. Inst. Environmental Health Science, Research Triangle Park, NC, 27709
TI - VALIDITY OF EXTRAPOLATION OF RESULTS OF ANIMAL STUDIES TO MAN (MEETING ABSTRACT).
SI - ICDB/78/27370
SO - The Scientific Basis for the Public Control of Environmental Health Hazards, held by the New York Academy of Sciences in New York, 21-30 June, 1978. The New York Academy of Sciences, New York, New York, 1978.
LA - ENG
AB - To prevent exposure of human populations to chemical carcinogens, laboratory or experimental animal systems must be used that will predict human carcinogenicity. Until recently control has not followed until epidemiological evidence of carcinogenicity has been developed. Whether or not to institute control measures based on laboratory evidence or on human evidence is a public policy decision. This decision must be based on good scientific evidence. The critical question is: Do tests in laboratory animals predict for cancer in man? Attempts to correlate quantitative aspects of carcinogenicity between laboratory animals and man are difficult. An NAS/NRC panel on pesticides attacked this problem. Six compounds, benzidine, chlornaphazine, aflatoxin B1, diethystilbestrol (DES), vinyl chloride and cigarette smoke, were reviewed. For benzidine, chlornaphazine and cigarette smoke the mg/kg lifetime exposures estimated for man and for the most sensitive animal species were close. With the other compounds the differences appear greater but with DES and vinyl chloride the human population is still at risk. Other data also suggest that the results of tests in laboratory animals can predict for the human population and therefore can be used to prevent human exposure and disease. (no Refs)

66 AU - Cottine BR
AD - U.S. Occupational Safety and Health Review Commission, Washington, DC
TI - PUBLIC HEALTH DECISION-MAKING AND THE LEGAL PROCESS IN THE UNITED STATES: THE REGULATION OF VINYL CHLORIDE (MEETING ABSTRACT).
SI - ICDB/78/27368
SO - The Scientific Basis for the Public Control of Environmental Health Hazards, held by the New York Academy of Sciences in New York, 21-30 June, 1978. The New York Academy of Sciences, New York, New York, 1978.
LA - ENG
AB - Public health decision-making on the hazards of vinyl chloride exposure occurred in the legal process of the United States through two functional systems. At a federal level 'public-ordering' was accomplished prospectively through authority delegated by Congress to several administrative agencies including the Consumer Product Safety Commission and the Occupational Safety and Health Administration. Investigatory hearings, rulemaking action, and enforcement actions were commenced. Public ordering also occurred retrospectively through State worker compensation systems. However, the retrospective systems do not integrate with, or provide data for, prospective action. Moreover, retrospective ordering has a limited sensitivity and field of view due to statutory limitations on the compensability of occupational disease, variable latency periods, access controls on the system, and data visibility. Though limited retrospective data were available on vinyl chloride, prospective regulatory actions necessarily relied on experimental and epidemiological data. Private ordering also occurred on a limited basis. (no Refs)

67 AU - Norpoth K
AD - Munster, W. Germany
TI - SAFEGUARDING THE QUALITY OF MICROBIOLOGICAL MUTAGENICITY TESTING OF FOREIGN SUBSTANCES IN ROUTINE LABORATORY.
SI - CARC/78/07321
SO - Staub-Reinhalt Luft; 38(6):235-239 1978
LA - GER
AB - General methodological and statistical questions relevant to the use of bacteria in mutagenicity tests of environmental compounds are discussed. The probability of carcinogenic effects can be assessed from the results of mutagenicity tests on microorganisms such as Salmonella typhimurium. The development of routine bacterial mutagenicity tests requires standardization, quality control, and statistical validation of the results. The prerequisites include positive and negative controls, continuous checks on the indicator bacteria, constant activity of the mammalian oxygenase used, species- specificity of the oxygenase, and attention to the influence of the solvent. 3,4-benzo(a)pyrene, aflatoxin B1, vinyl chloride, diaminotoluene, known carcinogens, and bis(chloroethyl)ether, a suspected carcinogen, were found to induce mutations in microorganisms. (10

Refs)

68 AU - Zeuthen J
AD - No affiliation given
TI - EVALUATING THE RISK OF CHEMICAL MUTAGENS.
SI - ICDB/78/25732
SO - Ugeskr Laeger; 140(13):728-730 1978
LA - DAN
AB - Recent studies on mutagenic chemicals are reviewed. Most carcinogenic substances but only few non-carcinogenic substances are mutagenic. Most mutagenic carcinogens cause frameshift mutations. DDT, dieldrin, aldrin, vinyl chloride and many hair dyes are mutagenic. (no Refs)

69 AU - Popper H ; Thomas LB ; Telles NC ; Falk H ; Selikoff IJ
AD - Stratton Lab. Liver Disease, Mount Sinai Sch. Medicine, City Univ. New York, New York, NY
TI - DEVELOPMENT OF HEPATIC ANGIOSARCOMA IN MAN INDUCED BY VINYL CHLORIDE, THOROTRAST, AND ARSENIC. COMPARISON WITH CASES OF UNKNOWN ETIOLOGY.
SI - CARC/78/07045
SO - Am J Pathol; 92(2):349-376 1978
LA - ENG
AB - Human hepatic angiosarcomas that occurred following exposure to vinyl chloride, Thorotrast, or arsenic (medicinal and industrial) and cases, including those in children, of unknown etiology were studied to establish diagnostic criteria and evolutionary features. The uniform evolution suggests that there is also an environmental factor in the cases of unknown etiology. The precursor stage is characterized by areas of combined hyperplasia of hepatocytes and a variety of sinusoidal and perisinusoidal cells associated with an excess of reticulin and with sinusoidal dilatation. Silver stainings indicated reticulum formation by the perisinusoidal cells, presumably the lipocytes. The hepatocytic proliferation suggested a hepatocarcinogenic, but usually not fully expressed, potential. The mixed hyperplasia of the various sinusoidal cells proceeded to an overgrowth of angiosarcoma cells, presumably derived from endothelial cells. In early stages they were usually in contact with hepatocyte (intralobular growth). A trabecular arrangement resulted from loosening of the lobular plate arrangement by dilatation of sinusoids, leading to primary peliosis. With disappearance of the hepatocytes, various growth patterns developed, terminating in nodular, solid angiosarcoma composed of either spindle-shaped or polyhedral cells that underwent necrosis or hemorrhage (secondary peliosis). The interaction between hepatocytes and sinusoidal cells requires elucidation. (110 Refs)

70 AU - Watanabe PG ; Zampel JA ; Pegg DG ; Gehring PJ
AD - Toxicology Res. Lab., Health and Environmental Res., 1803 Building, Dow Chemical Co., Midland, MI, 48640
TI - HEPATIC MACROMOLECULAR BINDING FOLLOWING EXPOSURE TO VINYL CHLORIDE.
SI - CARC/78/06973
SO - Toxicol Appl Pharmacol; 44(3):571-579 1978
LA - ENG
AB - Male Sprague-Dawley rats were exposed by inhalation to 1, 25, 50, 250, 1,000, or 5,000 ppm **14C-labeled vinyl chloride (VC) for 6 hr, and covalent binding of VC to hepatic macromolecules and nucleic acids was studied to determine if VC-induced carcinogenesis might be related to electrophilic alkylation of macromolecules in vivo. The total amount of VC metabolized and hepatic glutathione (GSH) content were also measured. The total amount of radioactivity bound to hepatic macromolecules did not increase proportionately to the increase in the exposure concentration of VC, but it was related directly to the total amount of VC metabolized. At exposure concentrations greater than 50 ppm, the total metabolism of VC and covalent binding appeared to correlate with the induction of hepatic angiosarcinomas in the rats. Isolation of RNA and DNA by a nondigestive procedure from the liver of rats exposed to 1, 100, 250, and 1,000 ppm VC failed to reveal any detectable radioactivity. Hepatic GSH was depressed significantly only at greater than or equal to 100 ppm, suggesting that VC carcinogenicity is related to a decreased ability to detoxify the reactive metabolites of VC. The results do not associate the carcinogenic effect of VC with a disproportionate increase in binding of electrophilic metabolites of VC to hepatic macromolecules as the exposure concentration is increased. Moreover, the lack of preferential binding of the metabolites to the hepatocyte nucleic acids suggests that the carcinogenicity of VC may not be associated directly with this commonly accepted mechanism of carcinogenesis. (27 Refs)

71 AU - Fleig I ; Thiess AM
AD - Dept. Occupational Medicine and Health Protection, BASF Aktiengesellschaft, 6700 Ludwigshafen, W. Germany
TI - MUTAGENICITY OF VINYL CHLORIDE. EXTERNAL CHROMOSOME STUDIES ON PERSONS WITH AND WITHOUT VC ILLNESS, AND ON VC EXPOSED ANIMALS.
SI - CARC/78/06937
SO - J Occup Med; 20(8):557-561 1978
LA - ENG
AB - Chromosome analysis was performed on lymphocyte cultures from 6 workers with an estimated degree of exposure to vinyl chloride (VC), 4 workers whose degree of exposure was monitored, 20 workers showing symptoms of VC illness after unknown degrees of exposure, and 1 patient with VC-induced angiosarcoma. Bone marrow cells from Chinese hamsters exposed to VC by inhalation (2,500 or 5,000 ppm for 4 hr/day x 5) or ip injection (300 or 600 mg/kg/day x 5) were also analyzed. The frequency of chromosome aberrations was not increased relative to controls in the exposed workers

with no signs of VC illness. The frequency of aberrant metaphases in the workers with VC illness was 5.2% excluding gaps and 11.2% including gaps, these values were significantly higher than the control values of 2.1% and 5.5%, respectively. The rate of aberrant metaphases in the angiosarcoma patient was 7.3% excluding gaps and isogaps and 16.6% including gaps and isogaps. The frequency of structural abnormalities in the VC-treated hamster cells was also significantly higher than that in the control cells, inclusive and exclusive of gaps. (15 Refs)

72 AU - Hansteen IL ; Hillestad L ; Thiis-Evensen E ; Haldaas SS
AD - Lab. Genetics, Telemark Central Hosp., Olavsgt. 26, 3900 Porsgrunn, Norway
TI - EFFECTS OF VINYL CHLORIDE IN MAN. A CYTOGENETIC FOLLOW-UP STUDY.
SI - CARC/78/06925
SO - Mutat Res; 51(2):271-278 1978
LA - ENG
AB - For comparison, a second cytogenetic study was made of 37/39 polyvinyl chloride workers 2-2.5 yr later, during which time the workers had minimal exposure to vinyl chloride monomer (VCM). The second study was performed with 32 matched controls selected from office employees at the same factory. Of the original 39 workers, 14 had been chosen at random, 13 because they had heavy exposure to VCM for years, and 12 because of abnormal clinical findings that later proved to be normal. Breaks, gaps, and stable rearrangements were scored as 100 metaphases/person from 48-hr lymphocyte cultures. In the first study, the mean number of chromosome breaks was significantly higher for the workers (3.41%) than for the controls (1.79%). No significant difference was found in the second study. In addition, there was no significant difference in mean number of breaks between the first control group and both groups of the second study. The results of the two studies provide evidence that VCM was the cause of the chromosome damage found in the first study. In the second study, the mean number of sister chromatid exchanges per cell was the same (7.6) for both workers and controls. Studies of bone marrow samples from four workers revealed that these samples had a higher mean number of chromosome breaks (4.2%) than normal bone marrow (literature values, 0.2%-1.7%) or the corresponding lymphocyte cultures. (19 Refs)

73 AU - Blendis LM ; Smithe PN ; Laurie CW ; Stephens MR ; Evans WD
AD - Room 112, Univ. Wing, Toronto General Hosp., University Ave., Toronto, Ontario, Canada M5G 1L7
TI - PORTAL HYPERTENSION IN VINYL CHLORIDE MONOMER WORKERS. A HEMODYNAMIC STUDY.
SI - ICDD/78/24126
SO - Gastroenterology; 75(2):206-211 1978
LA - ENG
AB - Hemodynamic studies were performed in five vinyl chloride monomer workers in whom splenomegaly or thrombocytopenia was detected during a screening program at a major chemical plant. Three patients had portal hypertension and collateral venous

circulations, with intrasplenic pressure between 20 and 29 mm Hg and normal wedged hepatic venous pressures, but the gradient between the wedged and free hepatic vein pressures was also increased. Splenic blood flows were increased in both hypertension and normotensive patients. There was no correlation between the splenic blood flow and the portal pressure or the presence of the portal fibrosis. The portal hypertension associated with vinyl chloride exposure is mainly presinusoidal in type, and may be attributed to an abnormality of the portal vein radicles, or hepatic sinusoids. (Author abstract) (23 Refs)

74 AU - Gehring PJ ; Watanabe PG ; Park CN
AD - Health and Environmental Res., Dow Chemical USA, Midland, MI, 48640
TI - RESOLUTION OF DOSE-RESPONSE TOXICITY DATA FOR CHEMICALS REQUIRING METABOLIC ACTIVATION: EXAMPLE--VINYL CHLORIDE.
SI - CARC/78/06903
SO - Toxicol Appl Pharmacol; 44(3):581-591 1978
LA - ENG
AB - The concept that the toxicity of many chemicals may not be a function of exposure to the chemical per se but rather to a biotransformation product is illustrated with vinyl chloride (VC). In such a case, it is necessary to determine the amount of the chemical undergoing biotransformation as a function of dose or exposure before a meaningful dose-response relationship can be established. Male Sprague-Dawley rats were exposed via inhalation to 1.4-4,600 ppm VC for 6 hr, and the total amount of VC metabolized was determined. Activation to the toxic form followed apparent Michaelis-Menten kinetics. A logarithmic probability plot of the incidence of hepatic angiosarcoma vs the amount of VC transformed, rather than the exposure concentration of VC, was linear. Assuming no threshold dose, extrapolation of the data below the range of doses causing experimentally observable responses predicted a 0.01% hepatic angiosarcoma incidence in rats exposed to 4.6 ppm VC. Theoretical extension of the extrapolation to humans exposed daily for 8 hr to 1 ppm led to a predicted incidence of 1.5/100,000,000. This incidence, although likely an overestimate in the light of evidence for at least a practical threshold in both rats and humans, is less than that expected to occur spontaneously. Although this method of estimation is not without flaws, the rationale involved represents a new approach that utilizes more logic than current extrapolation methods. The concepts that evolved from this analysis reveal why pharmacokinetics must be considered in designing toxicology experiments as well as in interpreting the resulting data. (22 Refs)

75 AU - Purchase IF ; Richardson CR ; Anderson D ; Paddle GM ; Adams WG
AD - Central Toxicology Lab., Central Medical Group and Mond Div., Imperial Chemical Industries Ltd., Alderley Park, Macclesfield, Cheshire, England
TI - CHROMOSOMAL ANALYSES IN VINYL CHLORIDE-EXPOSED WORKERS.
SI - CARC/78/06859
SO - Mutat Res; 57(3):325-334 1978
LA - ENG
AB - The chromosomal morphology of cultured peripheral lymphocytes from 81 men [57 employed in plants manufacturing vinyl chloride (VC) or polyvinyl chloride (PVC), 19 on-site controls, and 5 off-site controls] was studied. There was a significant increase in chromosomal abnormalities among the VC/PVC-exposed workers compared with the controls. Total B cells (those with a chromatid break or gap or a chromosome gap), total Cu cells (those with larger unstable chromosomal abnormalities), and total Cs cells (those with larger unstable chromosomal abnormalities) showed the greater increases in autoclave operators, with smaller increases in the other five job categories. The increase in chromosomal aberrations was correlated with length of exposure and with a history of exposure to excursion levels of VC during the year prior to sampling (1973-1974). There were no correlations between results of liver function tests and chromosome aberrations. Quantity of tobacco smoked 18 mo after blood sampling was correlated with total C cells, as was smoker vs nonsmoker status at 18 mo postsampling. It was not possible to determine whether smoking history, length of employment, or exposure to excursion levels of VC was the most important variable in determining C-cell abnormalities. (15 Refs)

76 AU - Magnusson J ; Ramel C
AD - Environmental Toxicology Unit, Wallenberg Lab., Univ. Stockholm, Stockholm, Sweden
TI - MUTAGENIC EFFECTS OF VINYL CHLORIDE ON DROSOPHILA MELANOGASTER WITH AND WITHOUT PRETREATMENT WITH SODIUM PHENOBARBITURATE.
SI - CARC/78/06790
SO - Mutat Res; 57(3):307-312 1978
LA - ENG
AB - Exposure of wild-type Karanas 60 Drosophila males (0-2 days old) to 10,000, 100,000 or 200,000 ppm vinyl chloride (VC) gas increased the number of complete and mosaic sex-linked recessive lethals. A threshold effect was observed that may be due to a limit of the mixed-function oxidase activity. In additional experiments, Drosophila were pretreated with a 1% soln of phenobarbital sodium (PB) dissolved in water containing 1% sucrose for 24 hr, followed immediately by exposure to 1,000 or 100,000 ppm VC gas (Group 1). Group 2 was treated with either concentration of VC alone, and Group 3 was not treated. PB pretreatment enhanced the number of recessive lethals over the numbers produced by Groups 2 and 3. Compared with Groups 2 (corresponding group) and 3, the total number of recessive lethals produced by PB + 10,000 ppm VC was significant, but not

the number produced by PB + 100,000 ppm VC. In Groups 1 and 2, the higher VC dose did not produce a higher frequency of recessive lethals than the lower dose; again, there was a lack of a dose-response effect. The results indicate that the mixed-function oxidase system can be induced in Drosophila in the same way as in mammals. (12 Refs)

77 AU - Stutte HJ ; Heusermann U
AD - Kiel, W. Germany
TI - THE CONDITION OF THE SPLEEN DURING VINYL CHLORIDE DISEASE (MEETING ABSTRACT).
SI - ICOB/78/23190
SO - Zentralbl Allg Pathol; 122(3):284 1978
LA - GER
AB - Contact with vinyl chloride during the production of various synthetic substances is unavoidable and may lead to severe organ alterations, the most frequently observed being splenomegaly with clinical signs of portal hypertension. Morphological examination indicates that the spleen is the target of fibrotic lesions with characteristic types, location, and dissemination. These parameters allow for successful histological confirmation of a clinically occult splenomegaly and the differentiation of a portal occluded spleen in case of hepatic cirrhosis. The most significant differential diagnostic criteria are presented in tabular form. With respect to these criteria, it is thought that the splenic alterations observed during vinyl chloride disease were not caused by portal hypertension due to vinyl chloride induced hepatic alterations, rather by a direct fibrotic process in the red and white pulpa and connective tissue of the spleen induced by vinyl chloride or its metabolites. (no Refs)

78 AU - Suzuki Y
AD - Environmental Science Lab., Mount Sinai Sch. Medicine, Fifth Ave. and 100th St., New York, NY, 10029
TI - PULMONARY TUMORS INDUCED IN MICE BY VINYL CHLORIDE MONOMER.
SI - CARC/78/06720
SO - Environ Res; 16(1/3):285-301 1978
LA - ENG
AB - The incidence of lung tumors due to vinyl chloride (VC) inhalation was studied in 27 CD1 Charles River male mice, and precancerous changes and the resulting tumor were characterized ultrastructurally. The mice were exposed to 2,500 or 6,000 ppm VC 5 hr/day, 5 days/wk, for 5 or 6 mo and then sacrificed 2, 6, or 37 days later. Pulmonary tumors were found in 26/27 mice but in none of the 16 controls. The tumors were round, whitish, multiple, and variable in size from 1 to 5 mm in diameter. The tumors were arranged in tubulocapillary or adenomatous formations. There were no metastases to regional lymph nodes or other organs, parenchymal fibrosis, or fibrotic adhesions of the pleura, although occasional mitotic divisions and invaginations into the bronchiolar lumen were noted. Under the electron microscope, the characteristic features of the neoplastic cells were short microvilli, tight junctions between two adjacent

cells, osmiophilic lamellar bodies, large irregularly shaped mitochondria, well-developed Golgi complexes, continuous or discontinuous basement membranes, occasional appearance of sequestration and of crystalloids, and a lack of cilia and mucous secretory granules. Some of the cells were poorly differentiated and were equipped with poorly developed organoids, without the formation of osmiophilic lamellar bodies. The gross anatomical and histological aspects of the tumors indicated that they were alveologenic tumors. The neoplastic cells were assumed to have been transformed from type II alveolar epithelium via its hyperplastic form, because of the ultrastructural similarities between normal type II cells and the neoplastic cells. It is concluded that the mouse lung is a sensitive indicator of the oncogenicity of VC. (40 Refs)

79 AU - Wilson R
AD - Dept. Physics, Harvard Univ., Cambridge, MA, 02138
TI - RISKS CAUSED BY LOW LEVELS OF POLLUTION.
SI - CARC/78/06623
SO - Yale J Biol Med; 51(1):37-51 1978
LA - ENG
AB - The theoretical and experimental evidence for the concept that pollutants in almost any concentration cause a small risk of death is reviewed. The hypothesis that cancer incidence is linear at low doses with applied dose of pollutant originated with radiation carcinogenesis. According to the linear theory, if the quantity of a carcinogen is constant and randomly distributed throughout the environment, the total number of cancers produced will be constant to within the square root of that number. Although there are various theoretical reasons for expecting to find a deviation from linearity, taking a linear dose-response relationship is recommended by most regulatory bodies. Data on cancers produced in humans by chemical carcinogens reveal few well-measured dose-response relationships, but there is a considerable amount of data on chemical cancers induced in animals. Many carcinogens such as vinyl chloride (VC) are indirect, and they only become carcinogenic as a result of the production of metabolites in the liver. The linearity of effect vs dose actually applies to the dose presented to the cell. The metabolic production of carcinogens in the liver might not be linear with the VC concentration. However, prudent public policy demands the assumption of linearity for exposure to the general public until further information is available. (50 Refs)

80 AU - Watanabe PG ; Zempel JA ; Gehring PJ
AD - Toxicology Res. Lab., Health and Environmental Res., Dow Chemical USA, Midland, MI, 48640
TI - COMPARISON OF THE FATE OF VINYL CHLORIDE FOLLOWING SINGLE AND REPEATED EXPOSURE IN RATS.
SI - ICDB/78/22165
SO - Toxicol Appl Pharmacol; 44(2):391-399 1978
LA - ENG
AB - The metabolic fate of vinyl chloride (VC) in rats exposed by

inhalation once or repeatedly. The activities of the microsomal enzymes (aniline hydroxylase and p-nitroanisole-O-demethylase) was essentially the same in both groups as well as nonexposed control rats. Repeated exposure to VC did not induce its biotransformation since covalent bonding to hepatic macromolecules was greater in rats repeatedly exposed. (17 Refs)

81 AU - Muller G ; Norpoth K ; Kusters E ; Herweg K ; Versin E
AD - Institut fur Staublungenforschung und Arbeitsmedizin, Westfahliche Wilhelms-Universitat, D-4400 Munster, W. Germany
TI - DETERMINATION OF THIODIGLYCOLIC ACID IN URINE SPECIMENS OF VINYL CHLORIDE EXPOSED WORKERS.
SI - ICDB/78/21017
SO - Int Arch Occup Environ Health; 41(3):199-205 1978
LA - ENG
AB - Thiodiglycolic acid (TDGA) content was measured in the urine of workers exposed to varying amounts of vinyl chloride (VC), and an improved analytical method for these determinations was described. The analytical procedure used made it possible to distinguish between normal values (in 20 non-exposed men) and values obtained from 18 slightly exposed workers (0.14-7.0 ppm VCM measured by personal air samplers) at the 1% significance level. In all cases TDGA concentrations exceeding 2.1 microg/ml urine can be distinguished from normal concentrations with a 99% probability of confidence. Mean values obtained from the normal group and two exposed groups suggested a correlation between the extent of exposure and the amount of TDGA excreted. Increasing metabolite concentrations were found in the urine with increasing exposure. The correlation was tested by a distribution free statistical procedure and was confirmed at the level of p less than 0.01. The increase in metabolite excretion began shortly after the initiation of exposure each day and reached a peak in the first or second urine samples obtained after the highest possible VC-uptake. Significant increases in metabolite excretion were observed even at VC-concentrations below 5 ppm. The usefulness of using this analytical procedure for monitoring VC concentration in work places is discussed. (36 Refs)

82 AU - Du JT ; Tamburro CH
AD - Digestion, Disease and Nutrition Section, Dept. Medicine, Cancer Center, Univ. Louisville Medical Sch., Louisville, KY, 40232
TI - ELEVATED GLUTATHIONE CONTENT, GLUTATHIONE-S-TRANSFERASE AND GLUTATHIONE REDUCTASE IN LIVER OF RATS EXPOSED TO VINYL CHLORIDE (MEETING ABSTRACT).
SI - ICDB/78/20956
SO - Fed Proc; 37(6):1545 1978
LA - ENG
AB - Vinyl chloride (VC) is believed to be metabolized to chloroethylene oxide (CEO) and chloroacetaldehyde, and detoxified by way of glutathione. Rats were exposed to 28,000 ppm VC, 7 hr/day, 5 days/wk for a 4 and 6 wk, the activity of glutathione epoxide-S-transferase (GEST) was elevated 30 to 54% over normal control and air control (9.71 +- 0.68 vs 7.52 +- 0.97 and 6.30 +-

0.68) respectively. However, the activity of glutathione aralkyl-S-transferase (GAST) was not significantly elevated until 6 wk of exposure to VC. The content of reduced glutathione was also elevated 45% in the VC treated group and the activity of the glutathione reductase, the enzyme to regenerate glutathione from the oxidized form was elevated 50%. These results demonstrate that VC exposed rats have the capacity to maintain glutathione reductase activity and glutathione concentration for detoxification. Further, it suggests that the primary route of VC metabolism is initial oxidation to CEO and then detoxification by GEST directly. With longer exposure and probable saturation of the direct route, there is greater rearrangement of CEO to chloroacetaldehyde, and detoxification with glutathione as supported by the delayed induction of GAST.

83 AU - Filser JG ; Bolt HM
AD - Institut fur Toxikologie, Universitat Tubingen, Wilhelmstrasse 56, D-7400 Tubingen, W. Germany
TI - PHARMACOKINETICS OF HALOGENATED ETHYLENES (MEETING ABSTRACT).
SI - ICDB/78/20792
SO - Naunyn Schmiedebergs Arch Pharmakol; 302(Suppl):R22 1978
LA - ENG
AB - The present discussion of toxic effects of vinyl chloride raises the question of interpretation of toxicological data. Evidently, biochemical and mechanistic concepts of action of healogenated ethylenes can only be correlated with toxicities observed in vivo, if differences in pharmacokinetics are taken into account. This consideration led to the present investigation. Rats were exposed in a closed system to atmospheric concentrations of fluoroethylene (vinyl fluoride) 1,1-difluoroethylene (vinylidene fluoride), chloroethylene (vinyl chloride), 1,1-dichloroethylene (vinylidene chloride), trans-1,2-dichloroethylene and cis-1,2-dichloroethylene, trichloroethylene, and bromoethylene (vinyl bromide). Pharmacokinetic analysis was done as previously described. The following principles could be derived. (1) 'Non-linear' (dose-dependent) pharmacokinetics may apply if the organism is exposed to higher concentrations of halogenated ethylenes. This is consistent with the concept of Watanabe, Young and Gehring. In the case of vinyl chloride, it refers to atmospheric concentrations higher than 250 ppm. (2) The equilibrium constant of distribution of the non-metabolized compound (concentration in the animal/concentration in the gas phase) increases from vinyl fluoride to vinyl bromide. (3) The rate of metabolism depends on the structural properties of the individual compound. Trans-1,2-dichloroethylene and vinylidene fluoride are extremely slowly metabolized, comparable to the rate of metabolism of 1,1,1-trichloroethane (methyl chloroform) which was used as a reference compound.

84 AU - Laib RJ ; Ottenwalder H
AD - Institut fur Toxikologie, Universitat Tubingen, Wilhelmstrasse 56, D-7400 Tubingen, W. Germany
TI - ALKYLATION OF DNA AND RNA BY METABOLITIES OF VINYL CHLORIDE AND VINYL BROMIDE (MEETING ABSTRACT).
SI - ICDB/78/20791
SO - Naunyn Schmiedebergs Arch Pharmakol; 302(Suppl):R21 1978
LA - ENG
AB - If rats are exposed to 14C-vinyl chloride, radioactivity is incorporated into nucleic acids of the liver. In previous investigations we showed incorporation of radioactivity from 14C-vinyl chloride into the physiological bases of RNA. In addition, alkylation of adenosine and cytidine moieties occurred leading to formation of radioactive 1,N**6-ethenoadenosine and 3,N**4-ethenocytidine. The time courses of 1,N**6-ethenoadenosine and 3,N**4-ethenocytidine in rat liver RNA after vinyl chloride inhalation are dissimilar: 92 hr after ending exposure the ethenoadenosine is only 1/5 of its original value whereas the content of ethenocytidine persists. This ought to be indicative for the relative importance of cytidine alkylation. Formation of labeled etheno derivatives of adenosine and cytidine was also observed if rats were exposed to 14C-vinyl bromide. To establish possible changes in DNA due to alkylation by vinyl chloride metabolites, DNA was incubated with rat liver microsomes, NADPH and 14C-vinyl chloride. Re-isolation of the DNA, hydrolysis and separation of the nucleosides on Aminex-A-6 showed that small amounts of radioactive 1,N**6-etheno 2'deoxyadenosine and 3,N**4-etheno 2'deoxycytidine were formed. In addition, a major alkylation product, presumably of 2' deoxyguanosine was isolated which, on Aminex-A-6-columns, showed the same chromatographic behavior as a compound which was obtained from chemical reaction of 2'deoxyguanosine with chloroacetaldehyde.

85 AU - Veltman G ; Lange CE ; Stein G
AD - Univ.-Hautklinik Bonn-Venusberg, D-5300 Bonn 1, W. Germany
TI - TOXIC EFFECTS OF VINYL CHLORIDE.
SI - CARC/78/06347
SO - Hautarzt; 29(4):177-182 1978
LA - GER
AB - The toxicological aspects of vinyl chloride (VC) are reviewed on the basis of examinations of workers occupationally exposed to VC over long periods of time. The liver histology revealed periportal, septal, and intralobular fibrosis; focal and reticular collagenization of the sinusoid walls; hepatocyte degeneration; and activation and proliferation of the sinusoid cells, with cell atypia and transition into angiosarcoma occurring in some cases. The metaphase analysis revealed no remarkable pathological changes; ie, no mutagenic effect of VC. (35 Refs)

86 AU - Ehrenberg L ; Holmberg B
AD - Dept. Radiation Biology, Wallenberg Lab., Univ. Stockholm, Stockholm, Sweden
TI - EXTRAPOLATION OF CARCINOGENIC RISK FROM ANIMAL EXPERIMENTS TO MAN.
SI - CARC/73/06300
SO - Environ Health Perspect; 22:33-35 1978
LA - ENG
AB - The hypothesis that one or more mutational events are involved in tumor initiation is supported not only by the strong, qualitative correlation between mutagenic and carcinogenic activities of chemicals, but also by certain reaction-kinetic considerations. Experiments with microorganisms, plants, and animals suggest that limiting step in tumor origin is one mutational event in one cell and that the dose-response curve is linear from dose zero onward. An inverse relationship between dose and latency time has been observed frequently and has been taken as an indication that it should be possible to extrapolate to such a low dose that the mean latency time would exceed the expected lifetime of the species studied. However, a small dose may give individual latency times within the expected lifetime, even though the mean latency time for a group exceeds the life span. The most important contribution of dose-response studies is in the application of mathematical models to epidemiologic data. It should be remembered, however, that a deviation from the linear dose-response relationship, with a higher effectiveness at lower doses, may occur for radiation, urethane, and vinyl chloride. (23 Refs)

87 AU - Laib RJ ; Ottenwalder H ; Bolt HM
AD - Inst. Toxikologie, Univ. Tubingen, Wilhelmstr. 56, D-7400 Tubingen, W. Germany
TI - FORMATION OF ETHENO DERIVATIVES OF NUCLEIC ACID BASES IN VIVO BY METABOLITES OF VINYL CHLORIDE (MEETING ABSTRACT).
SI - ICDB/78/10834
SO - Hoppe Seylers Z Physiol Chem; 359(3):293 1978
LA - ENG
AB - The detection of mutagenic and carcinogenic effects of vinyl chloride greatly stimulated research on the molecular mechanism of vinyl chloride disease. Rat liver microsomes were incubated with NADPH, (1,2-14C)vinyl chloride and polyadenylic acid or polycytidylic acid. The latter were re-isolated from the incubation mixtures and hydrolyzed. The radioactivity originating from (14C)vinyl chloride, which was irreversibly bound to the polyadenylic or polycytidylic acid, was confined to 1,N**6-ethenoadenosine or 3,N**4-ethenocytidine. When rats were exposed to (1,2-14C)vinyl chloride, part of the radioactivity was incorporated into the liver RNA. Analysis of hydrolysates of liver RNA showed that all natural nucleosides of RNA were labeled. Besides, small amounts of radioactivity could be detected which were confined to 1,N**6-ethenoadenosine and 3,N**4-ethenocytidine. DNA from livers of rats exposed to (1,2-14C)vinyl chloride also contained significant amounts of

radioactivity. When DNA was incubated with rat liver microsomes, NADPH and [14C]vinyl chloride, radioactivity was also incorporated into the DNA. Re-isolation of the DNA, hydrolysis and separation of the nucleosides showed that radioactive 1,N**6-ethano-2'-deoxyadenosine and 3,N**4-ethano-2'-deoxycytidine were formed. The experiments support the theory that vinyl chloride metabolites react with adenine or cytosine moieties of nucleic acids to form etheno analogues.

88 AU - Cowles SR
AD - Occupational Medicine Branch, Naval Regional Medical Center, Bremerton, WA, 98314
TI - CANCER IN THE WORKPLACE--PERCIVALL POTT TO THE PRESENT.
SI - CARC/78/06242
SO - Milit Med; 143(6):395-400 1978
LA - ENG
AB - Known and suspected carcinogens commonly found at Naval installations, particularly shipyards, are reviewed, and methods of controlling human exposure to these substances are outlined. The carcinogens include physical agents (cigarettes, asbestos), metals (Ni, As), and hydrocarbons (ethylenethiourea, 4,4'-methylenebis(2-chloroaniline), vinyl chloride, and polychlorinated biphenyls).

89 AU - Bolt HM
AD - Inst. Toxicology, Univ. Tubingen, Wilhelmstrasse 56, D-7400 Tubingen 1, W. Germany
TI - PHARMACOKINETICS OF VINYL CHLORIDE.
SI - CARC/78/06214
SO - Gen Pharmacol; 9(2):91-95 1978
LA - ENG
AB - Data on the pharmacokinetic behavior of vinyl chloride (VC), all of which have been obtained from studies with rats, are reviewed. Consistent evidence shows that, above a saturation concentration, which on inhalation exposure is reached at 250 ppm VC, nonlinear (dose-dependent) pharmacokinetics apply. Two different models describing the pharmacokinetics of VC have been published. They show that VC can leave the body very rapidly via expiration by the lungs. However, special conditions apply if rats are exposed to atmospheric VC: the compound equilibrates with the organism within 15-30 min and is removed from this equilibrium metabolically, probably by formation of the reactive epoxide. The rapid elimination of VC and its major metabolites from the organism agrees with the current theory that a reactive, short-lived metabolite, which occurs in low concentrations only, may be responsible for the toxic effects of VC. (25 Refs)

90 AU - Spirtas R ; Kaminski R
AD - Illness Effects Section, SB/DSHEFS/NIOSH, Robert A. Taft Labs., 4676 Columbia Parkway, Cincinnati, OH, 45226
TI - ANGIOSARCOMA OF THE LIVER IN VINYL CHLORIDE/POLYVINYL CHLORIDE WORKERS: 1977 UPDATE OF THE NIOSH REGISTER.
SI - CARC/78/06177
SO - J Occup Med; 20(6):427-429 1978
LA - ENG
AB - Data on 64 cases of angiosarcoma among vinyl chloride (VC) polymerization workers reported as of October 1977 are summarized. The material comprises 23 US and 41 foreign cases from 11 different countries. The age at diagnosis ranged from 37 to 71 yr, with a median of 49 yr. The latency period ranged from 9 to 33 yr (median of 21 yr), duration of exposure from 4 to 31 yr (median of 18 yr). The data suggest that the reported VC-induced angiosarcoma cases gradually increased over time. The 20-to 30-yr lag between the growth of the industry after World War II and the increase in the number of diagnosed angiosarcomas among VC/polyvinyl chloride (PVC) workers during the 1970's roughly coincides with the median latency period of 21 yr. Recent studies have also found VC to be associated with excesses in brain cancer and neoplasms of the respiratory and lymphatic systems. (6 Refs)

91 AU - Preussmann R
AD - Institut fur Toxikologie und Chemotherapie, Deutsches Krebsforschungszentrum, Im Neuenheimer Feld 230, D-6900 Heidelberg 1, W. Germany
TI - ENVIRONMENTAL CARCINOGENS: MECHANISMS OF ACTION AND OCCURRENCE.
SI - CARC/78/06160
SO - Zentralbl Bakteriol [Orig B]; 166(2/3):144-158 1978
LA - GER
AB - The mechanism of action of known environmental carcinogens is described. These compounds are not carcinogenic per se, but are metabolically bioactivated to electrophilic reactants by chemically reactive intermediates. The electrophilic reactants then form covalent bonds with nucleic acids. This change in the genetic code is in agreement with the mutation hypothesis of carcinogenesis. The bioactivation of aflatoxin B1 (AFB), N-nitroso compounds, and benzo(a)pyrene (BP) is presented to illustrate this mechanism. Threshold levels (no-effect levels) determined by animal experiments are compared with data on human exposure to BP, AFB, N-nitroso compounds, and vinyl chloride. The difficulties involved in risk evaluations are discussed.

92 AU - Hoffmann D ; Wynder EL
AD - Naylor Dana Inst. Disease Prevention, American Health Foundation, Valhalla, NY, 10595
TI - IDENTIFICATION AND REDUCTION OF CARCINOGENS IN THE RESPIRATORY ENVIRONMENT.
SI - CARC/78/06155
SO - Zentralbl Bakteriol [Orig B]; 166(2/3):113-135 1978
LA - ENG
AB - The three major factors responsible for the overall increase in lung cancer (tobacco, air pollution, and industrial chemical exposure) are reviewed. Concerning industrial carcinogenesis, particular attention is focused on bis(chloromethyl)ether, vinyl chloride, benzene, coke oven effluents, asbestos, and nitrosamines. Sources of atmospheric carcinogens and their reduction are outlined. The tumorigenic agents in cigarette smoke are being studied so that a less harmful cigarette can be developed.

93 AU - Guess HA ; Crump KS
AD - Environmental Biometry Branch, Natl. Inst. Environmental Health Sciences, Research Triangle Park, NC, 27709
TI - BEST-ESTIMATE LOW-DOSE EXTRAPOLATION OF CARCINOGENICITY DATA.
SI - CARC/78/06074
SO - Environ Health Perspect; 22:149-152 1978
LA - ENG
AB - A low-dose extrapolation technique was developed for dichotomous data and used to analyze carcinogenicity data for vinyl chloride, dieldrin, 1,1,1-trichloro-2,2-bis-(p-chlorophenyl)ethane (DDT), dimethylnitrosamine, and ionizing radiation. The results suggest that when the very flat and the gradually sloping (linear or nearly linear) dose-response curves are considered together, it is extremely difficult on mathematical grounds to reject the hypothesis that the dose-response curve is nearly linear in the dose range corresponding to increased risks over a background of less than or equal to 10**-6. These results have implications both for test design and for risk assessment. They suggest that if the hypothesis of a nearly linear dose-response curve in the low-dose range cannot be ruled out by assumption, then it seems questionable that it can be rejected by the data, even in cases in which it may be false. (no Refs)

94 AU - Delorme F ; Theriault G
AD - Dept. Pathology, Centre Hospitalier Regionale de la Mauricie, Shawinigan, Quebec, Canada
TI - TEN CASES OF ANGIOSARCOMA OF THE LIVER IN SHAWINIGAN, QUEBEC.
SI - CARC/78/05915
SO - J Occup Med; 20(5):338-340 1978
LA - ENG
AB - Of the 10 cases of angiosarcoma of the liver diagnosed in Shawinigan, Quebec, since 1955, all occurred in men who worked in a vinyl chloride (VC) polymerizing plant. All 10 men were very light drinkers, and only 4 smoked one or more packs of cigarettes

per day. The time between the first exposure of VC monomer and the diagnosis of angiosarcoma ranged from 11 to 29 yr, with an av of 20.5 yr. Exposure to VC monomer in the plant, although not documented, is believed to have been very high in the past. The benign liver lesions found in these workers included portal and perisinusoidal fibrosis. (15 Refs)

95 AU - Miller EC
AD - McArdle Lab. Cancer Res., Univ. Wisconsin Medical Center, Madison, WI, 53706
TI - SOME CURRENT PERSPECTIVES ON CHEMICAL CARCINOGENESIS IN HUMANS AND EXPERIMENTAL ANIMALS: PRESIDENTIAL ADDRESS.
SI - CARC/78/05456
SO - Cancer Res; 38(6):1479-1496 1978
LA - ENG
AB - Current concepts of chemical carcinogenesis in humans and experimental animals are reviewed. Topics discussed include: tumor induction as a multistage phenomenon; electrophilicity as a common property of ultimate carcinogens; examples of the metabolic activation and reactivity of chemical carcinogens; possible molecular mechanisms of chemical carcinogenesis; prevention of the promotion of initiated cells; and extrapolation of the basic knowledge of chemical carcinogenesis to the prevention of human cancer. Regarding the molecular mechanism of carcinogenesis, examples are cited to illustrate that metabolic activation is an essential step in the induction of neoplasia by most chemical carcinogens. The electrophilic ultimate carcinogens can react, probably more or less indiscriminately, with a number of nucleophilic sites in DNA, RNA, and proteins. Thus, the strong electrophilic nature of ultimate carcinogens is consistent with both genetic and epigenetic mechanisms of carcinogenesis or with mechanisms that include both genetic and epigenetic events. These mechanisms may or may not involve the expression of oncogenic viral information. Chemicals generally recognized as being carcinogens in humans include: 2-naphthylamine, benzidine (4,4'-diaminobiphenyl), 4-aminobiphenyl, 4-nitrobiphenyl, bis(chloromethyl) ether, bis(2-chloroethyl) sulfide, vinyl chloride, certain soots, tars, and oils, chromium compounds, nickel compounds, asbestos, cigarette smoke, betel nut or tobacco quids, N,N-bis(2-chloroethyl)-2-naphthylamine, and diethylstilbestrol.

96 AU - Kraybill HF
AD - Div. of Cancer Cause and Prevention, NCI, Bethesda, MD
TI - CARCINOGENESIS INDUCED BY TRACE CONTAMINANTS IN POTABLE WATER.
SI - CARC/78/05442
SO - Bull NY Acad Med; 54(4):413-427 1978
LA - ENG
AB - The following are some recognized and suspect carcinogens in US drinking water and their concentrations (in ug/liter, when given): aldrin (5.4), benzene (50), benzo(a)pyrene (0.0002-0.002), bis(2-chloroethyl)ether (0.42), lindane, carbon tetrachloride (2.0-3.0), chlordane (0.1), chloroform (0.1-311),

1,2-dibromoethane, dieldrin (8.0), dichlorodiphenyltrichloroethane (DDT), dichlorodiphenyldichloroethylene (DDE) (0.05), 1,4-dioxane (1.0), endrin (0.004), heptachlor, trichloroethylene, and vinyl chloride (10.0). Of these compounds, benzo(a)pyrene and vinyl chloride are the only recognized carcinogens. Only volatile organic compounds have been identified in US drinking water, and a much larger component of nonvolatile substances remains to be identified or quantified. In city water in the Netherlands and Germany, concentration ranges of inorganic contaminants such as arsenic, cadmium, chromium, and selenium are 1.0-8.1, 2.0-9.0, 4.5-10.0, and 3.1-6.0 ug/liter, respectively. Asbestiform materials or asbestos particles have been found in many river systems at concentrations greater than 10 ug/gallon. In a study of cancer mortality in 10 river basins in the US, nickel concentrations appeared to correspond with oral and intestinal cancer death rates, arsenic with cancer of the eye and larynx and myeloid leukemia. Beryllium correlated with bone cancer and with mortalities from breast and uterine cancer. Lead was associated with leukemia and lymphoma and with kidney, stomach, intestinal, and ovarian cancer. The results of various epidemiological studies throughout the US are reported. The need for in vitro bioassays to augment in vivo procedures in determining carcinogenicity is stressed. (30 Refs)

97 AU - Wagoner JK
AD - Office Assistant Secretary for OSHA, 200 Constitution Ave., Room N3660, Washington, DC, 20210
TI - VINYL CHLORIDE AND PULMONARY CANCER (LETTER TO EDITOR).
SI - CARC/78/05331
SO - J Environ Pathol Toxicol; 1(3):361-362 1978
LA - ENG
AB - In a previous article, the development of an undifferentiated adenocarcinoma of the bronchus in a 45-yr-old organic chemist was attributed to a 2-yr exposure to bis(chloromethyl)ether. This claim was made in spite of the patient's long-term involvement in vinyl chloride (VC) research. Since numerous animal and human studies have indicated a link between VC exposure and pulmonary cancer, it is suggested that VC was the agent that caused the tumor.

98 AU - Infante PF
AD - Industry-Wide Studies Branch, Div. Surveillance, Hazard Evaluations and Field Studies, Natl. Inst. Occupational Safety and Health, Center Disease Control, Dept. Health, Education and Welfare, Cincinnati, OH, 45202
TI - MUTAGENIC AND CARCINOGENIC RISKS ASSOCIATED WITH HALOGENATED OLEFINS.
SI - CARC/78/05314
SO - Environ Health Perspect; 21:251-254 1978
LA - ENG
AB - The mutagenicity and carcinogenicity of vinyl chloride (VC), vinylidene chloride, trichloroethylene, perchloroethylene, and

chloroprene are reviewed. Of the first four compounds, all except perchloroethylene have been shown to be mutagenic in test systems, and all have induced tumors in experimental animals. Studies with chloroprene have indicated that it causes sterility in male mice and rats. Rat studies have also indicated that concentrations ranging from 0.04 to 1.0 ppm result in a dominant lethal effect, affect sperm, cause testicular atrophy, and cause chromosomal aberrations in bone marrow cells. Human studies have indicated both an increase in chromosomal aberrations and a decrease in mobility of the sperm of exposed workers. Several studies have indicated an excess of lung and skin cancer in exposed workers, and one report confirmed a case of angiosarcoma of the liver in a worker with extensive exposure to finished polychloroprene. with VC have indicated that in addition to angiosarcoma, there appears to be a dose-response relationship between exposure and the induction of mammary cancer in rats. A study of women employed in the VC industry indicated a 33% excess of breast cancer in those exposed. These findings could indicate another site of VC carcinogenesis. (29 Refs)

99 AU - Reynolds ES ; Moslen MT
AD - Dept. Pathology, Univ. Texas Medical Branch, Galveston, TX, 77550, 77550
TI - DAMAGE TO HEPATIC CELLULAR MEMBRANES BY CHLORINATED OLEFINS WITH EMPHASIS ON SYNERGISM AND ANTAGONISM.
SI - CARC/78/05306
SO - Environ Health Perspect; 21:137-147 1978
LA - ENG
AB - The biochemical mechanisms responsible for the toxicity of vinyl chloride (VC), 1,1-dichloroethylene (1,1-DCE), trichloroethylene (TCE), and perchloroethylene (PCE) were investigated in male Sprague-Dawley rats pretreated with phenobarbital, 3-methylcholanthrene, hexachlorobenzene, spironolactone, or pregnenolone-16alpha-carbonitrile. The most nonsymmetrically depolarized compound, 1,1-DCE, was the most hepatotoxic and caused a unique pattern of hepatocellular injury involving mitochondria, plasma membranes, and chromatin. The injury induced by the other chloroethylenes appeared to affect the structural integrity of the endoplasmic reticulum profoundly, with the toxic potential in the following order: TCE greater than VC greater than PCE. Pretreatments that increased the cytochrome P-450 content (increased metabolic activation) enhanced or were synergistic to the hepatotoxic potential of TCE, VC, and PCE, but they were protective or antagonistic to 1,1-DCE hepatotoxicity. This suggests that the biologic response to 1,1-DCE may be expressed by a different metabolic pathway. Glutathione appears to be involved in the biologic response to all nonsymmetric chloroethylenes and to act as an antagonist against injury. Marked differences in the patterns of injury and the biologic responses suggest that more than one mechanism is involved in the production of injury by chloroethylenes. (37 Refs)

100 AU - Fortwengler HP ; Dever ME ; Tamburro CH ; Espinosa E
AD - Univ. Louisville Sch. Medicine, Louisville, KY, 40201
TI - LYMPHOCYTE TRANSFORMATION TESTS IN VINYL CHLORIDE (VC) WORKERS (MEETING ABSTRACT).
SI - ICDB/78/14658
SO - Fed Proc; 37(3):362 1978
LA - ENG
AB - Previous reports have shown circulating immune complexes in vinyl chloride (VC) workers and a tumor-associated antigen in VC-related liver angiosarcoma. This suggests immune stimulation by a tissue of plasma antigen induced by or conjugated with VC or a metabolite. In this work, the in vitro lymphocyte reactivity for such antigens was tested in 79 VC workers including 25 with liver abnormalities, and 20 normal individuals having no exposure to VC. The liver angiosarcoma antigen preparation included the tumor-associated antigen and other tissue antigens as shown by immunodiffusion. Stimulation indices (SI) were calculated from cellular incorporation of tritiated thymidine. Mean SI in the normal individuals for antigens of angiosarcoma and normal liver tissues were 4.7 (SE+-1.7) and 3.8 (+-0.9) and in VC workers, 1.8 (+-0.2) and 2.5 (+-0.3) respectively. Mean SI for phytohemagglutinin and concanavalin A in the normal individuals were 235 (+-35) and 209 (+-30) and in VC workers 201 (+-23) and 160 (+-19) respectively. Thus, these results suggest that VC workers have a decreased lymphocyte response to antigens of liver angiosarcoma and normal liver tissues rather than the hypothesized increased reactivity. This appears to be due to a lower overall lymphocyte responsiveness in these chemical workers.

101 AU - Heuse A
AD - Laboratoire de Medecine du Travail et Hygiene du Milieu, Universite Libre de Bruxelles, Brussels, Belgium
TI - TOXICOLOGY OF VINYL CHLORIDE.
SI - CARC/78/05111
SO - Brux Med; 58(1):13-34 1978
LA - FRE
AB - A review of the literature on vinyl chloride (VC) traces the history of the toxicity of the compound. Also reviewed are the toxic effects of polyvinyl chloride (PVC), relative risk of industrial exposure to VC and PVC, and potential danger of exposure of the general population to PVC. (196 Refs)

102 AU - Buffler PA ; Wood SM ; Suarez L ; Kilian DJ
AD - Dept. Preventive Medicine and Community Health, 140 Kedler Building, Univ. Texas Medical Branch, Galveston, TX, 77550
TI - MORTALITY FOLLOW-UP OF WORKERS EXPOSED TO 1,4-DIOXANE.
SI - CARC/78/04960
SO - J Occup Med; 20(4):255-259 1978
LA - ENG
AB - The carcinogenic effect of 1,4-dioxane was studied in 100 workers in the manufacturing area and 65 workers in the processing area of a dioxane manufacturing plant. The workers had been employed

between April 1954 and June 1975 and had served at least 1 mo in the given areas; the exposure in the areas was determined to be less than 25 ppb. There were seven deaths among the manufacturing area workers and five among the processing area workers. Of the former, one died of carcinoma of the stomach (28 mo exposure) and one of alveolar cell carcinoma (38 mo exposure); of the latter, one died of a malignant mediastinal tumor with generalized metastases (12 mo exposure). This total of three deaths from malignant tumor was not significantly greater than the 1.7 expected. A comparison of workers with intermittent exposure and those with continuous exposure revealed nearly identical incidences of mortality. The seven deceased persons in the manufacturing area also had exposure to other chemicals, and the five in the processing area were also exposed to vinyl chloride. These observations were based on small numbers of deaths of employees who were apparently exposed at low levels and for relatively short exposures. (12 Refs)

103 AU - Ott MG ; Townsend JC ; Fishbeck WA ; Langner RA
AD - Dow Chemical Co., Midland, MI
TI - MORTALITY AMONG INDIVIDUALS OCCUPATIONALLY EXPOSED TO BENZENE.
SI - CARC/78/04891
SO - Arch Environ Health; 33(1):3-10 1978
LA - ENG
AB - The long-term mortality experience among 594 individuals occupationally exposed to benzene was studied using a retrospective cohort design. Excluding 53 individuals who were also exposed to arsenicals, asbestos, or vinyl chloride, no statistically significant increases over US white male mortality rates were found among the benzene workers in any cause-of- death category. When the 53 patients were included, there were higher than expected incidences of anemia (2 vs 0.2 expected) and leukemia (3 vs 0.8). The records of these five decedents were examined in detail. One of those who died of leukemia had also been exposed to nitrobenzene, bromine, and vinyl and vinylidene chloride, another had been employed previously in the manufacture of veneer, and the third had probable exposure to p-chlorophenol, ethyl chloride, phenetidine, acetic anhydride, and phenacetin dust. Therefore, although the observed incidence of leukemia in the study group significantly exceeded the expected incidence, a retrospective assessment of the possible relationship to benzene exposure is difficult. (11 Refs)

104 AU - Rudolph RH
AD - Mason Clinic, P.O. Box 900, Seattle, WA, 98111
TI - BENIGN AND MALIGNANT LIVER NEOPLASMS. SOME NEW ETIOLOGIC ASSOCIATIONS.
SI - CARC/78/04717
SO - Postgrad Med; 63(3):56-60,62,65 1978
LA - ENG
AB - Recent studies of benign and malignant hepatic neoplasms have suggested associations between these tumors and oral contraceptives, androgens, hepatitis virus, and vinyl chloride.

It is suggested that hepatic arteriography is the best method for diagnosing hepatic adenomas in women using oral contraceptives. (20 Refs)

105 AU - Conolly RB ; Jaeger RJ ; Szabo S
AD - Dept. Physiology, Harvard Sch. Public Health, Boston, MA 02115
TI - ACUTE HEPATOTOXICITY OF ETHYLENE, VINYL FLUORIDE, VINYL CHLORIDE, AND VINYL BROMIDE AFTER AROCLOR 1254 PRETREATMENT.
SI - CARC/78/04565
SO - Exp Mol Pathol; 28(1):25-33 1978
LA - ENG
AB - The hepatotoxicity of ethane, vinyl ethylene, fluoride monomer (VFM), vinyl bromide monomer (VBM), and vinyl chloride monomer (VCM) was determined in male Holtzman rats pretreated with Aroclor 1254. All compounds except ethane caused degeneration and necrosis of the liver. Ethylene, VFM, and VBM should be evaluated for chronic effects in view of their similarity of acute action to VCM, a known carcinogen. (20 Refs)

106 AU - Laib RJ ; Bolt HM
AD - Institut fur Toxikologie, Universitat Tubingen, Wilhelmstrasse 56, D-7400 Tubingen, W. Germany
TI - FORMATION OF 3,N**4-ETHENOCYTIDINE MOIETIES IN RNA BY VINYL CHLORIDE METABOLITES IN VITRO AND IN VIVO.
SI - CARC/78/04381
SO - Arch Toxicol (Berl); 39(3):235-240 1978
LA - ENG
AB - Rats were exposed to **14C-vinyl chloride, and the in vivo liver metabolites were examined. In addition to RNA and 1,N**6-ethenoadenosine, 3,N**4-ethenocytidine was also radioactively labeled. In vitro experiments using vinyl chloride-exposed liver microsomes and NADPH produced the same results. These alkylation mechanisms are consistent with the mutagenic and carcinogenic properties of vinyl chloride. (22 Refs)

107 AU - Sharma RP ; Gehring PJ
AD - Utah State Univ., Logan, UT, 84322
TI - VINYL CHLORIDE EXPOSURE INDUCED LYMPHOCYTE TRANSFORMATION IN SPLENIC CULTURES (MEETING ABSTRACT).
SI - ICDB/78/10225
SO - Fed Proc; 37(3):502 1978
LA - ENG
AB - Vinyl chloride (VC) disease has been suggested as an immune complex disorder. The influence of VC exposure on selected immunologic parameters of mice and rabbits was studied. In male mice, inhalation of VC (10,000 and 1,000 ppm for 6 hr/day, 5 days/wk) for up to 8 wk caused no toxic effects, as indicated by body wt gain, clinical hematology, or organ wt, with the exception of an increase in spleen wt at the highest exposure level. After 2 wk of exposure to 1,000 ppm and after 4 and 8 wk to all levels, cultured splenic lymphocytes showed an increase in DNA synthesis (as measured by H3-thymidine uptake by cells in culture). The response of splenic lymphocytes to phytomitogens

(phytohemagglutinin and pokeweed mitogen) at the above levels of VC exposure was increased several fold. In rabbits, exposure to 1,000 ppm VC caused a slight but inconsistent rise in serum immunoglobulin levels. Rabbits immunized with tetanus toxoid and Freund's adjuvant revealed no VC-related changes in serum antitetanus titers, skin reactivity to tuberculin, or the number of plasma cells in popliteal lymph nodes. There was no increase in immunization induced lymphocyte transformation in either mice or rabbits. The results indicated an increase of lymphocyte transformation in splenic cultures that may be related to the immune complexes observed in VC syndrome.

108 AU - Laumbach AD ; Lee S ; Wong J ; Strelps UN
AD - Dept. Microbiology and Immunology, Univ. Louisville Sch. Medicine, Louisville, KY, 40201
TI - STUDIES ON THE MUTAGENICITY OF VINYL CHLORIDE METABOLITES AND RELATED CHEMICALS.
SI - CARC/79/06491
SO - Prevention and Detection of Cancer. Part I. Prevention. Vol. 1. Etiology. Proceedings of the Third International Symposium on Detection and Prevention of Cancer held 26 April - 1 May 1976 New York NY. Nieburgs HE, ed.New York, Marcel Dekker, Inc., 1193 pp., 1977.
LA - ENG
AB - The mutagenicity and potential mechanisms of action of several vinyl chloride (VC) metabolites (chloroacetaldehyde (CAA) monomer hydrate, CAA dimer hydrate, and CAA trimer) and epichlorohydrin (ECH, a carcinogenic chlorooxirane homolog) were studied. Indirect mutagenicity assays using repair-deficient Bacillus subtilis strains and direct mutagenicity assays using Salmonella typhimurium were performed. The mutagenicity of CAA and chlorooxirane was confirmed and that of the VC metabolites and ECH was found. Neither acetaldehyde, chloroacetic acid, nor chloroethanol showed a significant level of mutagenicity. There may be a molecular relationship involving the proximity of the chloride group to the aldehyde moiety for mutagenicity. Recombination repair appeared to be the mechanism for correcting VC metabolite-elicited damage. CAA decreased the biological activity of transforming DNA only if the cells were treated with the mutagen prior to DNA extraction. In vitro studies showed no such effect. The mode of action of ECH differed from that of the VC monomer metabolites. Although it caused similar base-substitution mutations in Salmonella strain TA100, it was a comparatively weaker alkylating agent. ECH also exhibited a lower toxicity level than VC monomer metabolites and thus demonstrated mutagenicity through a wider range of concentrations. ECH produced higher levels of mutation in Salmonella cultures that were actively replicating DNA than in cultures that were arrested in DNA replication. (29 Refs)

109 AU - Espinosa E
AD - Dept. Pathology, Univ. Louisville Sch. Medicine, Louisville, KY
TI - IMMUNOPATHOLOGIC OBSERVATIONS IN LIVER ANGIOSARCOMA.
SI - CARC/79/06471
SO - Prevention and Detection of Cancer. Part I. Prevention. Vol. 1. Etiology. Proceedings of the Third International Symposium on Dectection and Prevention of Cancer held 26 April - 1 May 1976 New York NY. Nieburgs HE, ed.New York, Marcel Dekker, Inc., 1193 pp., 1977.
LA - ENG
AB - To develop a more sensitive liver function test for the early detection of vinyl chloride liver disease, an attempt was made to discover antigenic changes in angiosarcomatous tissue and to test for the presence of an antibody response in the host. Serum, liver, and adjacent tissue samples were obtained at autopsy from 2 individuals with vinyl chloride-associated angiosarcoma and 10 control individuals with normal liver function and at biopsy from 10 patients with liver dysfunction with fibrosis. Immunodiffusion studies of angiosarcomatous tissue revealed the presence of an antigen not found in normal liver or kidney, but found in normal lung and spleen. This protein was inactivated by Pronase and trypsin, was heat- and acid pH-labile, and was found to precipitate at concentrations of 20-30% saturated ammonium sulfate and 30-70% ethanol. Immunoelectrophoretic assays of angiosarcomatous tumor extracts revealed the absence of one normal tissue antigen characterized as an entity unaffected by Pronase, trypsin, and heat treatment, inactivated by periodate and acid pH, and which precipitated over a wide range of conditions. Additionally, immunofluorescence assays of angiosarcomatous tissue indicated the presence of bound IgG. Further studies are necessary to determine whether this tumor-bound IgG represents specific antitumor antibody or antibody fixed by the tumor tissue nonspecifically. (29 Refs)

110 AU - Kupchella CE ; Tamburro CH
AD - Cancer Center, Dept. Medicine, Univ. Louisville Sch. Medicine, Louisville, KY, 40201
TI - URINARY AND TISSUE GLYCOSAMINOGLYCAN PATTERNS IN HEPATIC ANGIOSARCOMA.
SI - CARC/79/06470
SO - Prevention and Detection of Cancer. Part I. Prevention. Vol. 1. Etiology. Proceedings of the Third International Symposium on Dectection and Prevention of Cancer held 26 April - 1 May 1976 New York NY. Nieburgs HE, ed.New York, Marcel Dekker, Inc., 1193 pp., 1977.
LA - ENG
AB - To evaluate the use of glycosaminoglycan (GAG) patterns as an early indicator of vinyl chloride (VC)-induced liver injury or angiosarcoma (AS), GAG patterns were determined in urine samples of 9 patients with histories of exposure to VC and who had abnormal liver biochemistry, 6 with 'other' cancers prior to surgery, 3 with AS, 8 with viral hepatitis, 6 with cirrhosis, 2

with lung-liver metastases, and 4 with metabolic liver disorders. Determinations of GAG were carried out by creatinine and uronic acid assays. Additionally, tissue samples taken at autopsy from 2 patients with AS, 2 with cirrhosis, and 3 controls (who had gun-shot wounds) were similarly analyzed. Results showed that AS, hepatitis, cirrhosis, and liver metastases all involved elevated GAG excretion. Tissue data indicate that these elevated levels reflect GAG elevation in the liver. Furthermore, results disclosed that the chondroitin sulfates are the primary urinary GAG in both normal controls and in patients, while chondroitin sulfates and heparin are the dominant GAG present in fibrotic, nontumor portions of AS livers and tumor tissue, respectively. It is concluded that the increases in liver and urinary GAG levels may well reflect an important role of these substances in the process of fibrogenesis and tumor growth. (31 Refs)

111 AU - Kroes R
AD - Lab. Pathology, Natl. Inst. Public Health, P.O. Box 1, Bilthoven, Netherlands
TI - FOOD: A CARCINOGENIC HAZARD?
SI - CARC/79/06454
SO - Prevention and Detection of Cancer. Part I. Prevention. Vol. 1. Etiology. Proceedings of the Third International Symposium on Dectection and Prevention of Cancer held 26 April - 1 May 1976 New York NY. Nieburgs HE, ed.New York, Marcel Dekker, Inc., 1193 pp., 1977.
LA - ENG
AB - Information on the possible carcinogenic hazard of food is reviewed. Natural components of food that pose a carcinogenic threat include nitrate (in spinach, leeks, and purslane), fats, and proteins. Natural contaminants of food that are carcinogenic include aflatoxin, cycasin, safrole, sterigmatocystin, penicillic acid, patulin, luteoskyrin, cyclochlorotine, and pyrrolizidine alkaloids. Manmade chemicals that contaminate foods come from a wide range of sources. The food additives butter yellow, ponceaux SX, and 3R, guinea green, fuchsin, amaranth furfurylfuramide, and dulcin are now legislatively prohibited, based on recent findings that they may be carcinogenic. Contamination can occur from food packaging chemicals; ie, vinyl chloride, a proven carcinogen that is now federally regulated. Various agricultural chemicals still in use and under suspicion include dibromoethane, dibromochloropropane, aramite, chlordecone, lindane, DDT, aldrin, dieldrin, and nitrogen fertilizers. In addition, potentially carcinogenic substances used for disinfection, growth promotion, weed and insect control, and chemical synthesis reach food as a result of environmental pollution. The last source of carcinogenic contamination is from food processing: smoke curing introduces polycyclic aromatic hydrocarbons, nitrate and nitrite curing introduces nitrosamines, and processing through the use of fungi introduces mycotoxins into the diet. (25 Refs)

112 AU - Lehmann P
AD - New York Acad. Sciences, 2 East 63rd St., New York, NY, 10021
TI - CANCER AND THE WORKER.
SI - ICDB/79/16563
SO - Cancer and the Worker. New York, New York Academy of Sciences, 77 pp., 1977.
LA - ENG
AB - Volume 271 of the Annals of the New York Academy of Sciences, 'Occupational Carcinogenesis', has been rewritten for the general public. Basic cancer terms are defined, cancer hazards to the worker are reviewed, the prevention of occupational cancer is discussed, and the social issues involved are considered. Some of the specific hazards discussed are chemicals (vinyl chloride, anesthetics, bis(chloromethyl)ether, coke-oven emissions and coke by-products, benzene, rubber industry chemicals, chloroprene, benzpyrene, and lubricating oils), metals (arsenic, cadmium, lead), and dusts and fibers (asbestos, fibrous glass, radioactive dusts, wood dust, textile industry dusts). The effects of smoking on the risk of cancer among workers is briefly considered. Hazards to the communities surrounding industrial sites are discussed. Government regulations on occupational exposure to hazardous substances are reviewed. (4 Refs)

113 AU - Otsuki M ; Maeda M ; Yuu H ; Baba S
AD - Second Dept. of Internal Medicine, Koba Univ. Sch. Medicine, Kobe, Japan
TI - THE NATURE OF HYPERAMYLASEMIA IN PRIMARY LUNG CANCER; DEMONSTRATION OF A PRECURSOR OF THE SALIVARY TYPE ISOAMYLASE (MEETING ABSTRACT).
SI - ICDB/78/26400
SO - Summary Program and Abstracts of Papers, Proceedings of the 3rd Asian Cancer Conference Held by the Philippine Cancer Society under the Auspices of the Asian Federation of Organizations for Cancer Research and Control in Manila, 26-30 September, 1977. Philippine Cancer Society, Manila, Philippines., 184 pp., 1977.
LA - ENG
AB - The nature of the amylase in serum, pleural fluid and tumor extracts in patients with primary lung cancer was investigated. There seemed to be no correlation between histological structure of the tumors and the attendant hyperamylasemia. High amylase activity in the extracts of the diseased lung tissue has been found in pneumonia and tuberculosis, (chiefly salivary type isoamylases). Moreover, elevated amylase activity of the salivary type was observed in serum specimens sampled from the left atrium at autopsy, though there was no possibility of contamination of the salivary amylase during passage through the lung. In the extracts of primary and metastatic tumors of lung cancer and inflammatory lung tissues from a patient who died of vinyl chloride monomer poisoning, a peculiar isoamylase showing cathodic mobility on 5% polyacrylamide gel at pH 8.8 was found, in addition to the increased salivary type isoamylases. While in the extracts of metastatic liver nodules, only this peculiar

isoamylase was found. We herein demonstrate that the salivary type hyperamylasemia in primary lung cancer may be due to an increase in the amylase contained in normal lung tissues, resulting from activation and release into the blood stream by some inflammatory process. Ectopic production of amylase was also suggested in a particular case with primary lung cancer by findings of high amylase contents and a precursor of isoamylase both in the primary and metastatic lesions. (no Refs)

114 AU - Wagoner JK ; Infante PF
AD - Industry-wide Studies Branch, Div. Surveillance, Hazards Evaluations and Field Studies, Natl. Inst. Occupational Safety and Health, Cincinnati, OH, 45202
TI - VINYL CHLORIDE: A CASE FOR THE USE OF LABORATORY BIOASSAY IN THE REGULATORY CONTROL PROCEDURE.
SI - CARC/78/07396
SO - Human Risk Assessment, Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation. Vol. 4 (Book C), Hiatt HH, Watson JD, Winsten JA, ed. Cold Spring Harbor, Cold Spring Harbor Laboratory, Origins of Human Cancer., 583 pp., 1977.
LA - ENG
AB - The need for laboratory bioassays in the regulatory control of chemicals is illustrated using vinyl chloride (VC) as an example. The induction of skin, lung, and bone tumors in rats exposed by inhalation to high VC levels (levels not infrequently approached in the industrial setting) was first reported in 1971, 40 yr after VC's commercial introduction but 3 yr before three cases of liver angiosarcoma were reported among workers at a VC polymerization facility. A follow-up study, initiated as a result of these initial angiosarcoma cases, showed a significant excess of deaths from malignant neoplasms among VC workers, compared with US white male death rates. Excess cancer mortality was found for four organ systems: brain and CNS, respiratory system, hepatic system, and lymphatic and hematopoietic system. The cancer risk increased with increasing years of exposure. In the follow-up study, 11/14 confirmed cases of biliary or liver cancer were hepatic angiosarcoma. Among 8 bronchogenic carcinomas, 5 were large-cell undifferentiated and 3 were adenocarcinomas, which is not consistent with distributions previously reported for inhaled carcinogens. A recent bioassay was predictive not only for the carcinogenicity of VC but also for several of the target organs. VC is mutagenic in microbial test systems, and VC metabolites have induced mutations in mammalian cells. Wives of VC-exposed men have a significantly high risk of fetal loss. Thus, both mutagenic and carcinogenic assays predicted the potential hazards of VC. (34 Refs)

115 AU - Popper H ; Maltoni C ; Squire RA ; Thomas LB
AD - Stratton Lab. Study of Liver Diseases, Mount Sinai Sch. Medicine, City Univ. New York, New York, NY, 10029
TI - COMPARISON OF NEOPLASTIC HEPATIC LESIONS IN MAN AND EXPERIMENTAL ANIMALS.
SI - CARC/78/07373
SO - Human Risk Assessment, Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation. Vol. 4 (Book C), Hiatt HH, Watson JD, Winsten JA, ed. Cold Spring Harbor, Cold Spring Harbor Laboratory, Origins of Human Cancer., 583 pp., 1977.
LA - ENG
AB - The induction of hepatic tumors in animals and clinical observations of hepatic tumors in humans are compared. The progression from fibrotic lesions to angiosarcoma in man following exposure to vinyl chloride (VC), inorganic arsenicals, and Thorotrast is almost identical to changes observed in rodents treated with VC. This similarity in the evolution of hepatic lesions supports the predictive nature of animal experimental studies for human carcinogenesis. The major difference between the species was the greater fibroplastic reaction in man. The development of hepatocellular carcinoma in human and rodent nodules supports the concept of multiple cell populations in hepatocarcinogenesis. In the VC-associated lesions, the simultaneous proliferation of hepatocytes and sinusoidal cells, the latter potentially terminating in angiosarcoma, is stressed. The metabolic processes underlying this evolution remain to be established. (77 Refs)

116 AU - Infante PF ; Waggoner JK ; Young RJ
AD - Industry-wide Studies Branch, Div. Surveillance, Hazard Evaluation and Field Studies, Natl. Inst. Occupational Safety and Health, Cincinnati, OH, 45202
TI - CHLOROPRENE: OBSERVATIONS OF CARCINOGENESIS OF MUTAGENESIS.
SI - CARC/78/07215
SO - Incidence of Cancer in Humans, Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation. Vol. 4, Hiatt HH, Watson JD, Winsten JA, ed. Cold Spring Harbor, Cold Spring Harbor Laboratory, Origins of Human Cancer., 602 pp., 1977.
LA - ENG
AB - Observations of excessive lung and skin cancer associated with chloroprene production were reported in the Russian literature in 1972. However, it was not until 1974, when an epidemic of liver, brain, and lung cancer among vinyl chloride (VC) polymerization workers was identified, was attention in the US focused on the carcinogenic potential of chloroprene. Chloroprene is mutagenic in bacteria, causes recessive lethality in Drosophila, causes dominant lethality and chromosome aberrations in rat bone marrow cells, and has been associated with sterility in mice and rats. A significant excess of chromosome aberrations and a reduction in the numbers and motility of sperm have been reported in chloroprene workers, and a threefold excess of miscarriages has been reported among their wives. In the absence of adequate data,

a final evaluation of the carcinogenicity of chloroprene cannot be made. However, given its other effects, the possible carcinogenicity of chloroprene may be only of academic interest from a public health point of view. The data for VC anc chloroprene may serve as the basis for a more aggressive role by genetic toxicologists in the assay of industrial chemicals. (35 Refs)

117 AU - Gehring PJ ; Watanabe PG ; Young JD
AD - Toxicology Res. Lab., Health and Environmental Res., Dow Chemical, Midland, MI, 48640
TI - THE RELEVANCE OF DOSE-DEPENDENT PHARMACOKINETICS IN THE ASSESSMENT OF CARCINOGENIC HAZARD OF CHEMICALS.
SI - CARC/78/07214
SO - Incidence of Cancer in Humans, Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation. Vol. 4, Hiatt HH, Watson JD, Winsten JA, ed. Cold Spring Harbor, Cold Spring Harbor Laboratory, Origins of Human Cancer., 602 pp., 1977.
LA - ENG
AB - The use of data obtained after the lifetime daily administration of max tolerated doses of an agent to animals (usually rats or mice) to predict the hazard of low-level exposure to the agent is not justified. Changes in the fate of the chemical or in the metabolic status of the animals preclude the use of routine statistical processes to predict hazards from low doses. Metabolic thresholds may lead to a disproportionate increase in toxicity, including carcinogenesis. This concept is illustrated by pharmacokinetic studies with 1,4-dioxane and vinyl chloride (VC). The marked dose-dependent fate of dioxane and the strong metabolic induction by high doses, together with toxicologic data, negate extrapolation of high-dose carcinogenesis to predict the hazard of low doses. In rats, cancer induction occurs only at doses sufficient to cause marked pathology, metabolic alteration, and even death. These effects, including carcinogenesis, are correlative with the dose-dependent fate of dioxane. In light of this correlation, the hazard of low-level exposure to dioxane appears to be nil. Studies indicate that VC is metabolized by at least two different pathways. The fate of VC changes with dose because the primary pathway for its metabolism is saturated at high doses or exposures. However, both pathways for the metabolism of VC produce reactive metabolites that lead to the same end products. A correlation appears to exist between doses of VC that cause tumors and those that saturate metabolic or detoxifying pathways. There is a threshold of exposure in rats, in which the physiologic defense mechanisms remain fully operative. Thus, dose-dependent alterations in the fate of chemicals must be considered when using toxicological or carcinogenic data obtained at high doses to assess the hazard of low doses. (21 Refs)

118 AU - Maltoni C
AD - Inst. Oncology, Bologna, Italy 40138
TI - VINYL CHLORIDE CARCINOGENICITY: AN EXPERIMENTAL MODEL FOR CARCINOGENESIS STUDIES.
SI - CARC/78/07128
SO - Incidence of Cancer in Humans, Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation. Vol. 4, Hiatt HH, Watson JD, Winsten JA, ed. Cold Spring Harbor, Cold Spring Harbor Laboratory, Origins of Human Cancer., 602 pp., 1977.
LA - ENG
AB - The carcinogenicity of vinyl chloride (VC) was evaluated in Sprague-Dawley rats, Wistar rats, Swiss mice, and golden hamsters. In inhalation studies, 50-30,000 ppm VC produced Zymbal gland carcinomas, nephroblastomas, hepatic angiosarcomas (HAS) and angiosarcomas of other sites, sc angiomas, skin carcinomas, hepatomas, brain neuroblastomas, and mammary carcinomas in adult Sprague-Dawley rats after 52 wk of exposure. Rats exposed to only 25 ppm VC for 87 wk developed HAS. Reducing the length of treatment sharply reduced the onset of several tumor types, particularly HAS: when rats were treated for 5 wk at 10,000 and 6,000 ppm, no HAS were observed. VC also had a transplacental effect: exposure of pregnant rats to 10,000 or 6,000 ppm VC on days 12-18 of pregnancy produced VC-dependent tumors in the offspring. Newborn rats were also more susceptible to VC carcinogenesis than older ones. Exposure of Wistar rats to varying VC concentrations for 52 wk resulted in basically the same tumors as those produced in Sprague-Dawley rats. Exposure of Swiss mice to 50-10,000 ppm VC for 30 wk resulted in lung tumors, mammary carcinomas, HAS, vascular tumors of other types and/or sites, and epithelial tumors of the skin. In golden hamsters, the same VC concentrations resulted in HAS, skin trichoepitheliomas, melanomas, and forestomach epithelial tumors. In addition, the latency time of lymphomas was decreased from 82 wk (in controls) to 48 wk. Ingestion of 50, 16.65 or 3.33 mg/kg/day VC by Sprague-Dawley rats, 4-5 days/wk for 52 wk produced essentially the same spectrum of tumors as the inhalation studies. One nephroblastoma and one sc angiosarcoma were found among 240 Sprague-Dawley rats that had received one to four ip injections of 4.25 mg VC, and one nephroblastoma was found among 75 animals that had received the same dose sc. It is concluded that the neoplastic response to VC depends largely on the species and strain of animal and that age is also important with respect to tumor incidence and distribution. (5 Refs)

119 AU - Fonseca JJ ; Pena FM
AD - Catedra de Patologia, Facultad de Medicina, Universidad de Costa Rica, Costa Rica
TI - PRIMARY HEMANGIOSARCOMA OF THE LIVER ASSOCIATED WITH MICROANGIOPATHIC HEMOLYTIC ANEMIA AND THROMBOCYTOPENIA (KASSELBACH-MERRITT SYNDROME). REPORT OF TWO CASES.
SI - ICDB/78/23478
SO - Acta Med Costarric; 20(3):273-285 1977

LA - SPA
AB - Abnormal hematologic findings are reported in two cases of primary hemangiosarcoma of the liver: microangiopathic hemolytic anemia and thrombocytopenia in one case and chronic hypofuremic anemia in the other. Both patients succumbed to massive intraperitoneal bleeding, in one patient following a needle biopsy, in the other because of spontaneous rupture of the tumor. Both cases were diagnosed at autopsy. Exposure to thorium dioxide, arsenical solutions or vinyl chloride was denied. (47 Refs)

120 AU - Henschler D
AD - Institut fur Pharmakologie und Toxikologie, Univ. Wurzburg, D-87 Wurzburg, W. Germany
TI - METABOLISM OF CHLORINATED ALKENES AND ALKANES AS RELATED TO TOXICITY.
SI - CARC/78/06409
SO - J Environ Pathol Toxicol; 1(2):125-133 1977
LA - ENG
AB - Chlorine substitution in aliphatic compounds results in a destabilization in alkanes and a stabilization in alkenes. With alkanes, therefore, the main pathways of metabolic transformation to reactive intermediates are radical formation by a C-C break and dechlorination or dehydrochlorination. In the chlorinated ethylenes, the first metabolic transformation step is oxidation to electrophilic oxiranes. These compounds may be hydrolized enzymatically or nonenzymatically, react with cellular nucleophiles, or rearrange to either chlorinated aldehydes or acyl chlorides. With tetrachloroethylene, 1,2-cis-dichloroethylene, trans-dichloroethylene, 1,1-dichloroethylene, and vinyl chloride, the metabolies identified in in vivo experiments are identical to the thermal rearrangement products of the respective oxiranes. An exception is trichloroethylene, whose thermal rearrangement product is dichloroacetyl chloride; its metabolites in vivo, however, are entirely derived from trichloroacetaldehyde. Mutagenic and carcinogenic activities in the chlorinated ethylenes are determined by the stability of their chlorine substitution compounds: the relatively unstable and unsymmetric oxiranes of trichloroethylene, 1,1-dichloroethylene, and vinyl chloride are mutagenic in the Ames test, but the more stable asymmetric oxiranes of tetra-, 1,2-cis-, and trans-dichoroethylenes are inactive. (20 Refs)

121 AU - Holmberg B ; Kronevi T ; Winell M
AD - Section Occupational Toxicology, Natl. Board Occupational Safety and Health, Stockholm, Sweden
TI - SOME ASPECTS ON DOSE-RESPONSE IN VINYL-CHLORIDE-INDUCED LIVER INJURY AND TUMORS IN MICE (MEETING ABSTRACT).
SI - ICOB/78/19650
SO - Scand J Clin Lab Invest; 37(Suppl147):74 1977
LA - ENG
AB - Vinyl chloride monomer (VCM) induces liver injury and liver

hemangiosarcoma in PVC workmen and is also carcinogenic in rodents. Mice were exposed by inhalation to 50 and 500 ppm VCM during 12 and 6 mo respectively. Blood samples were taken every 6th wk for analysis of glutamic pyruvic transaminase (GPT), glutamic oxalacetic transaminase (GOT), acid phosphatase (AP), and total lactic dehydrogenase (LDH) as well as LDH isoenzymes. Some mice were sacrificed for histopathological examinations after 6 mo and the rest when dead or moribund. AP and total LDH activities were elevated in VCM exposed mice. The percentage of M form was also increased in exposed animals. The transaminases were not elevated. Enzyme activities were, however, increased after the appearance of tumors. A tendency to a dose-dependency was observed in total LDH activities as well as in the frequency of tumour-bearing animals. The significance of the data will be discussed with reference to possible early detectability of VCM induced tissue injury and with reference to current knowledge of dose-response relationships for chemically induced tumors.

122 AU - Nelson N
AD - Inst. Environmental Medicine, New York Univ. Medical Center, New York, NY, 10016
TI - INHALATION CARCINOGENESIS.
SI - CARC/78/05862
SO - Ecotoxicol Environ Saf; 1(3):289-295 1977
LA - ENG
AB - A limited review of the carcinogenicity of various inhaled substances is presented. Chemical hazards in the workplace include benzene, nickel carbonyl, mustard gas, vinyl chloride, chloroprene, and bis(chloromethyl)ether (BCME). To date, at least 35 cases of lung cancer in the US have been attributed to BCME. Several methods for the safe and controlled inhalation of experimental animals to carcinogenic material are outlined.

123 AU - Van Duuren BL
AD - Lab. of Organic Chemistry and Carcinogenesis, Inst. of Environmental Medicine, New York Univ. Medical Center, New York, NY, 10016
TI - CHEMICAL STRUCTURE, REACTIVITY, AND CARCINOGENICITY OF HALOHYDROCARBONS.
SI - CARC/78/05433
SO - Environ Health Perspect; 21:17-23 1977
LA - ENG
AB - The structural and carcinogenic properties of halohydrocarbons are reviewed, with particular emphasis on trichloroethylene (TCE). Based on studies of the chemical structure, reactivity, and possible metabolic pathways of TCE, the compound was predicted to be carcinogenic, particularly to the liver. These studies also suggested that TCE is metabolized to an epoxide and that this epoxide may be the activated carcinogenic intermediate of TCE in liver carcinogenesis. The binding of TCE to liver microsomal proteins of male B6C3F1 hybrid mice, which are susceptible to TCE-induced liver tumorigenesis, was found to be significantly higher than the binding of TCE to microsomal

proteins of male Osborne-Mendel rats, which are resistant to TCE-induced hepatocellular carcinoma. Also, the in vitro binding of TCE to liver microsomal proteins was higher for male than female B6C3F1 mice; females have been reported to show a lower incidence of TCE-induced hepatocellular carcinoma than males. The results of carcinogenicity assays of vinyl bromide and polyvinyl bromide are also given. Neither compound appeared to be carcinogenic when injected sc or when applied to the skin of mice. The carcinogenicity of other chlorinated hydrocarbons that are widely used in the chemical industry and that are structurally analogous to TCE and vinyl chloride is discussed briefly.

124 AU - Lee CC ; Bhandari JC ; Winston JM ; House WB ; Peters PJ
AU - Dixon RL ; Woods JS
AD - Pharmacology and Toxicology, Midwest Res. Inst., 425 Volker Blvd., Kansas City, MO, 64110
TI - INHALATION TOXICITY OF VINYL CHLORIDE AND VINYLIDENE CHLORIDE.
SI - CARC/78/05437
SO - Environ Health Perspect; 21:25-32 1977
LA - ENG
AB - Experiments on the inhalation toxicity and carcinogenicity of vinyl chloride (VC) and vinylidene chloride (VDC) in mice and rats are reported. The exposure of mice to 1,000 ppm VC for 6 hr/day, 5 days/wk caused some acute deaths with toxic hepatitis and marked tubular necrosis of the renal cortex. During the sixth month, mice exposed to 1,000, 250, or 50 ppm VC became lethargic, lost weight quickly, and died; only a few mice exposed to 50 ppm survived for 12 mo. In mice exposed to 50, 250, or 1,000 ppm VC, there was a high incidence of bronchioloalveolar adenoma, mammary gland tumors (including ductular adenocarcinoma), squamous and anaplastic cell carcinomas with metastasis to the lung, and hemangiosarcoma (HS) in the liver and, to a lesser extent, in other organs. The incidence and severity of these tumors were proportional to the levels and duration of exposure. Malignant lymphoma involving various organs was observed in a few mice. Rats were more resistant to the toxic effects of VC, and exposure to 1,000 ppm slightly depressed the body wt of females. Exposures of 250 and 1,000 ppm VC caused a number of deaths and hepatic HS during the 9th mo. Most rats with hepatic HS also developed HS in the lung. HS occasionally occurred in other tissues, including omentum, mesentery, or sc tissue, of rats exposed to 50, 250, or 1,000 ppm VC. The exposure of mice to 55 ppm VDC also caused a few acute deaths and a few hepatic HS. Inflammatory, degenerative, and mitotic changes occurred in the liver. No mouse exposed to VDC developed any mammary gland tumors. Several mice had a bronchioloalveolar adenoma. The exposure of rats to 55 ppm VDC slightly depressed body wt; HS occurred in the mesenteric lymph node or sc tissue of two rats.

125 AU - Hathway DE
AD - Imperial Chemical Industries Limited, Central Toxicology Lab., Alderley Park, Cheshire SK10 4TJ, England
TI - COMPARATIVE MAMMALIAN METABOLISM OF VINYL CHLORIDE AND VINYLIDENE CHLORIDE IN RELATION TO ONCOGENIC POTENTIAL.
SI - CARC/78/05434
SO - Environ Health Perspect; 21:55-59 1977
LA - ENG
AB - Possible mechanisms for the mammalian metabolism of vinyl chloride (VC) and vinylidene chloride (VDC) are discussed in relation to the oncogenic potential of these agents. Studies in rats indicate that VC probably yields chloroethylene oxide (CEO), which is then transformed spontaneously into chloroacetaldehyde (CAA). Since CAA and CEO are mutagenic in the Ames test and in Chinese hamster V79 cells, they may be relevant to VC carcinogenicity. Observations in rats exposed to VC indicate that a degree of DNA depurination occurs. The alkylation that produces imidazo- derviative formation with DNA labilizes the N9-purine beta-glycoside linkage, which leads to depurination. The gap so produced might then be filled by various bases, resulting in mispairing during DNA replication. In general, there is excellent agreement between the severe damaging effect of DNA depurination and mutagenicity. Thus, VC would be considered mutagenic/carcinogenic. Experiments with rats exposed to VDC indicate that chloroacetic acid (CA), which is a VDC metabolite per se, lies on a major metabolic pathway for VDC. There is a strong supposition that CA is detoxified through a glutathione S-acyltransferase-catalyzed reaction process and ensuing degradative sequence for the resulting carboxymethylglutathione and that this represents the principal metabolic pathway for CA and a major one for VDC. Thiodiglycollic acid (TDC) is the ultimate detoxification product. Comparative studies of the processing of VDC in mice and rats show that in mice, the metabolic pathway from CA to TDC seems to be readily saturable, possibly on account of an inadequacy in the reaction catalyzed by glutathione S-acyltransferase. Under these circumstances, detoxification of 1,1-dichloroethylene oxide by glutathione S-epoxide transferase and the modification of DNA by 1,1-dichloroethylene oxide or chloroacetyl chloride would be expected to be more significant in mice than in rats. This diagnosis of species susceptibility agrees with the discovery of VDC oncogenicity in the kidneys of mice. Overall, VDC emerges as an agent of low oncogenic potential that is likely to be damaging only under special biological circumstances. (26 Refs)

126 AU - Maltoni C
AD - Inst. Oncology and Tumor Center, Bologna, Italy
TI - RECENT FINDINGS ON THE CARCINOGENICITY OF CHLORINATED OLEFINS.
SI - CARC/78/05401
SO - Environ Health Perspect; 21:1-5 1977
LA - ENG
AB - Major factors affecting the carcinogenicity of vinyl chloride (VC) and vinylidene chloride (VDC) are discussed. Although the two compounds have very similar molecular structures, they have widely different biological effects. VS is a multipotential carcinogen, but VDC has produced tumors only in the murine kidney. Dose, concentration, length of treatment, route of administration, and animal species, strain, sex, and age also significantly affect the neoplastic response. These factors may alter the metabolic pathway of the test compounds. The carcinogenicity of VC and VDC is due to their active metabolites, probably epoxy derivatives. Animal species, strain, and sex greatly affect the production of active metabolites of VDC. In Swiss mice and Sprague-Dawley rats, there is a parallelism between the toxic and carcinogenic effects of VDC in relation to species and sex. Confirmation of this parallelism in other strains would indicate new routes for establishing experimental animal models, and for understanding the mechanisms of action of many organic carcinogens.

127 AU - Anderson D ; Hodge MC ; Purchase IF
AD - Central Toxicology Lab., Imperial Chemical Industries, Ltd., Alderley Park nr. Macclesfield, Cheshire SK10 4TJ, England
TI - DOMINANT LETHAL STUDIES WITH THE HALOGENATED OLEFINS VINYL CHLORIDE AND VINYLIDENE DICHLORIDE IN MALE CD-1 MICE.
SI - CARC/78/05317
SO - Environ Health Perspect; 21:71-78 1977
LA - ENG
AB - Vinyl chloride (VC) and vinylidene dichloride (VDC) were assessed by the dominant lethal test for mutagenic activity in fertile male CD-1 mice. Compared with control males exposed to air, VC and VDC did not cause dominant lethal mutations at 3,000, 10,000, and 30,000 ppm and at 10, 30, and 50 ppm, respectively.

128 AU - Radike MJ ; Stemmer KL ; Brown PG ; Larson E ; Bingham E
AD - Univ. Cincinnati, Inst. Environmental Health, Kettering Lab., Cincinnati, OH, 45267
TI - EFFECT OF ETHANOL AND VINYL CHLORIDE ON THE INDUCTION OF LIVER TUMORS: PRELIMINARY REPORT.
SI - CARC/78/05308
SO - Environ Health Perspect; 21:153-155 1977
LA - ENG
AB - A preliminary report of the effect of ethanol on vinyl chloride (VC) carcinogenicity in 320 male Sprague-Dawley rats is presented. Equal numbers of rats were divided into four groups. Group 1 received a normal diet and breathed filtered air for life. Group 2 received a normal diet plus 5% ethanol in the

drinking water and breathed filtered air for life. Group 3 received a normal diet but breathed 600 ppm VC 4 hr/day, 5 days/wk, for 1 yr. Group 4 received a normal diet plus ethanol starting 4 wk before VC exposure. The ethanol exposure lasted until the animal died or was sacrificed. Sixty weeks after the first exposure to VC, 55 rats had died or had been sacrificied. No tumors were noted in eight Group 1 animals that had died. Of six dead Group 2 animals, one had a kidney tumor. Of 13 dead Group 3 animals, 5 had liver tumors (2 of them being angiosarcomas) and 2 had lung tumors. Of 28 dead Group 4 animals, 21 had 26 liver tumors (5 angiosarcomas) and 2 had kidney tumors. These preliminary findings suggest a synergism between VC inhalation and ingested alcohol in tumorigenesis. (6 Refs)

129 AU - Bolt HM ; Filser JG
AD - Inst. Toxicology, Univ. Tubingen, Wilhelmstrasse 56, D-7400 Tubingen-1, W. Germany
TI - IRREVERSIBLE BINDING OF CHLORINATED ETHYLENES TO MACROMOLECULES.
SI - CARC/78/05301
SO - Environ Health Perspect; 21:107-112 1977
LA - ENG
AB - The binding of vinyl chloride (VC) and trichloroethylene (TCE) to male Wistar rat macromolecules was investigated and compared to that of carbon tetrachloride (CCl4). Saturation of the rat metabolizing systems was achieved at 250 ppm VC, 150 ppm TCE, and 250 ppm CCl4. Data on the uptake of the compounds, the urinary excretion of metabolites, and exhalation after exposure indicated that the chlorinated ethylenes were metabolized much faster than CCl4. The metabolites of all three compounds bound irreversibly to tissue proteins, mainly in the liver. Other sites of binding included the kidneys, small intestine, lung, and spleen. Irreversible binding of these compounds ranged within the same order of magnitude when related to the amount of the compound that had been absorbed. No differences in the relative portion of irreversibly bound metabolites were found after exposure of the rats to different atmospheric concentrations of the three compounds. In vitro studies indicated that TCE metabolism by rat liver microsomes in the presence of an NADPH-regenerating system leads to irreversible protein binding, mainly to albumin; similar findings have been reported for VC. Unlike VC, however, TCE metabolites also bind to non-SH proteins such as gamma-globulin and concanavalin A. Thus, TCE metabolites irreversibly bind not only to SH groups of a protein, but also to NH2 groups. (28 Refs)

130 AU - Henschler D
AD - Institut fur Toxikologie und Pharmakologie, Universitat Wurzburg, D-8700 Wurzburg, W. Germany
TI - METABOLISM AND MUTAGENICITY OF HALOGENATED OLEFINS--A COMPARISON OF STRUCTURE AND ACTIVITY.
SI - CARC/78/05183
SO - Environ Health Perspect; 21:61-64 1977
LA - ENG
AB - The metabolism of various halogenated olefins was studied in

vivo, and their mutagenicity was investigated in vitro in a modified Ames testing system. The results of the mutagenicity test were compared with in vivo carcinogenicity findings reported previously. In mammals, chlorinated ethylenes are first metabolized to epoxides, which may then undergo intramolecular rearrangement. This reaction has been studied in the entire series of chlorinated epoxyethanes. The rearrangement products found were acyl chlorides (tetrachloro-, trichloro-, and 1,1-dichloroethylenes) or chlorinated aldehydes (cis- and trans-1,2-dichloroethylene, vinyl chloride). In vivo experiments yielded products that were further derivatives of these rearrangement products, except that with trichloroethylene, the only rearrangement product was chloral. Tetrachloroethylene, trichloroethylene, cis-1,2-dichloroethylene, trans-1,2-dichloroethylene, 1,1-dichloroethylene, and vinyl chloride were then tested for mutagenicity in the Salmonella typhimurium assay. Vinyl chloride, trichloroethylene, and 1,1-dichloroethylene were mutagenic, suggesting that asymmetric chlorine substitution renders the epoxides unstable and mutagenic. High electrophilicity may be a prerequisite for the mutagenic and carcinogenic activity of these chlorinated ethylenes. (20 Refs)

131 AU - Watanabe PG ; Young JD ; Gehring PJ
AD - Health and Environmental Res. Toxicology Lab., Dow Chemical Co., Midland, MI, 48640
TI - THE IMPORTANCE OF NON-LINEAR (DOSE-DEPENDENT) PHARMACOKINETICS IN HAZARD ASSESSMENT.
SI - CARC/78/05009
SO - J Environ Pathol Toxicol; 1(2):147-159 1977
LA - ENG
AB - The importance of dose-dependent or nonlinear pharmacokinetics in interpreting animal toxicity data at high dose levels for subsequent assessment of the hazard of exposure to humans is illustrated by two examples, 1,4-dioxane and vinyl chloride. The biotransformation, excretion, and protein binding of many chemicals are capacity-limited processes, and the probability of encountering saturable processes in animal toxicity tests is high. Toxicity at high doses may be due to saturated detoxification or excretion mechanisms that, when fully operative at lower doses, do not result in the same toxic response. Knowledge of the pharmacokinetics of a chemical, therefore, is essential in evaluating animal toxicity tests. Pharmacokinetic data can also be used to assist in dose selection for chronic toxicity studies. In both cases, max information is obtained from a well-defined dose-response relationship. Massive doses that result in nonlinear pharmacokinetics should be avoided unless they approximate human exposure levels. (20 Refs)

132 AU - Greim H ; Bimboes D ; Egert G ; Goggelmann W ; Kramer M
AD - Abteilung Toxikologie, Gesellschaft fur Strahlen-und Umweltforschung Munchen, Ingolstadter Landstrasse 1, D-8042 Neuherberg, W. Germany
TI - MUTAGENICITY AND CHROMOSOMAL ABERRATIONS AS AN ANALYTICAL TOOL FOR IN VITRO DETECTION OF MAMMALIAN ENZYME-MEDIATED FORMATION OF REACTIVE METABOLITES.
SI - CARC/78/04097
SO - Arch Toxicol (Berl); 39(1/2):159-169 1977
LA - ENG
AB - The mutagenic activity of various chemicals was tested in bacterial and mammalian assay systems. Trichloroethylene, 1,1-dichloroethylene, vinyl chloride, tetrachlorocyclopentadiene, and the nitroso derivatives of the pesticides Carbaryl, Prometryn, and Dodin were mutagenic to Escherichia coli K12 and/or Salmonella typhimurium in the presence of metabolically active mouse liver microsomes. Under the same conditions, tetrachloroethylene, 1,2-cis- and trans-dichloroethylene, hexachlorocyclopentadiene, carbon tetrachloride, chloroform, halothane, trichlorofluoromethane, and styrene were not activated to mutagenic species. Incubation of human lymphocytes with dimethylnitrosamine in the presence of mouse liver microsomes induced chromosomal aberrations: there was a significantly increased number of gaps, but crossovers or translocations and breaks were less frequent. It is concluded that human lymphocytes can be successfully used in metabolizing test systems in combination with mouse liver microsomes to activate potential mutagens.

133 AU - Henschler D ; Bonse G
AD - Institut fur Toxikologie, Universitat Wurzburg, Versbacher Landstrasse 9, D-8700 Wurzburg, W. Germany
TI - METABOLIC ACTIVATION OF CHLORINATED ETHYLENES: DEPENDENCE OF MUTAGENIC EFFECT ON ELECTROPHILIC REACTIVITY OF THE METABOLICALLY FORMED EPOXIDES.
SI - CARC/78/04032
SO - Arch Toxicol (Berl); 39(1/2):7-12 1977
LA - ENG
AB - Investigations of the chemical reactivity, biotransformation, and toxicity of the chloroethylenes are reviewed. In chlorinated ethylenes, the chlorine susbstitution exerts, by its electron-withdrawal effect, a stabilization of the molecule that increases with the number of chlorine residues. Epoxides are short-lived metabolic intermediates that rearrange to give two possible products: acylchlorides (as with tetra-, tri-, and 1,1-dichloroethylenes) or aldehydes (1,2-cis- and 1,2-trans-dichloroethylenes and vinyl chloride). The aldehydes subsequently undergo reduction and oxidation to alcohols and acids, respectively. The chlorinated ethylenes were tested for mutagenic potential in a modified Ames system, and three members of the group were active: vinyl chloride, vinylidene chloride, and trichloroethylene. The molecular feature common to the active

molecules is an asymmetric chlorine substitution, but in the inactive compounds there is a symmetric distribution of the chlorine residues. It is hypothesized that the increased electrophilicity caused by the asymmetrical chlorine substituti offers an enhanced chance for alkylating reactions of the epoxides, which overpower the deactivation mechanisms of conjugation, rearrangement, and hydrolysis. The three mutagenic chloroethylenes have also produced carcinogenic effects in animals.

134 AU - Chudy JC ; Crosby NT
AD - Dept. Industry, Lab. Government Chemist, London SE1 9NQ, Englan
TI - SOME OBSERVATIONS ON THE DETERMINATION OF MONOMER RESIDUES IN FOODS.
SI - CARC/78/03995
SO - Food Cosmet Toxicol; 15(6):547-551 1977
LA - ENG
AB - Parameters that might affect the headspace gas chromatographic (HSGC) determination of vinyl chloride (VC) and acrylonitrile (AN) residues in foods were investigated. They included solvent type, monomer distribution between the headspace and the liquid, and storage duration and temperature. Samples of orange drink, wine, olive oil, and water, which previously had not been in contact with polyvinyl chloride (PVC), were poured into PVC bottles so that a minimum air space was left above the liquid and then sealed. At monthly intervals, 5-ml portions were removed and analyzed by HSGC. For VC, equilibrium was attained more rapidly in methyl ethyl ketone (MEK) than in water. At 30 C, full equilibrium was attained only after 2 hr; at 40 C, the equilibrium time was as short as 30 min. At 30 C, VC was 10 times more soluble in MEK than in water. After equilibrium was attained, the VC content of the headspace was stable for at least 5 hr. For AN, equilibirum was achieved in less than 30 min in water or dimethylformamide and at 60 or 80 C, and little change was observed over 7 hr. When dimethylacetamide and a storage temperature of 80 C were used, however, the AN concentration in the headspace fell rapidly for 2 hr, beginning 1 hr after equilibrium was reached. The reason for this is not clear. The concentration of VC in the headspace gases at different headspace volumes rose markedly at volumes greater than 10 ml. There was a clear distinction between the aqueous and organic solvent systems, a fact that may be important in the design of a standard method for the analysis of VC in foods. Migration of VC from the container into the fluids increased during the first 3 mo, followed by a leveling off and, in some cases, a slow decay. When the same four fluids, to which varying wts of VC had been added, were kept in open glass jars, the VC content fell to half its original value within 2-4 hr. (9 Refs)

135 AU - Libeskind M ; Lugagne F ; Malbran J ; Villemant JF
AU - Guyet-Rousset P
AD - Service de Gastroenterologie, Centre Hospitalier de Gonesse, F 95500 Gonesse, France
TI - HEPATOSPLENIC ANGIOSARCOMA. REPORT OF A CASE AND REVIEW OF THE LITERATURE.
SI - CARC/78/03553
SO - Gastroenterol Clin Biol; 1(12):1027-1034 1977
LA - FRE
AB - Primary angiosarcomas of the liver and spleen were diagnosed in a 37-yr-old man who had never been exposed to vinyl chloride. (28 Refs)

136 AU - Ungvary GY ; Hudak A ; Tatrai E ; Lorincz M ; Folly G
AD - Orszagos Munka- es Ueemegeszszegtan Intezet, Budapest, Hungary
TI - STUDY OF THE TERATOGENIC AND EBRYOTOXIC EFFECT OF VINYL CHLORIDE IN CFY RATS.
SI - CARC/78/03544
SO - Egeszsegtudomany; 21(4):363-369 1977
LA - HUN
AB - Inhalation of vinyl chloride (4,000 mg/m**3) between the 8th and 14th days of pregnancy increased the absolute and relative wt of the liver of pregnant CFY rats significantly, but there was no significant increase in resorption, embryonal mortality, and developmental anomalies. In addition, vinyl chloride was found in the maternal and fetal blood and amniotic fluid following exposure of the mothers to 5,500-33,000 mg/m**3 vinyl chloride for 2.5 hr on the 18th day of pregnancy. (31 Refs)

137 AU - Short RD ; Minor JL ; Winston JM ; Lee CC
AD - Pharmacology and Toxicology, Midwest Res. Inst., 425 Volker Blvd., Kansas City, MO, 64110
TI - A DOMINANT LETHAL STUDY IN MALE RATS AFTER REPEATED EXPOSURES TO VINYL CHLORIDE OR VINYLIDENE CHLORIDE.
SI - ICDB/78/00967
SO - J Toxicol Environ Health; 3(5/6):965-968 1977
LA - ENG
AB - Germinal mutations, as manifested by a dominant lethal effect, in male rats exposed to 0, 50, 250, or 1000 ppm vinyl chloride or 55 ppm vinylidene chloride (6 hr/day for 5 days/wk) were studied. The males were mated with untreated females after 11 wk of exposure. No evidence of pre- or postimplantation loss in the pregnant females was observed. (9 Refs)

138 AU - Reynolds ES
AD - Dept. Pathology, Univ. Texas Medical Branch, Galveston, TX, 77550
TI - ENVIRONMENTAL ASPECTS OF INJURY AND DISEASE: LIVER AND BILE DUCTS.
SI - CARC/78/03279
SO - Environ Health Perspect; 20:1-13 1977
LA - ENG
AB - Mechanisms by which environmental agents interact with the liver and cause liver and biliary damage are surveyed. Known

hepatotoxins (vinyl chloride, CCl4), potential hepatotoxins, cohepatoxins, mixed-function-oxidase inducers, and potential hepatoxins that could be encountered in various environments are listed. (27 Refs)

139 AU - Latarjet R
AD - Foundation Curie - Institut du Radium, 26 Rue de Ulm, 75231 Paris Cedex 05 France
TI - POLLUTION BY CHEMICAL MUTAGENS AND THE RAD-EQUIVALENT SYSTEM.
SI - CARC/78/03092
SO - Entropie; 13(78):6-11 1977
LA - FRE
AB - A rad-equivalent system applicable to pollution by chemical mutagens such as vinyl chloride and methyl methane sulfonate is described. The system is based on internationally accepted rules for radiation exposure, and it would permit calculation of the total mutagenic risk of exposure to radiation and chemicals. (11 Refs)

140 AU - Puech AM ; Fournet A ; Laulhere L ; Faure J ; Cau G ; Mallion JM
AD - Laboratoire de medecine legale, medecine du travail, toxicologie, La Merci, 38700 La Tronche, France
TI - INCLUDING ANGIOSARCOMAS, HEPATIC LESIONS IN FIVE SUBJECTS EXPOSED TO VINYL CHLORIDE.
SI - CARC/78/03087
SO - Arch Mal Prof; 38(9):787-795 1977
LA - FRE
AB - Five men who were occupationally exposed to vinyl chloride for 10-26 yr developed lesions of the liver (3 angiosarcomas, 1 adenosarcoma plus cirrhosis, 1 portal sclerosis). The patients ranged in age from 38 to 63 yr, and they had been employed in various aspects of polymer production (solution preparation, polymerization, filtration, drying, etc). Work conditions were conducive to intoxication, since the men ate at their place of work and the factories were poorly ventilated. The three angiosarcoma patients died within 4 mo of diagnosis despite hepatectomy and/or chemotherapy. The patient with portal vein sclerosis was not treated but was followed regularly without evidence of change in his symptoms. The last patient died of pulmonary metastases from hepatic adenocarcinoma 1 yr and 4 mo after liver biopsy revealed widespread cirrhosis. (8 Refs)

141 AU - Curran KL ; Kupchella CE ; Tamburro CH
AD - Cancer Center, Univ. Louisville, Louisville, KY 40201
TI - URINARY GLYCOSAMINOGLYCAN PATTERNS IN ANGIOSARCOMA OF THE LIVER.
SI - CARC/78/03036
SO - Cancer; 40(6):3050-3053 1977
LA - ENG
AB - The urinary chondroitin sulfate fraction was examined in a 46-yr-old man with advanced hepatic angiosarcoma who had worked in a vinyl chloride plant for 13 yr, a 54-yr-old man with moderately advanced hepatic angiosarcoma who had worked in a vinyl chloride plant for 28 yr, and two normal controls. The

specimens were separated into hyaluronic acid, chondroitin sulfate, and heparin fractions. Anion exchange chromatography of the hyaluronic acid and heparin fractions revealed no qualitative differences between controls and patients. The chondroitin sulfate fraction of the patients had an increased total amount of uronic acid in a hyaluronidase-resistant fraction and a decreased amount in a fraction susceptible to hyaluronidase digestion. These changes appeared to become more pronounced with advancing disease. The resistant fraction was heparin sulfate and the susceptible fraction was either chondroitin-4-sulfate and/or chondroitin-6-sulfate. These tests could be useful in the detection of vinyl chloride-induced liver disease. (22 Refs)

142 AU - Schmahl D
AD - Institut fur Toxikologie und Chemotherapie am Deutschen Krebsforschungszentrum, Im Novenheimer Feld 280, 69 Heidelberg, W. Germany
TI - TOXICOLOGY IN CANCER RESEARCH.
SI - CARC/78/02893
SO - Interdiscip Sci Rev; 2(4):305-311 1977
LA - ENG
AB - The role of toxicology in cancer research is reviewed. A study of occupational and geographic cancers indicated that there is a high prevalence of gastric cancer in Japan and a dietary factor in the etiology. It also implicated vinyl chloride in hemangiosarcoma induction and haloethers in the development of carcinomas of the bronchi. Natural products may also be carcinogenic. Certain or probable natural carcinogens include aflatoxins, arsenic, asbestos, betel nuts, Cycas circinalis, Pteris aquilina, pyrrolicidin alkaloids, Streptozotocin, and tobacco. In testing substances for carcinogenicity, species with responses similar to those of humans must be found. In addition, prenatal toxicological effects must be considered. An example of this is diethylstilbestrol-induced vaginal adenocarcinomas in daughters of women who took the drug. Various drugs used in cancer therapy are also known carcinogens (alkylating agents, arsenic, diethylstilbestrol, and procarbazine), but in many cases their benefits outweigh their adverse effects. Future toxicological research should focus on measures of reducing the toxic side effects of many cancer therapy drugs. It is generally thought that chemical carcinogens work by attacking genetic material. Carcinogens differ with respect to their dose-effect and dose-time relationships. (37 Refs)

143 AU - Biersack HJ ; San Luis T ; Lange CE ; Thelen M ; Veltman G
AU - Winkler C
AD - Inst. for Clinical and Experimental Nuclear Medicine, 5300 Bonn-Venusberg, W. Germany
TI - SCINTIGRAPHY OF LIVER AND SPLEEN IN VINYL CHLORIDE WORKERS.
SI - ICOB/78/06726
SO - Hepatogastroenterol (Stuttg); 24(5):357-361 1977
LA - ENG
AB - In 152 vinylchloride(VC)-exposed, workers of whom 124 were

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employed in the polyvinylchloride (PVC) production and 28 in VC-processing plants, liver and spleen imaging was performed using Tc99m-sulphur colloid and Hg197-BMHP. In 101 (81%) of the 124 workers of the PVC-production plant and in 18 (64%) workers of PVC-processing factories pathological liver and spleen scintigrams were found. The most frequent pathological change in the scintigraphic image was an increase in splenic colloid accumulation, when compared with the liver uptake. Three angiosarcomas of the liver were detected through circumscribed defects of colloid accumulation. Sequential liver scintigraphy was done in 15 cases. In 7 patients with esophageal varices considerable decrease in portal venous blood flow was demonstrated. Scintigraphically detectable changes are sensitive indicators of VC-induced lesions of the liver including liver fibrosis, portal hypertension and angiosarcoma. (Author abstract) (22 Refs)

144 AU - Radwan Z ; Henschler D
AD - Inst. Toxicology, Univ. Wurzburg, Versbacher Landstrasse 9, D-8700 Wurzburg, W. Germany
TI - UPTAKE AND RATE OF METABOLISM OF VINYL CHLORIDE BY THE ISOLATED PERFUSED RAT LIVER PREPARATION.
SI - CARC/78/02725
SO - Int Arch Arbeitsmed; 40(2):101-110 1977
LA - ENG
AB - The metabolism of vinyl chloride (VC) under controlled, steady-state exposure conditions in varying concentrations was examined in the isolated perfused rat liver. The solubility of VC in the RBC perfusion medium at 37 C was constant from 50 to 25,000 ppm. The amount metabolized, (14.6%) as determined by the difference between VC concentrations before and after passage of the liver, was also constant throughout this concentration range. This indicates that there is no saturation of those enzymes that initiate metabolic conversion of VC. Ethanol (constant addition to 12 mM) and pyrazole (single addition to 200 uM) reduced VC metabolism by 12.7% and 31.6%, respectively. Bromobenzothiazole also inhibited metabolism (48.9%), SKF 525A was inactive, and phenobarbital pretreatment increased the conversion rate by 20.9%. Fasted animals showed a 31.2% increase in the metabolic conversion rate. Determination of SGOT, SGPT, and the lactate/pyruvate coefficient revealed no VC-induced changes, even at the highest concentration tested (24,000 ppm), but slight liver damage was detectable after increased metabolic VC transformation. This suggests the formation of a reactive intermediate, an epoxide, as a result of the first-step oxidation. The epoxide would be expected if the oxidation were catalyzed by cytochrome P-450. The involvement of other oxidases, however, cannot be ruled out. (19 Refs)

145 AU - Basuk J ; Nichols A
AD - Science Council Canada, Ottawa, Canada
TI - AN OVERVIEW OF THE VINYL CHLORIDE HAZARD IN CANADA.
SI - CARC/78/02459
SO - Chem Can; 29(7):24-38 1977
LA - ENG
AB - The effects of occupational exposure to vinyl chloride monomer (VCM) are emphasized in this review, which also includes a discussion of the properties and processing of VCM. VCM came to attention as a health hazard in 1973, when three cases of a rare form of liver cancer, angiosarcoma, were reported in workers from a VCM factory. Since then, 48 victims have been identified; others who may have died from angiosarcoma are unknown because of difficulty in diagnosing the disease. VCM has chronic effects on human beings at high levels of exposure. It causes a specific occupational disease known as acroosteolysis, in which there is both Raynaud's syndrome and sclerodermiform lesions. In animal studies VCM has produced a wide range of tumors in rats, mice, and hamsters: Zymbal gland carcinomas, nephroblastomas, angiomas and angiosarcomas of the liver and other sites, trichoepitheliomas, hepatomas, lung adenomas, mammary adenomas and carcinomas, and lymphomas. Recent findings suggest that mammary carcinomas can be induced in laboratory animals at less than or equal to 1 ppm. Efforts to control the adverse health effects of VCM include the setting of standards for occupational exposure to VCM, improved manufacturing techniques to minimize VCM exposure and residual VCM in polyvinyl chloride resin, and increased research on the epidemiology of VCM-related diseases and on diagnosing preangiosarcoma tumors. (65 Refs)

146 AU - Nicholson WJ
AD - Dept. Community Medicine, Mt. Sinai Sch. Medicine, New York, NY 10029
TI - CANCER FOLLOWING OCCUPATIONAL EXPOSURE TO ASBESTOS AND VINYL CHLORIDE.
SI - CARC/78/99910
SO - Cancer (Suppl); 39(4):1792-1801 1977
LA - ENG
AB - A review is presented of occupational cancer caused by exposure to asbestos and vinyl chloride (VC). The population at risk for several asbestos-related cancers includes those handling the mineral directly, those working near the application or removal of asbestos materials, and those living near an asbestos operation or in the household of an asbestos worker. Asbestos exposure has been connected with death from lung cancer, gastrointestinal cancer, and mesothelioma. The interval from first exposure to cancer development is at least 20 yr. A synergistic effect has been demonstrated for lung cancer in asbestos workers who smoke cigarettes. Exposure to VC has caused hemangiosarcoma of the liver in addition to excess mortality from tumors of the brain, lung, and lymphatic and hematopoietic systems. Exposures in the polyvinyl chloride processing industry

have been reduced significantly by alteration of production methods to minimize residual VC monomer in the resin. Attempts t control asbestos exposures have not been as successful, partly a a result of significant differences between the two industries. new standard for occupational asbestos exposure of 0.1 f/cm**3 has been proposed, which if adopted and enforced will greatly lower the human risk from asbestos exposure. (39 Refs)

147 AU - Legrand J ; Puech AM
AD - No affiliation given
TI - VINYL CHLORIDE: HEPATIC ANGIOSARCOMA ASSOCIATED WITH ACROOSTEOLYSIS.
SI - CARC/78/02430
SO - Arch Mal Prof; 38(6):645-646 1977
LA - FRE
AB - A 42-yr-old man developed acrooosteolysis and an angiosarcoma of the liver after a relatively brief exposure to vinyl chloride. He had developed edema of arms and hands after only 2 yr occupational exposure to vinyl chloride. Ten years later, he again took a job involved with the carcinogen and the acrooosteolysis occurred. Symptoms of the angiosarcoma appeared 17 yr after initial exposure, and the patient died within 2 yr. (no Refs)

148 AU - Edmonds L
AD - Birth Defects Branch, Center Disease Control, Atlanta, GA
TI - BIRTH DEFECTS AND VINYL CHLORIDE.
SI - CARC/78/02425
SO - Proceedings Conference on Women and the Workplace, June 17-19, 1976, Washington, D. C. Society for Occupational and Environmental Health Washington, D.C., 364 pp., 1977.
LA - ENG
AB - A review of CNS birth defects in two cities that have vinyl chloride (VC)-producing plants revealed that the defect rates were higher than expected but they were not significantly different from the US rates at that time. There was no statistically significant excess of defects in offspring of men who worked at the plant, or of families residing near the plant. (no Refs)

149 AU - Wagoner JK ; Infante PF ; Brown DP
AD - Industrywide Studies Branch, Div. Surveillance, Hazard Evaluation and Field Studies, Natl. Inst. Occupational Safety and Health, Cincinnati, OH
TI - GENETIC EFFECTS ASSOCIATED WITH INDUSTRIAL CHEMICALS.
SI - CARC/78/02373
SO - Proceedings Conference on Women and the Workplace, June 17-19, 1976, Washington, D.C. Society for Occupational and Environmental Health, Washington, DC, 364 pp., 1977.
LA - ENG
AB - The carcinogenicity and mutagenicity of various chemicals found in the workplace are reviewed, with emphasis on their genetic effects. Women have been excluded from workplaces where vinyl

chloride (VC) may be inhaled, but studies have also shown an increased fetal death rate in the offspring of men exposed to VC. Two structural analogs of VC, vinylidene chloride and trichloroethylene, which have wide industrial use, have been shown to be carcinogenic in rodents and mutagenic in microbial and plant assays. However, human data for both are lacking. Functional disruption of spermatogenesis occurred among men occupationally exposed to chloroprene (2-chlorobutadiene) for less than or equal to 10 yr, and morphological disruption of spermatogenesis occurred among men exposed for greater than 10 yr. Wives of workers exposed to chloroprene have a threefold excess of miscarriage. (38 Refs)

150 AU - Guengerich FP ; Strickland TW
AD - Dept. Biochemistry, Vanderbilt Univ. Sch. Medicine, Nashville, TN 37232
TI - METABOLISM OF VINYL CHLORIDE: DESTRUCTION OF THE HEME OF HIGHLY PURIFIED LIVER MICROSOMAL CYTOCHROME P-450 BY A METABOLITE.
SI - CARC/78/02333
SO - Mol Pharmacol; 13(6):993-1004 1977
LA - ENG
AB - The NADPH-dependent, vinyl chloride (VC)-mediated destruction of cytochrome P-450 (Cy P-450) was demonstrated in rat liver microsomes and in highly purified reconstituted enzyme systems containing NADPH cytochrome P-450 reductase and cytochrome Cy P-450. This loss of Cy P-450 could be attributed to heme destruction, but not to lipid peroxidation or binding of electrophiles to free sulfhydryl groups. The system required all the components necessary for mixed-function oxidation, including molecular oxygen, and it was inhibited by carbon monoxide, suggesting strongly that oxidative metabolism of VC by Cy P-450 is necessary for destruction. The NADPH Cy P-450 reductase-catalyzed destruction of free and Cy P-450-bound heme was also observed in reconstituted systems in the absence of VC. Inhibition experiments with carbon monoxide and catalase suggested that the VC-mediated destruction of Cy P-450 heme differes from these processes. Two proposed VC metabolites, VC epoxide and 2-chloroacetaldehyde, do not appear to be responsible for the heme destruction. Evidence for the involvement of free radicals could not be demonstrated when the reaction was examined by electron paramagnetic resonance spectroscopy or when attempts were made to inhibit Cy P-450 destruction with radical-trapping agents. (56 Refs)

151 AU - Michelich VJ ; Bugen LC ; Brand KG
AD - Dept. Microbiology, Medical Sch., Univ. Minnesota, Minneapolis, MN 55455
TI - IMMUNOSUPPRESSION STUDIES IN FOREIGN BODY TUMORIGENESIS: NO EVIDENCE FOR TUMOR-SPECIFIC ANTIGENICITY.
SI - CARC/78/02154
SO - JNCI; 58(3):757-761 1977
LA - ENG
AB - The effect of immunosuppression on the frequency and latency of

foreign body (FB)-induced sarcomas and the antigenicity of these tumors was investigated. Sarcomas were induced in CBA/H strain mice by sc implantation of polyvinyl chloride vinyl acetate copolymer films. The mice had been immunosuppressed by azathioprine (4 mg/kg/day beginning 1 wk before implantation and continuing throughout the experiment), antilymphocyte globulin (0.25 ml of a 1:4 dilution ip on days 0, 1, 4, and 6 before tumor challenge and weekly thereafter), or thymectomy 48 hr after birth. Compared to nonimmunosuppressed controls, all three treatments did not affect the appearance of FB-induced sarcomas. No tumor-specific transplantation antigens could be demonstrated in the sarcomas of immunosuppressed mice. On the basis of these results, the concept of immune surveillance as a natural host defense mechanism against carcinogenesis does not apply to this model of tumor development. (36 Refs)

152 AU - Laib RJ ; Bolt HM
AD - Inst. Toxicology, Tubingen, W. Germany
TI - FORMATION OF IMIDAZOL DERIVATIVES OF NUCLEIC ACID BASES (DNA AND RNA) BY METABOLITES OF VINYL CHLORIDE IN VIVO AND IN VITRO (MEETING ABSTRACT).
SI - ICDB/78/04000
SO - Fourth Meeting of the European Association for Cancer Research Held at Universite de Lyon, September 13-15, 1977. European Association for Cancer Research, Lyon, France 1977.
LA - ENG
AB - Rat liver microsomes were incubated with NADPH, (1,2-C14) vinyl chloride and polyadenylic acid or polycytidylic acid. The latter were re-isolated from the incubations and hydrolyzed. The radioactivity originating from (C14) vinyl chloride, which was irreversibly bound to the polyadenylic or polycytidylic acid, was confined to 1,N**6-ethenoadenosine or 3,N**4-ethenocytidine. When rats were exposed to (1,2-C14) vinyl chloride, part of the radioactivity was incorporated into liver RNA. Analysis of hydrolysates of liver RNA showed that all natural nucleosides of RNA were labeled. Small amounts of radioactivity could be detected which were confined to 1,N**6-ethenoadenosine and 3,N**4-ethenocytidine. DNA of rat liver after exposure of the animals to (1,2-C14) vinyl chloride also contained significant amounts of radioactivity. When DNA was incubated with rat liver microsomes, NADPH and (C14) vinyl chloride, radioactivity was also incorporated into the DNA. Re-isolation of the DNA, hydrolysis and separation of the nucleosides showed that radioactive 1,N**6-etheno 2'deoxyadenosine was formed. The experiments support the theory that vinyl chloride metabolites react with adenine or cytosine moieties of nucleic acids to form etheno analogs. These alkylation mechanisms are consistent with the mutagenic properties of vinyl chloride. (no Refs)

153 AU - Fox AJ ; Collier PF
AD - Office Population Censuses and Surveys, St. Catherines House, 10 Kingsway, London WC2B 6Jp, England
TI - MORTALITY EXPERIENCE OF WORKERS EXPOSED TO VINYL CHLORIDE MONOMER IN THE MANUFACTURE OF POLYVINYL CHLORIDE IN GREAT BRITAIN.
SI - CARC/78/01959
SO - Br J Ind Med; 34(1):1-10 1977
LA - ENG
AB - The mortality incidence in 7,717 workers in the vinyl chloride industry in Great Britain was investigated. Approx 99% of these workers were traced; 12% had been exposed to constant high levels, but only 34 men had been exposed to constant high levels for greater than 20 yr because of the newness of the industry. The standard mortality ratio was below that expected. Four cases of liver cancer were found, one primary cancer (vs 0.71 expected), and three other liver cancers (vs 0.93 expected). Two were angiosarcomas, and the other two were carcinomas. The two workers with angiosarcoma died 8 and 21 yr after initiation of exposure to high concentrations. Other cancers vs their expected incidences were as follows: stomach 14 vs 15.33; lung, 46 vs 51.23; brain, 2 vs 3.66; and lymphatic and hematopoietic tissues, 9 vs 9.01. The observed death rate from all cancers was 115 compared to an expected 126.77; there is no evidence that cancer at sites other than the liver was associated with exposure to vinyl chloride. Conclusions drawn from this survey must be tempered by the reservation that the full impact of the problem may not yet be in evidence. (18 Refs)

154 AU - Osterman-Golkar S ; Hultmark D ; Segerback D ; Calleman CJ
AU - Gothe R ; Ehrenberg L ; Wachmeister CA
AD - Wallenberg Lab., Univ. Stockholm, Lilla Frescati, S-104 05 Stockholm 50, Sweden
TI - ALKYLATION OF DNA AND PROTEINS IN MICE EXPOSED TO VINYL CHLORIDE.
SI - CARC/78/01872
SO - Biochem Biophys Res Commun; 76(2):259-266 1977
LA - ENG
AB - Male CBA, BALB, and ATL mice (2-3 mo old) were exposed to various doses (98-160 ppm/hr) of **14C-labeled vinyl chloride in glass inhalation chambers for 2-10 hr, and alkylation products recovered from their testes protein, and liver DNA were quantitatively measured. Chromatographic results indicated that vinyl chloride is metabolically activated to form an alkylating agent that introduces the 2-oxoethyl group onto nucleophilic sites; alkylation by chloroethanol was neglible. The alkylation of cysteine and histidine in Hb and of guanine-N-7 in liver DNa varied with the strain of mice used. Considering the sensitivity of the alkylating agents to changes in nucleophilic strength, chloroethylene oxide appeared to be the main reactive metabolite. Male gonads were exposed to the alkylating intermediate, and a risk of heritable damage as well as cancer can be expected. (18 Refs)

155 AU - Styles JA
AD - Imperial Chemical Industries Limited, Central Toxicology Lab., Alderley Park, Macclesfield, Cheshire, England
TI - A METHOD FOR DETECTING CARCINOGENIC ORGANIC CHEMICALS USING MAMMALIAN CELLS IN CULTURE.
SI - CARC/78/01772
SO - Br J Cancer; 36(5):558-563 1977
LA - ENG
AB - A method for testing organic chemicals for their carcinogenic potential is described. Baby hamster kidney cells (BHK-21/Cl 13) were exposed to different doses of a test compound (nitrosofolic acid, diphenylnitrosamine) in liquid tissue culture medium containing rat liver post-mitochondrial supernatant and cofactors (S-9 mix) to aid metabolism, but without serum. Survival of cells following exposure to the compound was assessed by cloning in liquid growth medium. Transformation was assessed by colony growth in semi-solid agar. The dose-response curve for survival was used to determine the LC50 (50% lethal concentration) of the compound. A dose-response curve for transformation was constructed, and a five-fold increase in transformation frequency at the LC50 was regarded as a positive result. For application of the method to gases, cells grown in monolayers and overlaid with serum-free medium and S-9 mix were exposed to vinyl chloride gas mixed with air. After exposure, the treated cells were trypsinized, resuspended in growth medium, and survival and transformation assays performed. Increases in transformation frequency were seen with nitrosofolic acid and vinyl chloride gas. In a study using 120 compounds, the methods described were greater than 90% accurate in distinguishing between carcinogens and noncarcinogens. (19 Refs)

156 AU - Kline J ; Stein Z ; Strobino B ; Susser M ; Warburton D
AD - Columbia Univ. Coll. Physicians and Surgeons, New York, NY 10032
TI - SURVEILLANCE OF SPONTANEOUS ABORTIONS. POWER IN ENVIRONMENTAL MONITORING.
SI - CARC/78/01770
SO - Am J Epidemiol; 106(5):345-350 1977
LA - ENG
AB - The advantages of using spontaneous abortions rather than birth defects to monitor environmentally induced carcinomas are discussed. Theoretically, a change in the incidence of spontaneous abortions or of anomalies in spontaneous abortions should be detectable 6 mo or more before a change in the incidence of birth defects. Moreover, teratogens that cause many anomalies cannot be detected by studies of birth defects since the majority of anomalous conceptions lead to spontaneous abortions. Abortion specimens can also be preserved for future studies. The spontaneous abortion approach is illustrated by the potential teratogenic effects of paternal exposure to vinyl chloride (VC). VC may affect male germ cells by causing chromosome breaks, dominant or recessive lethal mutations, and/or chromosome abnormalities. Morphologic and karyotype analyses of a

sample series of spontaneous abortions are discussed. (14 Refs)

157 AU - Smith PM ; Williams DM ; Calderup LM
AD - Welsh Natl. Sch. Medicine, Penarth, Glamorgan, Wales
TI - ANGIOSARCOMA OF THE LIVER IN GREAT BRITAIN (LETTER TO EDITOR).
SI - CARC/78/01605
SO - Br Med J; 2(6095):1149-1150 1977
LA - ENG
AB - Only two cases of angiosarcoma of the liver following vinyl chloride exposure have been noted in Great Britain. In comparison, noncirrhotic portal fibrosis is commoner and therefore of greater importance. In the Netherlands, 27 cases diagnosed as angiosarcoma were reviewed, and only 9 were found to be definite. None of the nine patients had any contact with vinyl chloride, but one had been on long-term arsenic medication. (6 Refs)

158 AU - Popper H
AD - Mount Sinai Sch. Medicine, Stratton Lab. Study Liver Disease, Fifth Ave. and 100th St., New York, NY 10029
TI - LIVER TUMORS DUE TO ENVIRONMENTAL FACTORS.
SI - CARC/78/01568
SO - Internist (Berlin); 18(4):182-187 1977
LA - GER
AB - The histology and morphology of liver fibrosis and angiosarcoma due to long-term occupational exposure to vinyl chloride, inorganic arsenic, and thorium dioxide are reviewed along with the effect of anabolic steroids and oral contraceptives on hepatocellular adenomas and carcinomas. Reference is made to experiments with mice and rats. (56 Refs)

159 AU - Tomatis L
AD - Unit Chemical Carcinogenesis, International Agency Res. Cancer, 150 Cours Albert Thomas, 69372 Lyon Cedex 2, Fr
TI - VALIDITY AND LIMITATIONS OF LONG-TERM EXPERIMENTATION IN CANCER RESEARCH.
SI - CARC/78/01563
SO - IARC Sci Publ; (16):299-307 1977
LA - ENG
AB - The contribution of long-term experimentation to the detection of carcinogenic agents is considered. There is evidence in experimental carcinogenesis that, following chronic exposure, tumor incidence and induction time are dose-related. An acceptable exposure level would be a dose that one could assume would not produce cancer within the life span of the exposed individuals. One example of the contribution of animal experimentation to the prevention of human cancer is the case of acetylaminofluorene, which was ready to be marketed on a wide scale as an insecticide when it was withdrawn because one experiment had shown it to be carcinogenic. A large number of food additives, pesticides, and herbicides have been reviewed with regard to their toxicity during the past 15 yr, and for a number of them the experimental evidence of carcinogenicity was

sufficient to recommend a zero tolerance in food. This extrapolation from experimental data to man has not been widely applied occupationally, as evidenced by the aromatic amines and urinary bladder cancer, bis(chloromethyl)ether and lung cancer, vinyl chloride and liver cancer, and vinylidine chloride, 2-chlorobutadiene, and neoprene. (31 Refs)

160 AU - Biran D
AD - Rutgers Univ., The State University of New Jersey, New Brunswick, NJ
TI - SORPTION OF VINYL CHLORIDE BY SELECTED FOOD CONSTITUENTS.
SI - ICDB/78/03209
SO - Diss Abstr Int (B); 38(5):2105-B 1977
LA - ENG
AB - The association of vinyl chloride (VC) with carcinogenic effects has caused a proposal by the FDA to restrict the use of rigid unplasticized polyvinyl chloride for food packaging. A major area of concern involves the possible interaction between the VC and food. This study deals with parameters affecting the sorption of VC in the gaseous state by selected food constituents and particularly the mechanism of VC sorption by dry casein particles. Partition coefficients for VC distribution between head space and oil, water, oil/water emulsions and casein were determined. It was found that at concentration levels studied the partition coefficients are fairly constant for all cases. Chemical nature of the substrate, starting head space concentrations and temperature were found to be important factors affecting the extent of VC sorption. Dipole moment of the sorbate gas as well as the chemical nature and moisture content of the protein were found to be important parameters determining the sorption of VC by casein. Particle size affects the sorption to a lesser degree. Transient state sorption measurements as well as the inverse gas chromatographic technique showed an active site binding as the major component in the binding interaction between casein particles and VC. An empirical kinetic model for the sorption VC by dry casein particles is proposed. The model suggests a possible clustering effect at the low temperature and most likely a monolayer sorption at the higher temperatures tested. An active site adsorption model is suggested. A correlation between the two models is shown. (no Refs)

161 AU - Laib RJ ; Bolt HM
AD - Inst. Toxicology, Univ. Tubingen, D-7400 Tubingen-1, W. Germany
TI - ALKYLATION OF RNA BY VINYL CHLORIDE METABOLITES IN VITRO AND IN VIVO: FORMATION OF 1-N**6-ETHENO-ADENOSINE.
SI - ICDB/78/02914
SO - Toxicology; 8(2):185-195 1977
LA - ENG
AB - The incorporation of 14C radioactivity from vinyl chloride into RNA of liver is described, and the possibility of formation of etheno-adenosine moieties in liver RNA on exposure of rats to 14C vinyl chloride is examined. Rat liver microsomes were incubated with NADPH, 1,2-14C vinyl chloride and poly-adenosine.

Poly-adenosine was reisolated from the incubations and hydrolyzed. 14C vinyl chloride radioactivity was confined to 1-N**6-etheno-adenosine. When rats were exposed to 1,2-14C vinyl chloride, part of the radioactivity was incorporated into RNA of liver and exhibited a first maximum, 14 hr, and a second maximum, 72 hr after ending the exposure. Analysis of hydrolysate of liver RNA showed that all natural nucleosides of RNA were labeled, and that small amounts of radioactivity were confined to 1-N**6-etheno-adenosine. Thus, the experiments support the theory that vinyl chloride metabolites react with adenosine moieties of nucleic acid under formation of 1-N**6-etheno-adenosine. The results show that measurement of incorporation of radioactivity into nucleic acids after exposure of animals to radioactive vinyl chloride is not applicable as a means of determining the alkylating potency of vinyl chloride metabolites towards nucleic acids in vivo. (29 Refs)

162 AU - Kurliandskii BA ; Nevzorova NI
AD - Municipal Sanitary-Epidemiological Center, Moscow, USSR
TI - METHOD OF CALCULATION OF THE EFFECTIVE DOSE AND CONCENTRATION OF CHEMICAL BLASTOMOGENIC AGENTS.
SI - CARC/78/01409
SO - Vopr Onkol; 23(9):59-62 1977
LA - RUS
AB - Probit analysis according to Litchfield and Wilcoxon is recommended for the calculation of the effective blastomogenic doses and concentrations (BD16, BD50, BD84) of various chemical carcinogens. Examples and values are presented for N,N'-dinitrosodimethylethylene diamine, benzo(a)pyrene, 1,2,5,6-dibenzoanthracene, 2-amino-5-azotoluene and vinyl chloride. (17 Refs)

163 AU - Brady J ; Liberatore F ; Harper P ; Greenwald P ; Burnett W
AU - Davies JN ; Bishop M ; Polan A ; Vianna N
AD - Bureau Occupational Health and Chronic Disease Res., New York State Dept. Health, Empire State Plaza, Tower Building, Albany, NY 12237
TI - ANGIOSARCOMA OF THE LIVER: AN EPIDEMIOLOGIC SURVEY.
SI - CARC/78/01001
SO - JNCI; 59(5):1383-1385 1977
LA - ENG
AB - An epidemiology survey of angiosarcoma of the liver (ASL) revealed that the annual incidence rate (cases diagnosed 1970 through 1975) among residents of New York State (excluding New York City) was 0.25 per million. A case-control study of 26 patients indicated that direct exposure to arsenic, vinyl chloride (VC), and thorium dioxide was a significantly important factor in the etiology of ASL (p less than 0.02). Seven patients had documented exposure to these chemicals, but 19 did not. The fact that 5/19 lived nearer to VC fabrication or polymerization plants than did their matched controls indicated that indirect modes of exposure, not specifically related to occupation, might be an important factor in the etiology of ASL. The possibility

that other toxic substances (chlorinated hydrocarbons) may cause ASL was also mentioned. (17 Refs)

164 AU - Lu PY ; Metcalf RL ; Plummer N ; Mandel D
AD - Dept. Entomology and Inst. Environmental Studies, Urbana, IL 61801
TI - THE ENVIRONMENTAL FATE OF THREE CARCINOGENS: BENZO(ALPHA)PYRENE, BENZIDINE, AND VINYL CHLORIDE EVALUATED IN LABORATORY MODEL ECOSYSTEMS.
SI - CARC/78/00966
SO - Arch Environ Contam Toxicol; 6(2-3):129-142 1977
LA - ENG
AB - The degradation, environmental fate, bioaccumulation, and food chain transfer of radiolabeled benzo(alpha)pyrene (BP), benzidine (BD), and vinyl chloride (VC) were evaluated in two laboratory model ecosystems. In a closed aquatic system, 0.002 ppm BP and 0.006 ppm BD were applied directly to the water and allowed to pass through an aquatic food chain. Their transfer and degradation were observed over a 3-day period. In a terrestrial-aquatic ecosystem, 0.2 mg of BP and BD, either alone or with 1.0 mg pipronyl butoxide, were topically applied in acetone solution to Sorghum vulgare seedlings, representing chemical fallout. They were then allowed to pass through a food chain. The resulting food chain by-products were then allowed to interact in the ecosystem over a 33-day period. It was shown that BP is highly lipophilic and it can bioaccumulate to potentially hazardous levels. This problem was intensified in snails and other organisms deficient in microsomal oxidase, or when there was a presence of mixed function oxidase inhibitors. BD was not bioaccumulated or transfered through food chains to high levels. BD levels were not affected appreciably by the presence of mixed function oxidase inhibitors. Vinyl chloride did not bioaccumulate or transfer appreciably through the food chains, at least at the ordinary temperatures studied due to its high volatility. There was an excellent correlation between bioaccumulation and octanol/water partition, illustrating that this property and water solubility can be of predictive value in environmental toxicological studies. (19 Refs)

165 AU - Baxter PJ ; Anthony PP ; MacSween RN ; Scheuer PJ
AD - Health and Safety Executive, Employment Medical Advisory Service, London W2 4TF, England
TI - ANGIOSARCOMA OF THE LIVER IN GREAT BRITAIN, 1963-73.
SI - CARC/78/00902
SO - Br Med J; 2(6092):919-921 1977
LA - ENG
AB - Deaths attributed to primary angiosarcoma of the liver (ASL) in Great Britain between 1963 and 1973 were reviewed by submitting available histological material to a panel of histopathologists and by obtaining full occupational and residential histories for the cases considered as ASL by the panel. An av of four cases of ASL occurred annually, but in only one-third of the cases did the panel agree with the original diagnosis. Only one of the cases was definitely linked with exposure to vinyl chloride. (17 Refs)

166 AU - Reynolds ES
AD - Dept. Pathology, Peter Bent Brigham Hosp., Boston, MA 02115
TI - LIVER ENDOPLASMIC RETICULUM: TARGET SITE OF HALOCARBON METABOLITES.
SI - CARC/78/00873
SO - Adv Exp Med Biol; 84:117-137 1977
LA - ENG
AB - The hepatotoxic effects of carbon tetrachloride, vinyl chloride, trichloroethylene, and halothane are reviewed. Initial injury produced by exposure to these chemicals involves the endoplasmic reticulum. There is dispersion of the ergastoplasm, then vacuolization and degranulation of the rough endoplasmic reticulum with concomitant retraction of the smooth endoplasmic reticulum into tightly clumped tubular aggregates. Membranes in these tubular aggregates seem to undergo supramolecular disassembly. This structural disorganization is accompanied by a diminished functional capacity in the organelle. Activation of these halocarbons to toxic species by the endoplasmic reticulum is indicated (1) by the enhancement of their toxicity upon pretreatment with chemicals, such as phenobarbital, or Arcolor 1254 that induce components of the mixed function oxidase system and (2) by the formation of certain metabolites and/or covalently bound products. It is not clear whether the halocarbons cause liver injury by the covalent binding of free-radical metabolites to tissue macromolecules or by initiating lipid peroxidation. (51 Refs)

167 AU - Boyland E
AD - TUC Centenary Inst. Occupational Health, London Sch. Hygiene and Tropical Medicine, Keppel St., London WC1E 7HT, England
TI - BIOCHEMISTRY OF OCCUPATIONAL CANCER.
SI - CARC/78/00872
SO - J Soc Occup Med; 27(3):97-101 1977
LA - ENG
AB - Environmental, particularly occupational, causes of cancer are reviewed briefly in terms of chemical reactions and intermediates. Chemical carcinogens can be divided into two groups on biochemical grounds. The first group, which includes alkylating agents such as mustard gas, nitrogen mustard, Myleran, and the ethyleneimines plus related compounds, acts directly without metabolic transformation. The second group, including aromatic amines, nitrosamines, polycyclic hydrocarbons, aflatoxin, safrole, and carbon tetrachloride, requires metabolic activation, usually through the formation of epoxides or arene oxides, to carcinogenic forms. Recent studies have indicated that vinyl chloride, chlorobutadiene, and trichloroethylene are carcinogenic and are metabolized through epoxide intermediates. Some ethylene derivatives or unsaturated compounds, therefore, can be carcinogenic because they are metabolized to epoxides. Saturated compounds such as trichloroethane and tetrachloroethane may be less hazardous than the unsaturated trichloroethylene and tetrachloroethylene as solvents. (no Refs)

168 AU - Aryanpur J
AD - Public Health and Occupational Medical Services, Natl. Iranian Oil Company, P. O. Box 1863, Tehran, Iran
TI - VINYL CHLORIDE: ITS IMPACT ON OCCUPATIONAL MEDICINE PRACTICE IN IRAN.
SI - CARC/78/00775
SO - J Occup Med; 19(10):689-692 1977
LA - ENG
AB - Measures taken to protect the workers at the Abadan Petrochemical Company in Iran from the carcinogenic effects of vinyl chloride monomer (VCM) and polyvinyl chloride (PVC) are outlined. Since 1971, all workers have been required to undergo periodic medical examinations with an emphasis on liver function. Factors related to liver disease, such as endemic viral hepatitis, low alcohol and cigarette consumption, and dietary habits, are considered. To date, among 43 workers in the VCM and PVC production units, none have evidence of liver dysfunction or angiosarcoma. The threshold limit value for VCM has been set at 25 ppm time weighted av for 8 hr with revisions expected in the future. No leakage to the community has been detected except for some chlorine release. (11 Refs)

169 AU - Brown ER ; Sinclair T ; Keith L ; Beamer P ; Hazdra JJ ; Nair V
AU - Callaghan O
AD - Dept. Microbiology, The Chicago Medical Sch., 2020 West Ogden Ave., Chicago, IL 60612
TI - CHEMICAL POLLUTANTS IN RELATION TO DISEASES IN FISH.
SI - ICDB/78/00887
SO - Ann NY Acad Sci; 298:535-546 1977
LA - ENG
AB - The relationship between water pollution and health hazards in fish in two water systems (pollution-free Canadian 'Lake of the Woods' and the polluted Fox River) was investigated. Fish were caught from both rivers and examined for tumors and nononcogenic diseases. The nononcogenic diseases encountered included columnaris disease, hemorrhagic septicemia, Dee disease, black spot disease, saprolegnia, channel catfish virus disease, and lymphocystis. Lymphoreticular neoplasms were the most frequent neoplastic diseases observed. As these tumors mature, a large number of the malignant cells are intimately associated with fibers of the reticulum and appear to adhere to the walls of the capillaries in the mass being formed. Hepatomas appeared as large nodules of abnormal cells which developed within the liver, or ultimately the entire liver became a mass of these cells. Fathead minnows were grown in effluent taken from secondary treatment plants and effluent treated with disinfectants. The presence of polio virus in monkey kidney cultures plated with intestinal tract homogenates of these fish was used as an indicator of sewage contamination and the effectiveness of the disinfectants. Polio viruses were found in the intestinal tracts of fish raised in untreated effluent and effluent treated with bromochloride and ozone. The viruses were not present in fish raised in effluent

treated with chlorine. These results indicate that health hazards are associated with fish grown in sewage effluents. The toxicity of vinyl chloride was investigated in northern pike. The development of skin lesions in these fish is discussed. (7 Refs)

170 AU - Carter SA
AD - Environmental Science and Public Health, Cornell Univ., Ithaca, NY
TI - THE POTENTIAL HEALTH HAZARD OF SUBSTANCES LEACHED FROM PLASTIC PACKAGING.
SI - ICDB/78/00880
SO - J Environ Health; 40(2):73-76 1977
LA - ENG
AB - The health issues surrounding the leaching of four different groups of chemical compounds from plastic products are presented. These groups include: lead and ink from the printed material on plastic wrapping, stabilizers from soft plastic wraps, vinyl chloride from polyvinyl chloride (PVC) products, and plasticizers from various PVC products. Analysis of PVC peanut oil containers revealed vinyl chloride levels of 0.3-3.3 ppm. Traces of vinyl chloride have been detected in vinegars and alcoholic beverages packaged in PVC bottles. Plasticizers such as di-2-ethylhexyl phthalate and dimethoxyethyl phthalate were found in human and rat blood which had been circulated in PVC tubing, and in tissue samples taken from human patients who had received transfusions of blood stored in PVC bags. These findings and others are discussed in light of pertinent animal and human studies. (28 Refs)

171 AU - Hanschler D
AD - Toxikologisches Institut der Universitat, Koellikerstr. 2, 8700 Wurzburg, W. Germany
TI - ACTIVATION MECHANISMS IN CHLORINATED ALIPHATIC COMPOUNDS. EXPERIMENTAL POSSIBILITIES AND CLINICAL SIGNIFICANCE.
SI - CARC/78/00236
SO - Arzneim Forsch; 27(9b):1827-1832 1977
LA - GER
AB - Asymmetric chlorinated ethylene (tri-1,1-dichloroethylene and vinyl chloride) are mutagenic in a modified Ames test system whereas symmetrically substituted molecules are inactive. These differences are attributed to the electron withdraul effect of chlorine in the asymmetric molecules. The in vivo and in vitro rearrangement mechanisms in the biotransformation of these compounds are outlined. (20 Refs)

172 AU - Heath CW ; Dumont CR ; Gamble J ; Waxweiler RJ
AD - Cancer and Birth Defects Div., Bureau Epidemiology, Center Disease Control, Public Health Service, U.S. Dept. Health, Education and Welfare, 1600 Clifton Road, N. E., Atlanta, GA 30333
TI - CHROMOSOMAL DAMAGE IN MEN OCCUPATIONALLY EXPOSED TO VINYL CHLORIDE MONOMER AND OTHER CHEMICALS.
SI - CARC/78/00170
SO - Environ Res; 14(1):68-72 1977
LA - ENG

AB - Cytogenetic analyses were conducted on men employed at a rubber and plastics plant who were exposed to vinyl chloride monomer (VCM). Frequencies of chromosomal damage were measured in the peripheral blood lymphocytes of 35 men employed for greater than or equal to 10 yr: 14 in polyvinyl chloride (PVC) polymerization (high-exposure group), 4 in PVC processing (low exposure group), and 17 in rubber tire manufacture (negligible exposure group). In addition, four nonindustrial employees who had not been exposed to laboratory chemicals were included (controls). Breakage levels were significantly higher in all three test groups than in the controls. Chromatid gaps comprised the majority (86%) of aberrations seen. However, overall breakage levels were similar in the three industry groups, which indicates that VCM was not the sole cause of the damage. (9 Refs)

173 AU - Brinton-Darnell M ; Brand I
AD - Wistar Inst., 36th and Spruce Sts., Philadelphia, PA 19104
TI - DELAYED FOREIGN-BODY TUMORIGENESIS IN MICE INFECTED WITH LACTATE DEHYDROGENASE-ELEVATING VIRUS: BRIEF COMMUNICATION.
SI - CARC/77/08526
SO - JNCI; 59(3):1027-1029 1977
LA - ENG
AB - Delayed foreign-body (FB) tumorigenesis was studied in mice infected with lactate dehydrogenase-elevating virus (LDV). Eight-week-old CBA/H mice of both sexes were infected ip with LDV (10**3 ID50's). Two weeks later, these mice and noninfected controls received double sc implants of unplasticized vinyl chloride-vinyl acetate copolymer films (0.2 x 15 x 22 mm). FB tumorigenesis was delayed by 2 mo in infected animals of both sexes. Since cellular immunity is not known to influence the course of FB tumorigenesis, these results could not be explained by an LDV effect on cellular immunity. (35 Refs)

174 AU - Green T ; Hathway DE
AD - Imperial Chemical Industries Ltd., Central Toxicology Lab., Alderley Park, Cheshire SK10 4TJ, England
TI - THE CHEMISTRY AND BIOGENESIS OF THE S-CONTAINING METABOLITES OF VINYL CHLORIDE IN RATS.
SI - CARC/77/08421
SO - Chem Biol Interact; 17(2):137-150 1977
LA - ENG
AB - The biogenesis of the various urinary S-containing metabolites of vinyl chloride (VC) was investigated in adult male rats. Groups of rats were administered the following chemicals intragastrically: (1) **14C-VC (100 mg/kg; 10 muCi), (2) chloroacetaldehyde (50 mg/kg), (3) S-(2-hydroxyethyl)-L-cysteine (500 mg/kg), or (4) S-(carboxymethyl)-L-cysteine (CMC: 250 mg/kg), and a 24-hr urine sample was taken. Two rats were given repeated daily ip injections of L-(U-**14C) cysteine hydrochloride for 5 days and, 30 min after the final injection, a single dose of VC (100 mg/kg); a 24-hr urine sample was then taken. Two rats were given a single intragastric dose of **14C-VC (450 mg/kg) and sacrificed after 45 min; they were dissected and

their livers removed. N-Acetyl-S-(2-hydroxyethyl)cysteine (AHC) was a major VC metabolite, but, according to the method of protective esterification used, either N-acetyl-S-(2-chloroethyl)cysteine or AHC can be isolated from the body fluids. N-Acetyl-S-vinylcysteine was a second related metabolite. These S-containing VC metabolites were not mutagenic in S. typhimurium. Administration of the VC metabolites and related compounds to rats indicated that chloroacetaldehyde and CMC, but not chloroacetic acid, are on a pathway connecting VC with thiodiglycollic acid. The fact that chloroacetaldehyde produced both thiodiglycollic acid and AHC in the animal and that CMC was identified among the hydrolytic products from a hepatic extract of VC-treated animals is consistent (1) with the formation of chloroacetaldehyde and (2) with the reaction of chloroethylene oxide or chloroacetaldehyde with glutathione in the presence of a glutathione S-epoxide transferase to give the identified S-containing metabolites. (22 Refs)

175 AU - Rowley JD
AD - Dept. Medicine, Univ. Chicago, Chicago, IL 60637
TI - ARE NONRANDOM KARYOTYPIC CHANGES RELATED TO ETIOLOGIC AGENTS?
SI - CARC/77/08350
SO - Prog Cancer Res Ther; 3:125-136 1977
LA - ENG
AB - It is hypothesized that specific chromosomal abnormalities in human tumors may be related to particular etiologic agents. Chromosome banding techniques have shown nonrandom chromosomal abnormalities in chronic myelogenous leukemia and in acute leukemia. It appears that only certain chromosomes are abnormal in a particular tumor and that these same chromosomes may be aneuploid in a variety of tumors. Nonrandom chromosomal abnormalities occur in some animals exposed to chemical and viral mutagenic agents. When leukemia, sarcomas, and epithelial tumors were induced by 7,12-dimethylbenz(a)anthracene (DMBA) and 6,8,12-and 7,8,12-trimethylbenz(a)anthracene in rats, trisomy for the largest telocentric chromosome was observed. A different but very consistent karyotypic pattern was seen in sarcomas induced in the rat by Rous sarcoma virus. These observations suggest that the specific chromosomal abnormalities are associated with particular etiologic agents. In the rat, the order of carcinogenic potency is DMBA, methylcholanthrene, and benzo(a)pyrene, in decreasing order; the frequency of nonrandom changes shows the same order. It has been suggested that, if a given mutagen is more potent as a carcinogen, it may attack certain genes more selectively in the induction of malignancy. Several human tumors are associated with known environmental carcinogens, but none of these otherwise rare tumors have been studied cytogenetically. Tumors suggested for such investigation are thyroid carcinoma, in those who received therapeutic x-rays in the neck region, lung and gastric cancer in asbestos workers, oat cell cancers of the lung in workers exposed to halo ethers, hepatic angiosarcoma in vinyl chloride workers, clear cell adenocarcinoma in women exposed to diethylstilbestrol in utero,

and urinary bladder carcinoma in workers exposed to polycyclic aromatic compounds. (45 Refs)

176 AU - Zielhuis RL
AD - No affiliation given
TI - VASCULAR CHANGES IN VINYL CHLORIDE WORKERS.
SI - CARC/77/00173
SO - Ned Tijdschr Geneeskd; 121(29):1183-1184 1977
LA - DUT
AB - A possible method for the early detection of vinyl chloride (VC)-induced abnormalities is discussed. There were changes in the capillaries of the fingers of 55/152 workers who had been exposed to VC for 5-28 yr, but similar changes occurred in only 3/50 controls. The vascular changes consisted of dilated or tortuous vessels and many avascular sites. (8 Refs)

177 AU - Kurokawa S ; Inagaki T ; Okuyama S
AD - Nakatsugawa Municipal Hosp., Nakatsugawa-City, Gifu-Prefecture, Japan
TI - ELECTRON MICROSCOPIC OBSERVATION OF THE LIVER IN PORTAL HYPERTENSION FOLLOWING CHRONIC EXPOSURE TO VINYL CHLORIDE MONOMER.
SI - CARC/77/07996
SO - Gastroenterol Jpn; 12(2):64-69 1977
LA - ENG
AB - Two men with portal hypertension and splenomegaly following chronic exposure to vinyl chloride monomer (VCM) were studied histologically and ultrastructurally. The results suggest that VCM and its metabolites are not retained permanently in liver, because one patient who had been exposed for 12 yr, but not for the last 10 yr, had nearly normal appearing sinusoidal lining cells and Disse's spaces. (13 Refs)

178 AU - Border EA ; Webster L
AD - Natl. Res. Inst. Occupational Diseases, S. African Medical Res. Council, P O Box 4788, Johannesburg, 2000 S. Africa
TI - THE EFFECT OF VINYL CHLORIDE MONOMER, CHLOROETHYLENE OXIDE AND CHLORACETALDEHYDE ON DNA SYNTHESIS IN REGENERATING RAT LIVER.
SI - CARC/77/07834
SO - Chem Biol Interact; 17(2):239-247 1977
LA - ENG
AB - A study was made of the effects of vinyl chloride monomer (VCM) and two of its presumed metabolites, chloracetaldehyde (CA) and chloroethylene oxide (CEO), on DNA synthesis in the regenerating livers of 100-g Wistar rats subjected to partial hepatectomy. VCM (0.5 ml of a 0.19% solution) injected iv 30 min after partial hepatectomy reduced the first ensuing wave of DNA synthesis (at 21 hr) by about 50%; no effect on the second wave of DNA synthesis (at 30 hr) was evident. Similar treatment with CEO and CA also depressed the first wave of DNA synthesis by about 50%. However, these substances had different effects on the second wave: CEO raised the rate of DNA synthesis by about 50%, but CA tended to desynchronize the normally well-defined second wave. It is concluded that VCM, CEO, and CA have similar effects as

unrelated carcinogens in retarding DNA replication. (37 Refs)

179 AU - Li FP
AD - 35 Binney St., Boston, MA 02215
TI - CLINICAL STUDIES OF CANCER ETIOLOGY.
SI - CARC/77/07614
SO - Cancer; 40(1,Suppl):445-447 1977
LA - ENG
AB - Careful clinical observation can lead to clues relating to cancer etiology. Among the more recent examples are the relationships between vinyl chloride and angiosarcoma of the liver, diethylstilbestrol and vaginal adenocarcinoma, and ataxia telangiectasia and the risk of lymphoreticular neoplasia. Interactions among physicians are encouraged. (22 Refs)

180 AU - Bolt HM ; Laib RJ ; Kappus H ; Buchter A
AD - Inst. Toxicology, Univ. Tubingen, Tubingen, W. Germany
TI - PHARMACOKINETICS OF VINYL CHLORIDE IN THE RAT.
SI - CARC/77/07581
SO - Toxicology; 7(2):179-188 1977
LA - ENG
AB - When rats were exposed to **14C-vinyl chloride (VC) in a closed system, the VC in the atmosphere equilibrated with that in the animals tissues within 15 min. This course of equilibration was determined in male Wistar rats treated ip with 6-nitro-1,2,3,-benzothiadiazole at a dose (50 mg/kg) sufficient to block the metabolism of 200-1,200 ppm VC for 4 hr. Saturation of the VC-metabolizing enzymes occurred at an atmospheric VC concentration of 250 ppm. Pharmacokinetic analysis showed no significant accumulation of VC or its major metabolites following repeated administration of the compound. The results support the theory that a reactive, short-lived metabolite, which occurs only in low concentrations, may be responsible for the toxic effects of VC. (25 Refs)

181 AU - Watanabe PG ; Gehring PJ
AD - Toxicology Res. Lab., Health and Environmental Res., Dow Chemical Co., Midland, MI 48640
TI - DOSE-DEPENDENT FATE OF VINYL CHLORIDE AND ITS POSSIBLE RELATIONSHIP TO ONCOGENICITY IN RATS.
SI - CARC/77/07446
SO - Environ Health Perspect; 17:145-152 1977
LA - ENG
AB - Studies were made of the disposition of radioactivity from different doses of po administered or inhaled **14C-vinyl chloride (VC) in excreta, expired air, and body tissues of treated rats and of nonprotein sulfhydryl levels in the livers of treated rats. The disposition of VC was found to be a function of dose, particularly after administration po. The percentages of administered VC radioactivity in rats treated po with 0.05 mg/kg VC were 1.4%, 9.0%, 68.3%, 2.4%, and 10.1% in exhaled VC, exhaled carbon dioxide, urine, feces, and carcass, respectively; following 100 mg/kg VC, the corresponding values were 66.6%,

2.5%, 10.8%, 0.5%, and 1.8%; following inhalation of 10 ppm VC, the corresponding values were 1.6%, 12.1%, 68%, 4.5%, and 13.9%; following inhalation of 1,000 ppm VC, the corresponding values were 12.3%, 12.3%, 56.3%, 4.2%, and 14.5%. Exposure to 150, 250, 1,000 or 2,000 ppm VC caused a progressive depression of the hepatic nonprotein sulhydryl content; exposure to 50 ppm VC for 7 hr produced a small, inconsistent depression; no depression was observed in rats exposed to 10 ppm. These results indicate that statistical projections of data from rats exposed to high doses of VC are not valid for predicting effects of low-level exposure, because the metabolism of VC at different dose levels is not the same. (13 Refs)

182 AU - Hill HZ ; Lin HS
AD - Dept. Biochemistry, Marshall Univ. Sch. Medicine, Huntington, WV
TI - CARCINOGENESIS AND TUMOR GROWTH.
SI - CARC/77/07432
SO - Clinical Oncology. Horton J, Hill GJ, ed. Philadelphia, W. B. Saunders Co., 1977.
LA - ENG
AB - This review article begins with tabulated data on the relative percentage of incidence of (1955-1964) and mortality from (1974) cancer by site and sex in the US and on estimated new cases and deaths by site and sex for 1976. This is followed by a lengthy discussion of the causes of cancer. RNA animal viruses can be transmitted horizontally by infection and vertically by congenital infection or by genetic processes. Reverse transcriptase (RT) has been discovered in a number of cancer cells of several animals and man. The presence of RT in a tumor is often taken as clear-cut evidence of a viral etiology. RNA C-type viruses have been found in human cells after long-term culture, and, recently, C-type viral antigens were found in WBC of five patients with acute leukemia. These antigens cross-reacted with those from C-type viruses from a woolly monkey and a gibbon ape. B-type RNA viruses, or mouse mammary tumor viruses, are present in the milk of certain strains of mice. Several facts are given that suggest that RNA viruses are also involved in the induction of human breast cancer. Oncogenic DNA viruses (papillomaviruses, polyomaviruses, simian virus 40, and herpesviruses) are also discussed. Herpesviruses are the most likely of the DNA viruses to produce cancer in humans. Recent findings are given concerning environmental carcinogens, such as benzo(a)pyrene, asbestos, and vinyl chloride, and physical carcinogens, such as irritation, trauma, radiation, and radionuclides, and their proposed mechanisms of action. Cellular transformation, cancer genetics (mutation theory, inheritance factor, chromosomal aberrations, gene action), tumor progression (immune surveillance, influence of sex hormones and chalones, differentiation, stem line evolution, biochemical factors), and tumor cell population kinetics are also surveyed. (164 Refs)

183 AU - Blum B
AD - Criteria and Standards Div., Office of Water Supply, Environmental Protection Agency, Washington, DC 20460
TI - DRINKING WATER AND HEALTH: RECOMMENDATIONS OF THE NATIONAL ACADEMY OF SCIENCES.
SI - CARC/77/07185
SO - Fed Regist; 42(132):35764-35779 1977
LA - ENG
AB - Recommendations of the National Academy of Sciences concerning the contamination of water supplies with harmful substances are summarized. Four principles relevant to the assessment of risk from long-term exposure to carcinogenic substances at low doses are outlined: (1) effects in animals, properly qualified, are applicable to man; (2) methods to establish a threshold for long-term effects of toxic agents are not in existence; (3) the exposure of experimental animals to high doses of toxic agents is a necessary and valid method of discovering possible carcinogenic hazards in man; (4) materials should be assessed in terms of human risk, rather than as safe or unsafe. Risk estimates have been made for some known water supply contaminants for which data were available. Estimates of lifetime cancer risks (with a 95% upper confidence limit) are 5.1 X 10-**7, 2.6 X 10-**4, 4.4 X 10-**4, 1.2 X 10-**6, 3.1 X 10-**6, and 3.7 X 10-**7 (expressed as risk/ug/liter) for vinyl chloride, dieldrin, Kepone, DDT, polychlorinated biphenyls (with data for arochlor 1260), and carbon tetrachloride, respectively. The highest observed concentrations in drinking water of these substances are 10, 8, unknown, unknown, 3, and 366 ug/liter, respectively. The max observed levels of a large number of organic pesticides and other organic contaminants in drinking water are listed, together with recommended acceptable daily intake levels. (no Refs)

184 AU - Stokinger HE
AD - Natl. Inst. Occupational Safety and Health, Robert A. Taft Labs., Center Disease Control, U.S. Public Health Service, Cincinnati, OH
TI - TOXICOLOGY AND DRINKING WATER CONTAMINANTS.
SI - CARC/77/07154
SO - J Am Water Work Assoc; 69(7):399-402 1977
LA - ENG
AB - The concept of a threshold level of exposure to carcinogens and the extrapolation of carcinogenesis data from animal studies to man are discussed. It is contended that the threshold level (below which no biological response is observed) is a valid concept in carcinogenesis and that genetic inborn errors of metabolism may cause a shift in carcinogen thresholds. This genetic basis may underlie the susceptibility of certain exposed workers to the induction of liver hemangiomas by vinyl chloride (ie, 50 cases of hemangioma were reported among 25,000 heavily exposed workers). It is also stated that fallacies are involved in the extrapolation of data from high-dose animal experiments to normal low-dose human situations. This point is illustrated by a discussion of chloroform carcinogenesis. Chloroform levels

currently found in drinking water are not believed to constitute a danger to health. (27 Refs)

185 AU - Mukerji A
AD - Catalytic, Inc., 1500 Market st., Philadelphia, PA. 19102
TI - UNLOADING AND STORAGE TECHNIQUE FOR VINYL CHLORIDE MONOMER.
SI - ICDB/77/30075
SO - Chem Eng News; 84(19):155-160 1977
LA - ENG
AB - An unloading and storage technique for vinyl chloride monomer (VCM) is described. The method is based on a vapor-liquid-exchange process. With this process a compressor draws vapor from a plant's storage tanks and feeds the compressed vapor into a tank car, forcing VCM from the tank car up through a dip tube and into the transfer piping system. Monitoring systems for this carcinogen are described also. (10 Refs)

186 AU - Murdoch IA ; Hammond AR
AD - Standard Telecommunication Lab. Limited, Harlow, Essex, England
TI - A PRACTICAL METHOD FOR THE MEASUREMENT OF VINYL CHLORIDE MONOMER (VCM) IN AIR.
SI - ICDB/77/29155
SO - Ann Occup Hyg; 20(1):55-61 1977
LA - ENG
AB - A new method for the determination of vinyl chloride monomer in air is described which uses gas chromatography and a sealable trap sampling system. For practical purposes the detection limit is 0.1 vol/million, since below this level there is a possibility of peaks from minor impurities. (3 Refs)

187 AU - Picciano DJ ; Flake RE ; Gay PC ; Kilian DJ
AD - Occupational Health and Medical Res., Dow Chemical, Freeport, TX 77541
TI - VINYL CHLORIDE CYTOGENETICS.
SI - ICDB/77/28642
SO - J Occup Med; 19(8):527-530 1977
LA - ENG
AB - This report presents cytogenetic findings from a group of 209 workers employed for up to 28 yr in the manufacture of vinyl chloride monomer at the Texas Division of Dow Chemical USA. Cytogenetic evaluation results from this group were compared to results found in examination of individuals being considered for employment. Statistical analyses were performed on a group basis for chromatid aberrations, chromosome aberrations and proportion of abnormal cells; no statistical difference of significance was found between the two groups. Comparison of these results with reported studies suggests that the level of cytogenetic aberrations in vinyl chloride workers is probably related to the length and level of exposure, and that risk of adverse genetic effect can be avoided in controlled, minimal-exposure environments. (Author abstract) (31 Refs)

188 AU - Strickland TW ; Guengerich FP
AD - Vanderbilt Univ, Nashville, TN 37232
TI - VINYL CHLORIDE-MEDIATED CYTOCHROME P-450 DESTRUCTION (MEETING ABSTRACT).
SI - ICDB/77/23311
SO - Fed Proc; 36(3):991 1977
LA - ENG
AB - The vinyl chloride (VC)-mediated destruction of cytochrome P-450 (P-450) and loss of mixed-function oxidase activity were demonstrated in rat liver microsomes. This P-450 destruction was also demonstrated in highly-purified reconstituted systems consisting of P-450, NADPH-P-450 reductase (Fp), phosphatidylcholine, deoxycholate, VC, O2, and NADPH; all components were required and destruction was inhibited 80% by the addition of 20% CO, suggesting that oxidative metabolism of VC by P-450 to a reactive metabolite is responsible for the destruction. Loss of heme paralleled P-450 destruction while the free sulfhydryl content was not lowered during incubation; several experiments indicate that lipid peroxidation does not play a role in the process. The destruction is not due to VC-epoxide or chloroacetaldehyde. Fp (in the presence of NADPH and O2) also destroys both free heme (ferriprotoporphyrin IX) and P-450 heme in the absence of P-450 substrates. The latter two processes appear to be similar, but distinct from VC-mediated P-450 destruction, as judged by their sensitivity to catalase and insensitivity to CO. (Author Abstract)

189 AU - Schattenberg PJ ; Totovic V ; Gedigk P ; Marsteller HJ
AD - Pathologisches Institut der Universitat Bonn, Postfach 2120, D-5300 Bonn, Bundesrepublik Deutschland
TI - ULTRASTRUCTURE OF LIVER DAMAGE IN CHRONIC VINYL CHLORIDE INTOXICATION.
SI - ICDB/77/21634
SO - Virchow Arch Pathol Anat Histol; 373(3):233-247 1977
LA - GER
AB - Liver biopsies taken from 15 workers at a PVC-producing factory were examined by electron microscopy. The hepatocytes showed focal hydropic swelling, disseminated toxic steatosis, peculiar para-crystalline inclusions in enlarged mitochondria, focal cytoplasmic degradations, and occasional single cell necroses. These regressive changes were more prominent in cases with a shorter interval of non-exposure prior to the biopsy. Further, a focal compensatory hyperplasia of the smooth endoplasmatic reticulum was found. With increase of the non-exposure time interval, a regression of the degree of steatosis as well as an age-independent excessive lipofuscin deposition was seen in the hepatocytes. Apparently, these are secualae of increased autophagia of lipids and increased lipid oxidation by the vinylchloride. In the sinusoids, activation, enlargement and proliferation of Kupffer cells was noted. The tendency of these cells to proliferate is apparently caused by the cancerogenic stimulation by vinylchloride. The prominent hyperplasia of

lipocytes is probably connected with the deposition of collagen and the peculiar perisinusoidal fibrosis. (28 Refs) (Author Abstract)

190 AU - Dahl GA ; Miller EC ; Miller JA
AD - McArdle Lab., Univ. Wi, Madison, Wi. 53706
TI - VINYL CARBAMATE, A POTENT CARCINOGEN AND A POSSIBLE URETHAN METABOLITE IN THE MOUSE (MEETING ABSTRACT).
SI - ICDB/77/16265
SO - Proc Am Assoc Cancer Res; 18:6 1977
LA - ENG
AB - The ethyl group of urethan (U), CH3CH2-O-CO-NH2, a multipotential carcinogen (Tannenbaum, Natl. Cancer Inst. Monogr. 14, 341, 1964), is essential for carcinogenicity (Mirvish, Adv. Cancer Res. 11, 1, 1968). Covalent binding of the ethyl group or a derivative thereof to cellular macromolecules occurs in vivo (Pound et al. Chem.-Biol. Interact. 14, 149, 1976). These facts and the induction of hepatic mesenchymal tumors by U and vinyl chloride suggested that vinyl carbamate (VC), CH2=CH-O-CO-NH2, might be a proximate carcinogenic metabolite of U. VC was prepared from NH3 and vinyl chloroformate; the latter was obtained in low yield from the pyrolysis of ethylene glycol bis-chloroformate (Schaefgen, J. Polymer Sci. Part C, No. 24, 75, 1968). VC proved to be much more toxic than U in the mouse with the lung as a primary target. Likewise, in this species VC was much more carcinogenic than U in the lungs and skin. VC was not mutagenic towards S. typhimurium TA1535, but became mutagenic upon incubation with rat or mouse liver microsomes plus NADPH and O2. U was not mutagenic in TA1535 with or without microsomal activation. Studies so far in the mouse and in vitro with mouse tissues have failed to detect the metabolic conversion of U to VC. However, the high carcinogenicity of VC relative to that of U and the mutagenicity of metabolically oxidized VC suggests that VC and its epoxide may be proximate and ultimate carcinogenic metabolites, respectively, of U. (Author Abstract)

191 AU - Loprieno N ; Barale R ; Baroncelli S ; Bartsch H ; Bronzetti G
AU - Cammellini A ; Corsi C ; Frezza D ; Nieri R ; Leporini C
AU - Rosellini D ; Rossi AM
AD - Laboratorio di Mutagenesi e Differenziamento C.N.R. Via Cisanello 147/B, 56100 Pisa, Italy
TI - INDUCTION OF GENE MUTATIONS AND GENE CONVERSIONS BY VINYL CHLORIDE METABOLITES IN YEAST.
SI - ICDB/77/05901
SO - Cancer Res; 37(1):253-257 1977
LA - ENG
AB - Chloroethylene oxide and 2-chloroacetaldehyde, two metabolites of vinyl chloride, and 2-chloroethanol, a putative metabolic intermediate, were assayed for their genetic activity in the yeasts Schizosaccharomyces pombe and Saccharomyces cerevisiae. Chloroethylene oxide was found to be the most effective in inducing forward mutations in Sch pombe and gene conversions in S cerevisiae, increasing the mutation and conversion frequencies

340 and 50 times, respectively, over those of the controls. In either the presence or the absence of mouse liver microsomes, 2-chloroacetaldehyde showed only feeble genetic activity, and 2-chloroethanol was completely inactive in both yeast strains. In contrast to vinyl chloride, 2-chloroacetaldehyde did not induce forward mutations in Sch pombe in the host-mediated assay in mice. The results strongly support the hypothesis that chloroethylene oxide is one of the principal mutagenic agents formed from vinyl chloride in the presence of mouse liver enzymes. (Author Abstract)

192 AU - Veltman G ; Lange CE ; Stein G
AD - Bonn, W. Germany
TI - NEW DISCOVERIES AND OBSERVATIONS ON THE PROGRESS OF VINYL CHLORIDE DISE (MEETING ABSTRACT)ASE.
SI - ICDB/77/27330
SO - Z Hautkr; 52(6):196 1977
LA - GER
AB - The symptomatology of vinyl-chloride (VC) disease with special attention to newer discoveries and the danger to the worker in VC-related industries are discussed. Variousperiodic checks on skin and bone changes, thrombocytes and liver functions are available. The preventive measures that have arisen from this knowledge have generally removed the immediate threat at the factory. (no Refs)

193 AU - Vicary FR
AD - Univ. Coll. Hosp., London, England
TI - PROGRESS REPORT. ULTRASOUND AND GASTROENTEROLOGY: TECHNICAL CONSIDERATIONS.
SI - ICDB/77/26998
SO - Gut; 18(5):386-397 1977
LA - ENG
AB - Advances in the use of ultrasound in gastroenterology are reviewed. The underlying principle of ultrasonic tissue examination is that, at certain frequencies, sound is reflected when passed between two tissues of unequal acoustic density. An interface, such as that between liver and diaphragm, reflects much sound, while fluid reflects virtually no sound. Recent advances have made it possible to record different levels of sound in varying shades of grey, between black and white, with the loudest sounds being the most white. This means that tissues of relatively similar, but different, acoustic textures can be portrayed as different shades of grey. Thus it is possible to differentiate such tissues as a solid hepatic metastasis from normal liver tissue. The uses of ultrasound in liver imaging; biliary system examination in cases of jaundice; the diagnosis of liver tumors, hepatic and abdominal abscesses, hepatic cysts, and vinyl chloride liver disease; the determination of liver volumes; pancreatic investigation; and examination of abdominal masses are discussed. (68 Refs)

194 AU - Veltman G ; Lange CE
AD - Univ. Hautklinik, Bonn-Venusberg, 5300 Bonn, W. Germany
TI - INDUSTRIAL MEDICINE AND VINYL CHLORIDE.
SI - ICDB/77/26059
SO - Berufsdermatosen; 25(2):67-77 1977
LA - GER
AB - After a short review of the history of some other occupational diseases, the institutions and government agencies in West Germany concerned with regulating industrial medicine and occupational hazards are listed. The vinyl chloride (vc) syndrome is recognized as an occupational hazard, and patients are eligible for workmen's compensation. Directions for dealing with vc are described: teaching the employees the hazards of vc, criteria for selecting new employees, regular medical examinations, and recommendations and rules governing hazard-free working conditions. New products of economic importance should be examined carefully before being commercialized. (4 Refs)

195 AU - Anonymous
AD - No affiliation given
TI - ACRYLONITRILE LINKED TO CANCER IN WORKERS.
SI - CARC/77/05586
SO - Chem Eng News; 55(22):6 1977
LA - ENG
AB - Due to acrylonitrile's (AN) structural similarity to vinyl chloride, a study was conducted on 470 AN workers at a textile fibers plant in Camden. There were 16 cases of cancer reported, all occurring in workers initially exposed to AN during the startup of the plant in 1950-52. This preliminary study does not provide definitive evidence of the carcinogenicity of AN in man. Follow-up studies and investigations at other plants are planned. (no Refs)

196 AU - Lee FI ; Harry DS ; Adams WG ; Litchfield M
AD - Dept. Medicine, Victoria Hosp., Blackpool, England
TI - SCREENING FOR LIVER DISEASE IN VINYL CHLORIDE WORKERS.
SI - CARC/77/05484
SO - Br J Ind Med; 34(2):142-147 1977
LA - ENG
AB - The results of screening for liver disease in workers exposed to vinyl chloride are presented. There was no significant difference in liver function tests of workers exposed to vinyl chloride as compared to men in the same factory who were not exposed. However, four exposed workers had splenomegaly. (21 Refs)

197 AU - Leonard A ; Decat G ; Leonard ED ; Lefevre MJ ; Decuyper LJ
AU - Nicaise C
AD - Lab. Genetics, Dept. Radiology, C.E.N.-S.C.K. B 2400 Mol, Belgium
TI - CYTOGENETIC INVESTIGATIONS ON LYMPHOCYTES FROM WORKERS EXPOSED TO VINYL CHLORIDE.
SI - CARC/77/05218
SO - J Toxicol Environ Health; 2(5):1135-1141 1977
LA - ENG
AB - Eleven male workers from the polymerization department of a VC factory, seven people employed in the laboratory of another VC plant, and ten controls from outside the factory environment were examined for the presence of chromosome aberrations in blood lymphocytes and these cytological findings were viewed in light of the occupational and medical histories of the subjects. Most of the workers from the polymerization department had chromosome anomalies such as fragments, rings, translocations, and dicentrics. However, since these workers received frequent radiographs of the hands, feet, vertebral column and digestive tract, it is impossible to determine whether these chromosome anomalies result from vinyl chloride exposure or from diagnostic exposure to ionizing radiations. It is concluded that the risk of significant increase in chromosome aberrations due to occupational exposure to VC seems small and that present working conditions in VC plants are within acceptable safety limits. (17 Refs)

198 AU - Reimer RR ; Fraumeni JF ; Ozols PF ; Bender R
AD - Environmental Epidemiology and Medicine Branches, NCI, Bethesda, MD 20014
TI - PANCREATIC CANCER IN FATHER AND SON (LETTER TO EDITOR).
SI - CARC/77/04930
SO - Lancet; 1(8017):911 1977
LA - ENG
AB - The occurrence of a pancreatic tumor in successive generations is reported. A 63-yr-old chemical worker and his 36-yr-old son both developed pancreatic cancer. Several years before he died, the son worked briefly with his father, and both were exposed to vinyl chloride and other chemicals. Neither patient smoked or had any condition that predisposes to pancreatic cancer. The patients consumed large quantities of pistachio nuts, and they may have ingested some that were contaminated with mycotoxins. The occurrence of this tumor in successive generations may be due to chance or genetic transmission. Some characteristics of the case suggest an environmental influence. (8 Refs)

199 AU - John JA ; Smith FA ; Leong CK ; Schwetz BA
AD - Toxicology Res. Lab. Health Environmental Res., Dow Chemical U.S.A., Midland, MI 48640
TI - THE EFFECTS OF MATERNALLY INHALED VINYL CHLORIDE ON EMBRYONAL AND FETAL DEVELOPMENT IN MICE, RATS, AND RABBITS.
SI - CARC/77/04798
SO - Toxicol Appl Pharmacol; 39(3):497-513 1977
LA - ENG
AB - Groups of pregnant CF-1 mice, Sprague-Dawley rats and New Zealand white rabbits were exposed to an atmosphere of gaseous vinyl chloride (VC: mice, 50 or 500 ppm; rats and rabbits, 500 or 2500 ppm) for 7 hr/day during the period of major organogenesis. Some animals were given 15% ethanol in their drinking water. Maternal toxicity was observed in all three species. Among the effects were: a decrease in maternal gain and in absolute liver wt and an increase in maternal deaths for mice exposed to 500 ppm VC; a decrease in maternal wt gain and an increase in liver wt for rats exposed to 500 and 2500 ppm VC, respectively; and a decrease in food consumption for all three species ($p < 0.05$ for all differences). VC alone did not cause consistent significant embryonal or fetal toxicity. Some decrease in fetal body wt and crown-rump length was observed in fetal mice and rats but not in rabbits. Inhalation of VC was not teratogenic in any of the species at the concentrations tested. Except for dilated ureters in litters of rats exposed to 2500 ppm VC, no external or soft tissue anomalies were observed at a significantly higher incidence than observed in the control animals. Examination of the fetal skeletons showed minor but no major skeletal variations in the VC groups. Ethanol treatment enhanced maternal toxicity more than embryo toxicity. (11 Refs)

200 AU - Newell GR ; Golumbic N
AD - Natl. Cancer Program, NCI, Bethesda, MD 20014
TI - WHAT YOU CAN DO TO PROTECT YOURSELF AGAINST CANCER.
SI - ICOB/77/20285
SO - AORN J; 25(5):909-910,912,914,916,918,922,924 1977
LA - ENG
AB - The prevention and early detection and diagnosis of cancer are discussed. Individuals can make a significant contribution to cancer prevention through their decisions about life style and their concern for the environment. Individuals who smoke, are frequently overexposed to direct sunlight, or are exposed to occupational carcinogens such as vinyl chloride or x-rays run an increased risk of developing cancer. Scientists estimate that perhaps 70% to 90% of all cancers are associated with cancer-causing elements in the environment and that most could be avoided. Individuals can increase their chances of detecting early cancer and obtaining effective treatment by becoming aware of the early signs of cancer and by having regular physical examinations. (2 refs)

R&S 138924

201 AU - Bonneton G ; Champetier J ; Fournet J ; Guidicelli H ; Legrand J
AU - Dupre A ; Hostein M ; Marty F ; Pahn M
AD - Service de Chirurgie Vasculaire, C.H.U. de Grenoble, F 38700 La Tronche, France
TI - ANGIOSARCOMA OF THE LIVER AND PORTAL SCLEROSIS IN VINYL CHLORIDE WORKERS. REPORT OF TWO CASES.
SI - CARC/77/04618
SO - Nouv Presse Med; 6(9):735-742 1977
LA - FRE
AB - A 63-yr-old man developed an angiosarcoma of the liver after 12 yr occupational exposure to polyvinyl chloride. He entered the hospital with acute abdominal pain and hypochromic anemia. Hepatosplenomegaly and ascites were evident clinically and confirmed by endoscopic and arteriographic studies. Hepatic scintigraphy showed a multilacunar area near the margin of the right lobe. Laparotomy revealed abdominal hemorrhage and a large, hemorrhagic cyst on the liver. Hepatectomy and splenectomy were performed with immediate satisfactory results; however, rupture of the esophageal varices as a result of portal hypertension led to fatal hemorrhage on the 16th postoperative day. In addition to angiosarcoma of the right lobe of the liver, areas of infarct and intrahepatocytic biliary retention were observed in the left lobe at autopsy. In the second case, the worker developed portal fibrosis and collagenous sclerosis of the liver after more than 20 yr exposure to polyvinyl chloride. A splenectomy was performed in 1968 for splenomegaly; the spleen proved to be inflamed and fibrous without evidence of malignancy. Five years later, the patient was hospitalized for melena and found to have hypochromic anemia, moderate hepatomegaly, and significant esophageal varices. At surgery, the liver appeared to have disseminated micronodules, but no tumor was detected. The portal vein was fibrosed and a mesenterico-vena cava anastomosis was performed with excellent postoperative results. (13 Refs)

202 AU - Kay K
AD - Mount Sinai Sch. Medicine, City Univ. New York, New York, NY 10029
TI - CHLOROFORM TOXICITY (LETTER TO EDITOR).
SI - CARC/77/04381
SO - Am Ind Hyg Assoc J; 38(2):A-24-A-25 1977
LA - ENG
AB - The author criticizes a previous paper that covered tests of chloroform toxicity over 6 mo. During that time, as might be expected from what is known about chemical carcinogenesis, cancers did not develop. The report is misleading, because the question as to whether cancers might have developed over the longer exposure period used in the NCI chloroform tests was not answered. The noncarcinogenicity of chloroform in a 6-mo test may indeed be inconsequential in comparison with its carcinogenicity, as was the case with vinyl chloride. (0 Refs)

203 AU - Ivanetich KM ; Aronson I ; Katz ID
AD - Dept. Physiology Medical Biochemistry, Univ. Cape Town Medical Sch., Cape Town, South Africa
TI - THE INTERACTION OF VINYL CHLORIDE WITH RAT HEPATIC MICROSOMAL CYTOCHROME P-450 IN VITRO.
SI - CARC/77/04085
SO - Biochem Biophys Res Commun; 74(4):1411-1418 1977
LA - ENG
AB - The interaction of vinyl chloride (VC) in vitro with the cytochrome P-450 enzyme system of the hepatic endoplasmic reticulum of Long Evans male rats was investigated. The binding of VC to cytochrome P-450 in vitro was studied spectrally in microsomes from uninduced, 3-methylcholanthrene (3-MC)-induced, and phenobarbital (PB)-induced rats. VC bound to hepatic microsomal cytochrome P-450 in all types of microsomes, with production of a type I difference spectrum. Hanes plots of the spectral binding of VC to cytochrome P-450 were linear for all types of microsomes. VC increased CO- inhibitable NADPH consumption by hepatic microsomes from induced rats. Induction by 3-MC did not increase the apparent max velocity much above that obtained for uninduced microsomes. However, for PB-induced microsomes, max velocity was approx fivefold greater than the apparent max velocity obtained with uninduced microsomes. The effects of inhibitors on the interaction of VC with cytochrome P-450 were determined. SKF 525A fully inhibited the binding of VC to cytochrome P-450, but it did not decrease the enhancement of CO- sensitive NADPH consumption by VC. However, metyrapone did not significantly inhibit the binding of VC to cytochrome P-450 but did inhibit the enhancement of CO- sensitive NADPH consumption by VC. The influence of incubation of hepatic microsomes from induced rats with VC on microsomal enzyme levels was assessed. The levels of cytochrome P-450, cytochrome b5, and NADPH-cytochrome c reductase were not altered after incubation of hepatic microsomes with either VC, NADPH, or NADH. Cytochrome b5 and NADPH-cytochrome c reductase were not affected after incubation of hepatic microsomes with VC plus NADPH, but cytochrome P-450 was decreased. The VC-mediated decrease in cytochrome P-450 was slight in control (8%) and 3-MC (7%) microsomes, but was significant in PB microsomes (31%). In PB-induced microsomes, microsomal heme was decreased by approx 30% of the decrease in cytochrome P-450. Reduced glutathione and CO inhibited the VC-mediated decrease in cytochrome P-450 in PB-induced microsomes by approx 30% and 80%, respectively. NADH supported the VC-mediated decrease in cytochrome P-450 by approx 30% in comparison to NADPH. The results may provide an explanation for the observation that prior exposure of laboratory animals to VC protects them against the toxic effects of VC. (17 Refs)

204 AU - Hoffmann D ; Wynder E
AD - Naylor Dana Inst. for Disease Prevention., American Health Foundation, Valhalla, NY, 10595
TI - ENVIRONMENTAL RESPIRATORY CARCINOGENESIS.
SI - IC08/79/16167
SO - Am Chem Soc Mongr Ser; (173):324-365 1976
LA - ENG
AB - Three factors are implicated in the overall increase of lung cancer: tobacco (especially cigarette smoking), urban pollution, and the emergence of new industrial environments. A review is presented of the relationship of lung and other cancer to tobacco, urban air pollution, and exposure to industrial carcinogens. Topics discussed include carcinogenic stimuli in occupational respiratory environments, such as radioactive aerosols in mining of radioactive ores, arsenicals, chromium in chromate workers, nickel and its relationship to lung and nasal cancer, coke oven effluent and its relationship to skin as well as lung cancer, chloromethyl ethers and lung cancer, vinyl chloride and liver angiosarcoma, the possible carcinogenicity of nitrosamines, and other less common respiratory carcinogens. The possible role of air pollution on the induction of respiratory cancer is reviewed. Polynuclear aromatic hydrocarbons in urban atmosphere are listed, and their sources identified. Indoor pollution is discussed briefly. Air pollution is probably one factor which increases the risk of urban populations, especially cigarette smokers, of developing lung cancers. Cigarette smoke, which is by far the most important single factor contributing to increased risk of developing respiratory tract, especially lung cancer is discussed. Epidemiological observations are reviewed. The characteristics of tobacco smoke are reviewed, including major smoke components, particle sizes in smoke, temperature reached in the burning cone, and pH of the smoke. Studies dealing with experimental tobacco carcinogenesis are briefly reviewed, and the identification of carcinogens in the gas and particulate phases of smoke are outlined. Some experimental approaches for the reduction of tumorigenicity of cigarette smoke are discussed. (148 Refs)

205 AU - Bartsch H
AD - Unit of Chemical Carcinogenesis, International Agency for Research on Cancer, 150 cours Albert Thomas, 69008 Lyon France.
TI - MUTAGENICITY TESTS IN CHEMICAL CARCINOGENESIS.
SI - CARC/78/01571
SO - Environmental Pollution and Carcinogenic Risks. Lyon, International Agency for Research on Cancer, IARC Scientific Publications No 13, INSERM Symposia Series, vol. 52, 1976.
LA - ENG
AB - The use of mutagenicity tests in the assessment of chemical carcinogenicity is assessed. The validity of this application is demonstrated with the vinyl chloride experiments in rats, mice, human liver, and Salmonella typhimurium and the N-nitrosamine activities in rats, human liver, and S. typhimurium. The

usefulness of mutagenicity tests in predicting possible carcinogenic effects of chemicals in man is valid only if the short-term bioassay is corroborated by data from long-term tests in experimental animals and is then taken together with epidemiologic studies. Mutagenicity tests, therefore, although effective in predicting the carcinogenic potential of chemicals, are not able to indicate organ and species specificity of the carcinogenic activity of the chemical or correlate mutagenic potency with carcinogenic potency. (50 Refs)

206 AU - Henschler D ; Bonse G ; Greim H
TI - CARCINOGENIC POTENTIAL OF CHLORINATED ETHYLENES. TENTATIVE MOLECULAR RULES.
SI - CARC/77/07537
SO - Environmental Pollution and Carcinogenic Risks. Lyon, International Agency for Research on Cancer, IARC Scientific Publications No 13, INSERM Symposia Series, Vol. 52, 1976.
LA - ENG
AB - The mechanisms of bioactivation and the mutagenic activity of the chlorinated ethylenes were studied with a short-term in vitro system using metabolic activating liver microsomal enzymes. Chlorinated ethylenes were activated in mammalian metabolism to oxiranes. Asymmetric chlorine substitution of the ethylenes and oxiranes rendered the molecules unstable and mutagenic. Vinyl chloride was the most active; trichloroethylene and vinylidene chloride were far less active but still significantly so. Chlorinated ethylenes metabolized via symmetric oxiranes (tetrachloroethylene, cis- and trans-1,2-dichloroethylene) were relatively stable, and were not mutagenic. It was concluded that mutagenic activity and possible carcinogenic potential were related directly to oxirane stability. (13 Refs)

207 AU - Lawther PJ ; Waller RE
TI - COAL FIRES, INDUSTRIAL EMISSIONS AND MOTOR VEHICLES AS SOURCES OF ENVIRONMENTAL CARCINOGENS.
SI - CARC/77/07533
SO - Environmental Pollution and Carcinogenic Risks. Lyon, International Agency for Research on Cancer, IARC Scientific Publications No 13, INSERM Symposia Series, Vol. 52, 1976.
LA - ENG
AB - The rural/urban difference in the concentrations of benzo(a)pyrene was for many years thought to be a notable factor in the occurrence of lung cancer; but now that industrial emissions and domestic smoke have been controlled considerably in Great Britain, the concentration of benzo(a)pyrene in the urban environment has been reduced by a factor of ten. In addition, traffic contribution to the benzo(a)pyrene level, although variable, is small in Great Britain. Correlations with a reduction in lung cancer are not yet possible, partly because recent cancers could have been induced by the former high levels and because the effect of cigarette smoking is now known to be an important etiological factor in lung cancer. Of other possible carcinogenic materials dispersed into the environment, asbestos

has undergone the most investigation. The established association between asbestos and lung cancer and pleural mesothelioma is predominantly occupational; thus the general public is at very low risk. Similarly, many metals in trace amounts, eg, nickel, chromium, beryllium and vinyl chloride monomer, are suspected of being occupational carcinogens. Careful monitoring of urban air is advisable when investigating possible etiologies of lung cancers. (37 Refs)

208 AU - Antweiler H
AD - Universitat Dusseldorf, Dusseldorf, W. Germany
TI - STUDIES ON THE METABOLISM OF VINYL CHLORIDE.
SI - CARC/77/07435
SO - Environ Health Perspect; 17:217-219 1976
LA - ENG
AB - Current ideas concerning the metabolism of vinyl chloride (VC) in mice and in humans are discussed. It is believed that VC is first metabolized by oxidases to chloroethylene oxide, a strong mutagen. Spontaneous conversion to chloroacetaldehyde (CA) follows; CA may be mutagenic and carcinogenic. Dehydrogenation of CA leads to chloroacetic acid (CAA), a substance of known toxicity but unknown mutagenicity. Conjugation of CAA with glutathione leads to the formation of the principal urinary metabolites of VC; namely S-carboxymethylcysteine and thiodiacetic acid. CAA may also be converted, via glycolic acid, to oxalic acid. (13 Refs)

209 AU - Wolff MS
AD - Environmental Sciences Lab., Dept Community Medicine, Mount Sinai Sch. Medicine, City Univ. New York, New York, NY 10029
TI - EVIDENCE FOR EXISTENCE IN HUMAN TISSUES OF MONOMERS FOR PLASTICS AND RUBBER MANUFACTURE.
SI - CARC/77/07281
SO - Environ Health Perspect; 17:183-187 1976
LA - ENG
AB - Discussion is made of the storage in fat of lipophilic substances such as DDT, polychlorinated biphenyls, tetrachloroethylene, and trichloroethylene, which are chemically similar to many industrially-used monomers, plus styrene, acrylamide, and vinyl chloride. Data on the uptake, metabolism, storage, and excretion of these substances in humans are provided when available. The storage and removal of lipophilic substances from fat tissues depend on fat solubility, volatility, and metabolism. Styrene is very soluble in blood and fat: following exposure at 100 ppm, blood levels of 0.2-15 ppm styrene have been determined. The urinary and breath half-lives of styrene metabolites and styrene, respectively, are about 8 hr and 1-3 hr, respectively. Detectable levels of styrene were present in the fat of styrene workers greater than 2 days following exposure, a much longer period than that over which styrene could be detected in the breath of people experimentally exposed to 100 ppm styrene for sustained periods. (28 Refs)

210 AU - Maltoni C
TI - OCCUPATIONAL CHEMICAL CARCINOGENESIS: NEW FACTS, PRIORITIES AND PERSPECTIVES.
SI - CARC/77/06880
SO - Environmental Pollution and Carcinogenic Risks. Lyon, International Agency for Research on Cancer, IARC Scientific Publications No 13, INSERM Symposia Series, vol. 52, 1976.
LA - ENG
AB - The results of experiments on the carcinogenicity of vinyl chloride (VC) are presented in 18 tables as part of a paper calling for a more active approach to the problem of environmental oncogenesis. VC was inhaled at doses from 30,000 ppm to 1 ppm for 4 hr/day, 5 days/wk for 52 wk by rats (Sprague-Dawley, Webster), mice (Swiss), and hamsters (Chinese); 50 ppm was the dividing dose in carcinogenic potential, and a variety of cancers resulted from the higher dosages. VC was also administered by inhalation at 10,000 ppm and 6,000 ppm, 4 hr/day for 1 wk. The resulting cancers were monitored in the animals and their offsprings. In addition, VC was ingested at 50.00, 16.65, and 3.33 mg/g body weight, once daily, 4-5 days/wk for 52 wk; liver angiosarcomas were the predominant resulting neoplasms. Lower dosages of 1, 0.3, and 0.03 mg/g body weight produced no tumors. Subcutaneous administration into rats of 30 mg of compound in 1 cc of water of chromite, neochromium, chromium allumen, lead chromate, molybdenum orange, cadmium sulphide, iron oxide, zinc chromate, and titanium oxide resulted in rhabdomyosarcomas and fibrosarcomas in all cases but chromite, iron oxide (red), titanium oxide, and zinc chromate. Adriamycine was tested in rats by sc injection of 2 mg in 1 cc olive oil. Tumors resulted in 35% of females and 30% of males after an average latency of 31-32 wk. Plans of experiments to test the oncological effectiveness of styrine, vinylidene chloride, and acrylonitrile are also given in tabular form. (14 Refs)

211 AU - Winell M ; Holmberg B ; Kronevi T
AD - Section Occupational Toxicology, Dept. Occupational Medicine, Natl. Board Occupational Safety and Health, S-100 26 Stockholm, Sweden
TI - BIOLOGICAL EFFECTS OF VINYL CHLORIDE: AN EXPERIMENTAL STUDY.
SI - CARC/77/06811
SO - Environ Health Perspect; 17:211-216 1976
LA - ENG
AB - Liver damage caused by the exposure of albino NMRI mice to atmospheric vinyl chloride (VC) was assessed by estimating the plasma activities of alkaline phosphatase (AP), the transaminases, and lactate dehydrogenase (LDH). Three groups of 24 mice each were exposed by inhalation for 6 hr/day, 5 days/wk, to 50 ppm (52 wk) or 500 ppm VC (26 wk), or to air only (controls). The animals were also autopsied, and the tissue pathology was studied. Liver damage was indicated by a significant increase in total LDH levels after about 40 wk. After 46 wk, total LDH levels were increased about 2.5-fold following

exposure to 500 ppm. A significant shift in the LDH isoenzyme profile to the M form also occurred. There was no corresponding elevation in transaminase activities, which might have served as an alternative indication of liver injury. AP activities also increased after about 40 wk: at this time levels were elevated 30%-40% and 50%-60% following exposure to 50 and 500 ppm VC, respectively. This elevation could indicate lesions in the hepatobiliary tract. Upon autopsy 12 mo after the start of exposure, no control mice had any lung adenomas or hemangiosarcomas, and 24 mice exposed to 24 ppm VC had lung adenomas and 8 had hemangiosarcomas. (30 Refs)

212 AU - Bartsch H ; Malaveille C ; Barbin A ; Bresil H ; Tomatis L
AU - Montesano R
AD - International Agency Res. Cancer, Unit Chemical Carcinogenesis, 69008, Lyon, France
TI - MUTAGENICITY AND METABOLISM OF VINYL CHLORIDE AND RELATED COMPOUNDS.
SI - CARC/77/06804
SO - Environ Health Perspect; 17:193-198 1976
LA - ENG
AB - Experimental data concerning the metabolism and mutagenicity of vinyl chloride (VC) and related compounds are reviewed. The data suggest that the biological effects of VC are related to its conversion by microsomal enzymes into chemically reactive alkylating agents that can bind covalently to various cellular macromolecules. The mutagenicity of VC to Salmonella typhimurium strain TA1530, which is reverted to his+ by single base-pair substitutions, was increased 28-fold after exposure to an atmosphere of 20% VC (volume/volume) in air. Hepatic microsomal mixed function oxidases from rats, mice, and humans were equally effective in transforming VC into alkylating agents in vitro. Two of the products of reaction with the microsomal enzyme system, chloroethylene oxide and 2-chloroacetaldehyde, demonstrated potent mutagenicity in microorganisms and Chinese hamster V79 cells. (31 Refs)

213 AU - Byren D ; Engholm G ; Englund A ; Westerholm P
AD - Kema Nord, 85013 Sundsvall, Sweden
TI - MORTALITY AND CANCER MORBIDITY IN A GROUP OF SWEDISH VCM AND PCV PRODUCTION WORKERS.
SI - CARC/77/06792
SO - Environ Health Perspect; 17:167-170 1976
LA - ENG
AB - Mortality and cancer morbidity data are presented from studies of 750 workers employed in a Swedish vinyl chloride (VC)/poly(vinyl chloride) plant since 1940. Observed/expected deaths from various causes were: 2/0.33 (brain cancer), 3/1.78 (lung cancer), 4/0.97 (cancer of liver/pancreas, including 2 angiosarcomas of the liver), 28/18.26 (total circulatory disease), 6/3.02 (cerebrovascular disease), 15/9.15 (myocardial infarction), and 5/1.48 (cerebral hemorrhage). Observed/expected morbidities were: 3/1.30 (lung cancer) and 2/0.48 (cancer of liver/pancreas). The

excess of cancers of the liver/pancreas increased with latency time (time between first employment and end of follow-up). The possible etiology of the cardiovascular deaths is discussed. (7 Refs)

214 AU - Gokel JM ; Liebezeit E ; Eder M
AD - Pathologisches Institut der Universitat, Thalkirchner Str. 36, D-8000 Munchen 2, Federal Republic of Germany
TI - HEMANGIOSARCOMA AND HEPATOCELLULAR CARCINOMA OF THE LIVER FOLLOWING VINYL CHLORIDE EXPOSURE A REPORT OF TWO CASES.
SI - ICDB/77/10635
SO - Virchow Arch Pathol Anat Histol; 372(3):195-203 1976
LA - ENG
AB - A report is given of the clinical and autopsy findings of two men who died from malignant liver neoplasm following occupational exposure to vinyl chloride. The first patient was a 44-year-old man with an hemangiosarcoma of the liver, the second patient a 67-year-old man with an hepatocellular carcinoma. So far an hepatocellular carcinoma due to vinyl chloride has not yet been observed in man. Its occurrence, however, has been suggested from the results of animal experiments. The connection of hepatocellular carcinoma with exposure to vinyl chloride is discussed. (Author Abstract)

215 AU - Loprieno N ; Abbondandolo A ; Barale R ; Baroncelli S ; Bonatti S
AU - Broncetti G ; Cammellini A ; Corsi C ; Corti G ; Frezza D
AU - Leporini C ; Mazzaccaro A ; Nieri R ; Rosellini D ; Rossi AM
AD - Laboratorio di Mutagenesi e Differenziamento, CNR e Istituto di Genetica della Universita, Pisa, Italy
TI - MUTAGENICITY OF INDUSTRIAL COMPOUND: VINYL CHLORIDE, STYRENE AND THEIR POSSIBLE METABOLITES (MEETING ABSTRACT).
SI - ICDB/77/10294
SO - Third International Symposium On Detection And Prevention Of Cancer. 1976.
LA - ENG
AB - It has been proposed that mutagenicity tests are at the present the most appropriate for the prescreening of substances for possible carcinogenic activity. It is therefore interesting to develop biological analyses to assess the mutagenic activity of toxic industrial compounds already known as human carcinogens or those compounds under suspicion. In our analyses we have applied mutagenicity methodologies in the study of vinyl chloride (human carcinogen) and to styrene (under carcinogenic analysis at the present): the same analyses have been applied also to their possible metabolites (2-chloroethylene oxide, 2-chloroethanol, 2-chloroacetaldehyde, and styrene oxide) in order to correlate the mammalian metabolic fate of the compounds with their biological activity. The compounds have been studied by means of liver microsomal assay and host mediated assay (mice), employing as a test organism the yeast S pombe and S. cerevisiae on which the induction of gene-mutations and of gene-conversions has been analyzed. Preliminary experiments have been done also with somatic mammalian cells (V79 chinese hamster), on which the

induction of 8-azaguanine resistant clones has been assessed. From our analyses it has been found that vinyl chloride is mutagenic in the presence of liver microsomal preparations (in vitro) or in the host mediated assay (in vivo). (Author Abstract)

216 AU - Banerjee S ; Van Duuren BL
AD - Laboratory of Organic Chemistry & Carcinogenesis, Institute of Environmental Medicine, New York University Medical Center, New York, N.Y. U.S.A.
TI - INTERACTION BETWEEN TRICHLOROETHYLENE AND HEPATIC ENDOPLASMIC RETICULUM (MEETING ABSTRACT).
SI - ICDB/77/10279
SO - Third International Symposium On Detection And Prevention Of Cancer. 1976.
LA - ENG
AB - Trichloroethylene (TCE) is a structural analog of vinyl chloride, which is known to induce angiosarcoma of the liver in rodents and is also a human carcinogen. TCE is a widely used organic solvent in industry and has also been used for many years as an anesthetic. We predicted recently that TCE is likely to be carcinogenic and that its epoxide probably is the activated carcinogenic intermediate. Subsequently, the National Cancer Institute reported that TCE induces hepatocellular carcinoma and other tumors in B6C3F1 hybrid mice. TCE epoxide is expected to be highly reactive toward cellular nucleophiles, eg proteins and nucleic acids. Hence, the microsomal metabolism of TCE and its covalent binding to microsomal protein was examined. Rat liver microsomes were incubated in vitro with **14C-TCE. The results showed that TCE binds covalently to microsomal protein since extensive organic extractions and pronase digestion do not dissociate the TCE-protein complex. The binding was decreased by 7,8-benzoflavone, blocked by SKF-525A and enhanced by intraperitoneal administration of phenobarbital. The possibility that TCE epoxide, once formed, could be converted to water-soluble products through enzymatic hydrolysis by epoxide hydrase was also investigated. Addition of 3,3,3-trichloro propane oxide, a potent inhibitor of epoxide hydrase to the incubation system markedly enhanced the binding of TCE. These observations support the view that TCE is metabolized to its epoxide, which is most likely involved in TCE carcinogenesis and toxicity. (Author Abstract)

217 AU - Aranha GV ; Gold J ; Grage TB
AD - University of Minnesota Hospitals, Department of Surgery, P.O. Box 90, Minneapolis MN 55455.
TI - HEMANGIOSARCOMA OF THE SPLEEN: REPORT OF A CASE AND REVIEW OF PREVIOUSLY REPORTED CASES.
SI - ICDB/77/04781
SO - J Surg Oncol; 8(6):481-487 1976
LA - ENG
AB - Splenic hemangiosarcomas are rare tumors, usually discovered at autopsy. In a few instances the diagnosis was made premortem, at the time of splenectomy for spontaneous rupture. The tumors

usually present with abdominal pain, left upper quadrant mass and tenderness, and occasionally with a microangiopathic type of anemia. The histogenesis of the tumor is in dispute. Some authors feel that they are degenerations of hemangiomas. Others feel that they arise de novo in the spleen. There is no proven association of thorotrast administration or vinyl chloride exposure to the development of hemangiosarcomas in the spleen. The prognosis of the tumor is uniformly poor and most of the patients surviving laparotomy have followed a uniformly fatal clinical course. In a few cases treated with chemotherapy there has been no evidence of clinical benefit. The case report in this article presented with essentially all the features enumerated above. (Author Abstract)

218 AU - Whelan JG ; Creech J ; Tamburro CH
AD - Digest Dis and Nutri Sect and Cancer Ctr, Univ Louisville, Sch Med, Louisville, KY 40201
TI - PRIMARY LIVER CANCER DETECTION IN VINYL CHLORIDE WORKERS (MEETING ABSTRACT).
SI - ICDS/77/04524
SO - Third International Symposium On Detection And Prevention Of Cancer. 1976.
LA - ENG
AB - The recent discovery of hepatic angiosarcoma in vinyl chloride polymerization workers led to a medical screening program which utilized radioisotopic scanning as a primary screening procedure among asymptomatic workers. Nine hundred employees underwent medical examination, biochemical blood studies and **99mTc hepatic scanning. Sixty-six of these employees had hepatic angiographic studies and hepatic biopsy. Thirty five were studied because of pathological abnormalities on liver scan and 30 because of biochemical abnormalities with normal scans. Thirty one percent of those with abnormal liver scans had angiographic lesions. Five had angiosarcoma, 2 of whom had no biochemical abnormalities at the time their scan indicated a lesion present. Four had cirrhosis and 2 peliosis hepatis. Of the 31 employees with normal scan, only 7% (2) had angiographic lesions; both had peliosis hepatis. Within one year, one developed a positive liver scan associated with the progression of his peliosis hepatis and the development of hepatic arterialportal venous shunts. The majority of those with positive liver scans without angiographic lesions did have significant histological disease including portal fibrosis, granulomatosis and fatty metamorphosis. In contrast, only minor nonspecific histological abnormalities were found in those with normal scans and negative angiographic studies. These data illustrated the effectiveness of the liver scan as a primary screening procedure both by its early detection of hepatic tumors and its low incidence of false positivity (less than 3%) in this cohort of asymptomatic vinyl chloride polymerization workers. In addition, vascular abnormalities such as peliosis hepatis, possibly a pre-malignant lesion, may also be detected in the absence of biochemical abnormalities. (Author Abstract)

219 AU - Laumbach AD ; Wong JL ; Streips UN
AD - Dept Microbiol and Immunol, Sch Med, Dept Chem, Univ Louisville, Louisville, KY 40201
TI - STUDIES ON THE MUTAGENICITY OF VINYL CHLORIDE METABOLITES AND RELATED COMPOUNDS (MEETING ABSTRACT).
SI - ICDB/77/03900
SO - Third International Symposium On Detection And Prevention Of Cancer. 1976.
LA - ENG
AB - The mutagenic potential of several purified metabolites of vinyl chloride monomer (VCM) was determined by utilizing bacterial assay methods. First, a preliminary screen, the repair assay, using DNA repair deficient mutants of Bacillus subtilis was performed, then the compounds were tested quantitatively for mutagenicity with Salmonella typhimurium LT-2 strains obtained from B N Ames. From all the tested compounds the following were found to be mutagenic in the bacterial assays: chlorooxirane (chloroethyleneoxide), chloroacetaldehyde, chloroacetaldehyde hydrate, chloroacetaldehyde dimer hydrate, and chloroacetaldehyde trimer. In additional epichlorohydrin (1-chloro-2,3 epoxypropane), a related compound to chlorooxirane, was weakly mutagenic in our assays. All of the above compounds specifically reverted the Salmonella tester strain TA 100, indicating base pair substitution type of mutations. A recombination repair deficient strain of B subtilis, MC-1, was specifically inhibited in growth by the VCM metabolites. However, several excision repair deficient strains and the wild type (repair-positive) strain were relatively unaffected. These experiments suggest that VCM metabolites elicit recombination repair, an error prone process, for correction of damage. epichlorohydrin was not reactive in these experiments, indicating that either epichlorohydrin-induced lesions or the repair of these lesions differ from those caused by VCM metabolites. (Author Abstract)

220 AU - Garro AJ ; Guttenplan JB ; Milvy P
AD - Mt. Sinai Sch Med, NY, NY 10029
TI - VINYL CHLORIDE DEPENDENT MUTAGENESIS: EFFECTS OF LIVER EXTRACTS AND A FREE RADICAL GENERATING SYSTEM (MEETING ABSTRACT).
SI - ICDB/77/03879
SO - Third International Symposium On Detection And Prevention Of Cancer. 1976.
LA - ENG
AB - The relationship between vinyl chloride (VC) dependent mutagenesis and metabolic activation of VC by hepatic extracts was examined. VC itself was observed to be mutagenic for Salmonella typhimurium and mutagenesis was enhanced by the presence of mouse or rat liver extracts. The extracts prepared from mice pretreated either with VC or the microsomal enzyme inducer, Aroclor 1254, did not produce any greater stimulation of VC dependent mutagenesis than extracts from untreated animals. These same extracts, however, differed markedly in their capacity to stimulate the mutagenic activity of dimethylnitrosamine, a

compound which is converted to a mutagen by an NADPH-dependent microsomal mixed function oxidase. In contrast to what was seen with dimethylnitrosamine, the stimulatory effect of the liver extracts on VC mediated mutagenesis did not require NADPH and was still evident in liver extracts in which the microsomal mixed function oxidase had been heat inactivated. Since VC polymerizes by a free radical reaction mechanism and since free radicals are known to be mutagenic, the possibility that a free radical generating system would stimulate VC dependent mutagenesis was examined. Free radicals were generated by photo-excitation of riboflavin and it was observed that this system did stimulate the mutagenic activity of VC. We have concluded that the mutagenic effect of VC may involve a free radical process and that the stimulatory effect of liver extracts may not be due to enzymatic activation of VC by a microsomal mixed function oxidase. (Author Abstract)

221 AU - Anderson HA ; Snyder J ; Lilis R ; Selikoff IJ
AD - Mt. Sinai Sch Med, NY, NY 10029
TI - LEVELS OF CEA AMONG VINYL CHLORIDE AND POLYVINYL CHLORIDE EXPOSED WORKERS (MEETING ABSTRACT).
SI - ICDB/77/03073
SO - Third International Symposium On Detection And Prevention Of Cancer. 1976.
LA - ENG
AB - In 1965, the term carcinoembryonic antigen (CEA) was first used to describe an antigen found in extracts of fetal gut and carcinoma of the digestive tract. The refinement of a rapid, highly sensitive radioimmunoassay for the detection of this antigen has made the test available for use on a larger scale. CEA was initially felt to be specific for entodermally derived tumors. However, further studies have described significant CEA elevations in other malignancies and in some non-malignant inflammatory disorders. Cigarette smoking has also been demonstrated to have an effect on the CEA titer. Rather than tumor specificity, CEA titers less than 20 ng/ml are now felt to reflect active disease processes, both malignant and nonmalignant. Titers above 20 ng/ml are more indicative of an occult malignancy. Whether individuals with CEA titers less than 20 ng/ml are at higher risk of developing a malignant disease has not been adequately evaluated. We are evaluating the use of the CEA titer as a possible method of identifying specific individuals at high risk in occupational groups already known to have an increased risk of developing malignancies. One such group has been vinyl chloride and polyvinyl chloride exposed workers. We have examined 1,177 workers from three VC/PVC polymerization plants and 254 workers from a PVC extrusion plant manufacturing PVC textile leather, obtaining respectively 1140 and 253 CEA titers. After removing the confounding effects of past medical illnesses, cigarette and alcohol use, the distribution of CEA titers among the polymerization workers was significantly different from the extrusion group and an unexposed comparison group. The extrusion group was not significantly different from

the unexposed group. CEA titers also correlated well with other VC/PVC related changes such as liver chemistry abnormalities and hepato-splenomegally. Our investigation demonstrates that occupational exposures in VC/PVC polymerization plants can cause elevations in the CEA titers of otherwise healthy individuals. The exposures experienced by the extrusion workers did not appear to have a similar effect on the CEA titer distribution. Prospective follow-up is necessary before conclusions can be drawn concerning the relative health risks of these two occupational groups and the usefulness of the CEA titer as an indication of possible increased risk. (Author Abstract)

222 AU - Espinosa E
AD - Univ Louisville, Sch Med, Louisville, KY 40202
TI - IMMUNOPATHOLOGIC OBSERVATIONS IN LIVER ANGIOSARCOMA (MEETING ABSTRACT).
SI - ICDB/77/03872
SO - Third International Symposium On Detection And Prevention Of Cancer. 1976.
LA - ENG
AB - Two patients with liver angiosarcoma and ten with liver dysfunction with fibrosis, all with histories of industrial vinyl chloride exposure, were tested for anti-tissue serum antibodies and for circulating tissue antigens associated with liver damage. Tumor-associated antigens and bound immunoglobulins were searched for in the angiosarcomatous tissue. No significant levels of serum autoantibodies to nuclei, mitochondria, smooth muscle, other normal human and rat tissue components, and liver tissue from rats intoxicated with vinyl chloride could be demonstrated by indirect immunofluorescence. Liver-damage-related circulating tissue antigens, with or without liver specificity, were not detected. Immunoglobulin G was found bound to angiosarcomatous tissue but not to adjacent liver tissue or to liver tissue from normal controls. Antigenic analysis of angiosarcomatous tissue by immunodiffusion using anti-angiosarcoma rabbit serum revealed an antigen in angiosarcoma not detected in normal liver but found to be present in normal spleen and lung. This antigen was susceptible to Pronase and trypsin, relatively thermolabile, affected by acid pH, and precipitated at 20 to 30% saturated ammonium sulfate and at 50 to 70% ethanol concentration. In conclusion neither anti-tissue antibodies nor circulating tissue antigens associated with liver damage were detected in patients with liver angiosarcoma or other liver abnormalities related to vinyl chloride exposure. In angiosarcomatous tissue, bound immunoglobulin G and an antigen not detected in normal liver were demonstrated. (Author Abstract)

223 AU - Kupchella CE ; Tamburro CH
AD - Univ Louisville, Louisville, KY 40208
TI - URINARY AND TISSUE GLYCOSAMINOGLYCAN PATTERNS IN ANGIOSARCOMA AND OTHER VINYL-CHLORIDE-EXPOSURE-ASSOCIATED LIVER INJURY (MEETING ABSTRACT).
SI - ICDB/77/03871
SO - Third International Symposium On Detection And Prevention Of Cancer. 1976.
LA - ENG
AB - Both the presence of certain cancers and disorders of connective tissue metabolism are accompanied by alterations in urinary glycosaminoglycan patterns. Because both fibrosis and angiosarcoma of the liver have been connected to vinyl chloride exposure, we evaluated glycosaminoglycan patterns associated with vinyl chloride injury to assess the usefulness of the patterns in early detection. Urines from fifty patients were analyzed for glycosaminoglycans. These included two angiosarcomas, ten cases of vinyl-chloride, work-related, liver injury other than angiosarcoma, and cases of hepatitis, cirrhosis, other cancers, metabolic disorders of the liver, and normal controls. Examined both histochemically and biochemically for glycosaminoglycans were liver tissue samples including two liver angiosarcomas--both tumor tissue and non-tumor tissue--five normal livers, and two cirrhotic livers. The urine of patients with vinyl chloride-associated liver injury other than angiosarcoma exhibited a characteristic shift toward the chondroitin sulfates. Tissue analysis revealed up to four-fold greater concentrations of hyaluronic acid and heparin in tumor tissue than in adjacent non-tumor tissue. Angiosarcomatous livers exhibited greater concentrations of glycosaminoglycans than were found in normal livers. Biochemical results confirmed histochemical studies. One patient whose urinary glycosaminoglycan excretion patterns were followed for a two-week period prior to death from liver failure exhibited a pulse of glycosaminoglycan excretion peaking ten days prior to death. Several of these observations appear to have diagnostic significance. (Author Abstract)

224 AU - Tamburro CH ; Kupchella CE ; Greenberg R
AD - Cancer Ctr, Univ Louisville, Sch Med, Loisville, KY 40202
TI - PROSPECTIVE MEDICAL SURVEILLANCE PROGRAM FOR DETECTION AND PREVENTION OF INDUSTRIALLY RELATED CANCER (MEETING ABSTRACT).
SI - ICDB/77/03870
SO - Third International Symposium On Detection And Prevention Of Cancer. 1976.
LA - ENG
AB - Most industry related cancers have been recognized retrospectively as illustrated by vinyl chloride (VC) induced hepatic angiosarcoma. The discovery of this rare liver cancer among VC polymerization workers led to the development of a prospective industrial medical surveillance cancer control program. This program is designed to identify, at the earliest possible time, potentially harmful chemicals and to reduce

exposure related injuries. This is being accomplished by an early evaluation system relating exposure to screening studies. Screening and detection methods include biochemical, radiological, radioisotopic and immunological studies. These are applied to all members of the high risk population in, as far as possible, an economical, safe and effective method and without significant interference with industrial function or employment of workers. This prototype program includes a data bank for ongoing systematic collection and evaluation of all data obtained; it is appliable to any industrial complex utilizing potentially carcinogenic chemicals. The data bank includes an early warning system, an exposure index system and an epidemiological program. Also included is a concomitant educational program for both industry and labor concerning the new concept of preventive medical surveillance requiring voluntary participation by individuals who, for all intense purposes, are medically and physically well. Finally, this program is designed with diagnostic, therapeutic and rehabilitative components for individuals discovered to have industrial related precancerous lesions or cancer and for the adaptation to either small (250-350) or larger (1,200-2,000) industrial complexes dealing with potential carcinogenic chemicals. (Author Abstract)

225 AU - Hoffmann D ; Schmeltz I ; Hecht SS ; Brunneman KD ; Wynder EL
AD - Amer Health Found, Valhalla, NY 10575
TI - VOLATILE CARCINOGENS: OCCURRENCE, FORMATION AND ANALYSIS (MEETING ABSTRACT).
SI - ICDB/77/03780
SO - Third International Symposium On Detection And Prevention Of Cancer. 1976.
LA - ENG
AB - In certain occupational as well as general respiratory environments, we can detect known human and/or animal carcinogens. The occurrence and formation of such respiratory carcinogens will be discussed for nickel carbonyl, arsine, nitroolefins, nitrosamines, vinyl chloride and hydrazines. Special consideration is given to the detection of minute amounts of these agents in man's respiratory environment. (Author Abstract)

226 AU - Bartsch H
AD - International Agency for Research on Cancer, Unit of Chemical Carcinogenesis, 150 cours Albert Thomas, 69008 Lyon, France.
TI - TISSUE MEDIATED MUTAGENICITY AND CARCINOGENESIS (MEETING ABSTRACT).
SI - ICDB/77/03775
SO - Third International Symposium On Detection And Prevention Of Cancer. 1976.
LA - ENG
AB - Studies on the mechanism of the organotropic action of chemical carcinogens provide better criteria for an extrapolation from animal data to tumorigenic processes in man if human tissues or

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fluids are included in the experimentation. For many chemical carcinogens, the generation of specific ultimate reactive metabolites by one or multi-step activation processes and their subsequent covalent binding to information controlling cellular macromolecules is thought to induce mutagenesis and carcinogenesis. Mutagenicity assays permit a quantitative comparison of the enzymic capacity for carcinogen activation in animal and human target and non-target tissues. Tissue mediated mutagenicity of vinyl chloride and certain N-nitroso compounds was measured using S typhimurium strains in agar-plate assays containing 9,000 x g liver or lung fractions from untreated rats or from humans, either by exposing the Petri dishes to gaseous mixtures of the test compound with air (vinyl chloride, 20% by volume for 6 hours) or by incorporation of the substrate into the soft agar (0.5-10 microMol of N-nitrosamines per plate). The relative capacity of tissues from human individuals (represented by A, B, C, D, X, Y and Z) to convert various substrates into mutagens was as follows (rat = 100); vinyl chloride; A, B, C, D(275, 101, 93, 80); N-nitrosomorpholine: A, B, C, D (90, 50, 40, 30); N-nitrosopyrrolidine: Z, X, Y (115, 90, 50); N-nitrosopiperidine: Z, Y, X (215, 185, 85); N-nitroso-N'-methylpiperazine: Z, Y, X (3,200, 1800, 400). Liver fractions from untreated rats and human specimens Z and Y were unable to convert N-nitrosodi-n-propylamine and N-nitroso-di-n-butyl-amine into mutagens. With the latter two compounds a tissue mediated mutagenicity was detected with liver fractions from phenobarbitone pretreated rats. With the hepato-carcinogen N-nitrosomorpholine as substrate, no mutagenic action was detected after incubation with rat and human lung fractions. The data indicate that human liver specimens can convert some N-nitroso compounds and vinyl chloride into electrophilic mutagenic metabolites as efficiently as rat tissues. Enzymic capacity of different human specimens varied 2 to 8-fold. Analysis of a larger number of human individuals by this technique may eventually allow a correlation between genetic background or induced state of carcinogen activating enzymes and the individual susceptibility towards certain carcinogens. Organ specific activation of chemical carcinogens appears to be a prerequisite but not a finally determining factor for the induction of tumours in experimental animals and probably man: examples will be presented from the in vitro studies which support the concept that, for certain carcinogens, the formation of short-lived ultimate metabolites in situ can be correlated with the site of tumour formation. (Author Abstract)

227 AU - Elmore JD ; Wong JL ; Laumbach AD ; Streips UN
AD - Department of Chemistry, University of Louisville and Department of Microbiology, University of Louisville, Louisville, Ky. 40208 (U.S.A.)
TI - VINYL CHLORIDE MUTAGENICITY VIA THE METABOLITES CHLOROOXIRANE AND CHLOROACETALDEHYDE MONOMER HYDRATE.
SI - ICDB/77/02416
SO - Biochim Biophys Acta; 442(3):405-419 1976

LA - ENG
AB - Mutagenicity tester strains of Bacillus and Salmonella were used to assay vinyl chloride in nutrient broth at a practical concentration level. Also screened without exogenous activation were seven potential metabolites of vinyl chloride in their pure forms as well as the related epichlorohydrin. Chlorooxirane, chloroacetaldehyde, chloroacetaldehyde monomer hydrate, chloroacetaldehyde dimer hydrate, chloroacetaldehyde trimer, and epichlorohydrin produced significant mutagenic activity in Salmonella typhimurium strains sensitive to base-pair mutation. A recombination repair deficient strain of Bacillus subtilis was inhibited in growth by these compounds, whereas excision repair deficient and wild type strains of Bacillus subtilis were relatively unaffected. On the basis of these assays a working hypothesis for the vinyl chloride carcinogenesis mechanism is proposed which involves chlorooxirane and chloroacetaldehyde monomer hydrate as the ultimate carcinogenic metabolites of vinyl chloride. (Author Abstract)

228 AU - Brand KG ; Buoen LC ; Brand I
AD - Department of Microbiology, Medical School, University of Minnesota, Minneapolis, Minnesota 55455
TI - MULTIPHASIC INCIDENCE OF FOREIGN BODY-INDUCED SARCOMAS.
SI - ICDB/77/02332
SO - Cancer Res; 36(10):3681-3683 1976
LA - ENG
AB - Single or multiple plastic films (unplasticized vinyl chloride vinyl acetate copolymer) of different sizes and shapes were implanted sc in female CBA/H and CBA/H-T6 mice. Tumor incidence increased and accelerated with increased total surface area of multiple implants or with increased size of single implants. Tumor distribution curves over time were generally multiphasic. The profiles changed in proportionate relation to implant size. These findings indicate class differences between tumors according to latency. Since latency is known to be a predetermined characteristic of foreign body-induced tumors, class differences seem to exist at the originator cell level, reflecting diversity of intrinsic carcinogenic factors. (Author Abstract)

229 AU - Bartsch H ; Malaveille C ; Barbin A ; Planche G ; Montesano R
AD - International Agency for Research on Cancer, 69008 Lyon, France
TI - ALKYLATING AND MUTAGENIC METABOLITES OF HALOGENATED OLEFINS PRODUCED BY HUMAN AND ANIMAL TISSUES.
SI - ICDB/77/03874
SO - Proc Am Assoc Cancer Res; 17:17 1976
LA - ENG
AB - S typhimurium TA100 in the presence of a 9,000 x g sup of PB-pretreated mice was exposed to gaseous mixtures of I-IX/air. Mutation rates (his*** rev colonies/umol/ hr/plate) taken from linear regions of dose and time dependent assays either with or without (figures bracketed) NADP***, were as follows: I: Vinyl acetate 0(0); II: 1,1-difluoroethylene 0(0); III:

trichloroethylene 0(0); IV: vinyl chloride 6(2); V: 1,1-dichloroethylene 15(1); VI: vinyl bromide 26(9); VII: 2-chloro-1,3-butadiene 51(9); VIII: 1-chloro-1,3-butadiene 157(81); IX: 3,4-dichlorobutene-1 490(345). Liver fractions from 8 human biopsies converted compounds IV, VI, VII into mutagens with an activity comparable to those of untreated mouse liver. 1,4-Dichloro-butene-2 was mutagenic for TA100 and liver microsomal fractions from mouse or humans enhanced the mutagenic effect. Epoxide formation from vinyl chloride and vinyl bromide by mouse liver microsomes was demonstrated by trapping with 4-nitro (4-benzyl) pyridine. Using the same system, compound VII yielded an alkylating intermediate while compounds II, III and V did not. Thus, the conversion of these compounds to potential carcinogenic metabolites by human and animal tissues has been demonstrated. (Author Abstract)

230 AU - Whelan JG ; Creech JL ; Tamburro CH
AD - Department of Radiology, St. Anthony Hospital, 1313 St. Anthony Place, Louisville, Ky. 40204
TI - ANGIOGRAPHIC AND RADIONUCLIDE CHARACTERISTICS OF HEPATIC ANGIOSARCOMA FOUND IN VINYL CHLORIDE WORKERS.
SI - ICDB/76/15588
SO - Radiology; 118(3):549-557 1976
LA - ENG
AB - Hepatic angiosarcoma, recently discovered in a large series of vinyl chloride workers, demonstrates characteristic angiographic and radionuclide changes. Tumors exhibiting central hypovascularity with puddling are usually surrounded by a peripheral stain. A negative peripheral defect is demonstrated on hepatic scan. Healing hepatic infarction secondary to wedged hepatic venography creates a false-positive lesion on angiography similar to angiosarcoma. Splenomegaly and systemic venous hypertension develop in a number of these patients.

231 AU - Colvin M ; Brundrett RB ; Cowens W ; Jardine I ; Ludlum DB
AD - Johns Hopkins Oncology Center, B2-South, Baltimore City Hosps., 4940 Eastern Ave., Baltimore, MD 21224)
TI - A CHEMICAL BASIS FOR THE ANTITUMOR ACTIVITY OF CHLOROETHYLNITROSOUREAS.
SI - ICDB/77/22923
SO - Biochem Pharmacol; 25(6):695-699 1976
LA - ENG
AB - Studies are reported that are consistent with the hypothesis that chloroethyl carbonium ion generation is responsible for the cytotoxicity of chloroethylnitrosoureas against murine L1210 leukemia cells. The decomposition products of 1-chloroethyl-1-nitrosourea (CNU), 1,3-bis-chloroethyl-1-nitrosourea (BCNU), 1-chloroethyl-3,3-dimethyl-1-nitrosourea (CMCNU), 1,3-bis-fluoroethyl-1-nitrosourea (BFNU), and 1-chloroethyl-3-cyclohexyl-1-nitrosourea (CCNU) were analyzed. CCNU, BCNU, and CNU all yielded vinyl chloride, acetaldehyde, chloroethanol and dichloroethane. BFNU yielded the corresponding

fluoro compounds fluoroethanol and vinyl fluoride, as well as acetaldehyde. Evidence is presented that these products are derived from an intermediate haloethyl carbonium ion. Decomposition of dMCNU did not yield vinyl chloride, chloroethanol, or dichloroethane, but it did produce acetaldehyde along with smaller quantities of two other unidentifiable volatiles. The decomposition rate of CNU in aqueous soln proceeds rapidly, that of BCNU less so, and that of dMCNU very slowly. Both BCNU and CNU were very cytotoxic to L1210 cells in vitro at 25 nanomoles (nmol)/ml, but dMCNU had no effect on the viability of these cells at concentrations to 100 nmol/ml. (20 Refs)

232 AU - Selikoff IJ
TI - CARCINOGENS IN THE HUMAN ENVIRONMENT.
SI - CARC/77/04949
SO - Advances in Cancer Surgery. Najarian JS, Delaney JP, ed. New York, Stratton Intercontinental Medical Book Corp, 1976.
LA - ENG
AB - Estimates indicate that 60%-95% of human cancer is due to environmental causes. Associations have been demonstrated between bladder cancer and aromatic amines, scrotal cancer and chimney ash, lung cancer and cigarette smoking, and bladder cancer and aniline dyes. In most cases, there is a long latent period between onset of exposure to an environmental carcinogen and first clinical evidence of disease. Prospective cohort studies in asbestos workers have repeatedly shown an excess of deaths due to cancer (bronchogenic cancer, mesothelioma, gastrointestinal cancer). Less than 3 mo exposure to asbestos can result in an important increase in cancer risk. However, excess deaths due to bronchogenic cancer among asbestos workers occur only among cigarette smokers, the result of multiple factor interaction. Cigarette smoking is also associated with increased lung cancer among uranium miners, and occupational exposure to benzene with increased risk of leukemia among survivors of the Hiroshima bombing. Dissemination of asbestos from industrial sources is also associated with a significant cancer risk; pleural plaques and mesothelioma are increased in persons living with asbestos workers or near asbestos mills, and asbestos bodies are routinely found in lung smears from routine autopsies. Potential causes of cancer include the contamination of Lake Superior by taconite tailings and the dissemination of vinyl chloride into the general environment. (No references)

233 AU - Lassiter DV
AD - Occupational Safety and Health Admin., US Dept. Labor, Washington, DC 20210
TI - CASE STUDY 3: VINYL CHLORIDE--BEST AVAILABLE TECHNOLOGY.
SI - ICDD/77/21773
SO - Ann NY Acad Sci; 271:176-178 1976
LA - ENG
AB - Several tumors have been directly linked with occupational exposure to various carcinogens. Guidelines that determine policy for the regulation of occupational carcinogens, as set forth by

the Occupational Safety and Health Administration, are quoted and commented upon. Any regulations should ideally assure minimum risk of cancer to the employee while allowing the manufacturer to remain competitive in a situation in which costly controls must be instituted to restrict exposure. (0 Refs)

234 AU - Lloyd JW
AD - Natl. Inst. Occupational Safety and Health, Public Health Service Center Occupational Safety and Health, Rockville, MD 20852
TI - CANCER RISK AMONG WORKERS EXPOSED TO CHLOROPRENE.
SI - ICDB/77/21768
SO - Ann NY Acad Sci; 271:91-93 1976
LA - ENG
AB - The limited information on the potential carcinogenicity of chloroprene is discussed, along with some recently initiated assessments of this carcinogenicity. Chloroprene is used primarily as a monomer for the manufacture of neoprene synthetic rubber (introduced by duPont in 1931). No excess of any disease related to vinyl chloride, including angiosarcoma of the liver, has been observed at duPont upon investigation of employees' records. Although a recent increase in deaths from lung cancer in this population was observed, further investigation revealed no relationship to work assignment. Two studies of approx 45,000 chloroprene workers in Russia are also discussed with respect to the development of lung and skin cancer in these individuals. (2 Refs)

235 AU - IARC Working Group
TI - BENZYL CHLORIDE.
SI - ICDB/77/21735
SO - IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man. Cadmium, Nickel, Some Epoxides, Miscellaneous Industrial Chemicals and General Considerations on Volatile Anaesthetics. International Agency for Research on Cancer, Lyon France, Vol 11, 1976.
LA - ENG
AB - The chemical and physical data; production, use, occurrence, and analysis; and biological data relevant to the evaluation of carcinogenic risk to man of benzyl chloride are described. Approx 65%-70% of the total US production of benzyl chloride is used as an intermediate in the manufacture of butyl benzyl phthalate, a vinyl resin plasticizer. Of 14 14-wk-old BD rats given weekly sc injections of 40 mg/kg body wt benzyl chloride in arachis oil for 51 wk (total dose, 2.1 g/kg), 3 developed local sarcomas within 500 days. Of eight rats given 80 mg/kg weekly for 51 wk (total dose, 3.9 g/kg), six developed local sarcomas by 500 days. Lung metastases were observed in most animals. The injection of arachis oil alone did not produce local tumors in control rats. (18 Refs)

236 AU - Smith PM ; Crossley IR ; Williams DM
AD - Dept. Medicine, Llandough Hosp., Penarth, South Glamorgan, Wales
TI - PORTAL HYPERTENSION IN VINYL-CHLORIDE PRODUCTION WORKERS.
SI - ICDB/77/21715
SO - Lancet; 2(7986):602-604 1976
LA - ENG
AB - Portal hypertension was observed in seven patients who had been involved in the production of vinyl-chloride monomer (VCM) for 4-15 yr. The patients were 36-57 yr old at the time of presentation, and they had been exposed to VCM gas for 4-15 yr. Four had hematemesis from esophageal varices, and two of these had had prior splenomegaly and thrombocytopenia. At laparotomy, the liver appeared finely nodular and cirrhotic, but biopsy revealed a noncirrhotic fibrosis in four patients and slight fibrosis in two. Of the four patients who bled from the esophageal varices, one died 2 mo after an esophageal transection from hepatic failure and Escherichia coli septicemia. The other three have done extremely well after end-to-side portacaval shunts. They have survived so far for 3, 6, and 8 yr, respectively. With improvements in technology, workers should no longer be exposed to VCM gas levels > 5 ppm. (15 Refs)

237 AU - Watanabe PG ; Hefner RE ; Gehring PJ
AD - Toxicology Res. Lab., Health and Environmental Res. 1803 Building, Dow Chemical Company, Midland, MI 48640
TI - VINYL CHLORIDE-INDUCED DEPRESSION OF HEPATIC NON-PROTEIN SULFHYDRYL CONTENT AND EFFECTS ON BROMOSULPHALEIN (BSP) CLEARANCE IN RATS.
SI - ICDB/77/21683
SO - Toxicology; 6(1):1-8 1976
LA - ENG
AB - The effects of acute inhalation exposure to vinyl chloride on the non-protein sulfhydryl content in male Sprague-Dawley rat liver were studied. The rats were exposed to 2,000, 1,000, 250, 150, 50, or 10 ppm. Exposure to 2,000 ppm resulted in a progressive depression of hepatic non-protein sulfhydryl content reaching 33% within 2 hr, 47% after 4 hr, and 62% after 7 hr. An apparent max depression was observed after 4 to 5 hr of exposure to vinyl chloride at 1,000, 250 or 50 ppm. Depression after 7 hr exposure to 50 ppm was inconsistent. Exposure to 1,000 ppm vinyl chloride did not alter the serum clearance of bromosulphalein. (25 Refs)

238 AU - Potter HR
AD - No affiliation given
TI - VINYL CHLORIDE--PART I.
SI - ICDB/77/20548
SO - Food Cosmet Toxicol; 14(4):347-349 1976
LA - ENG
AB - Workers involved in the production of polyvinyl chloride (PVC) are exposed to differing levels of vinyl chloride monomer, the greatest exposure being to those involved in cleaning the polymerization autoclaves. These exposures can lead to

acro-osteolysis and to angiosarcoma. Less severe exposure can occur during the subsequent processing of PVC, and although clinical changes may not be manifest, patholoqical tests detect effects characteristic of clinically advanced cases. An association of PVC manufacture with hemangiosarcoma was first suspected as a result of several deaths in the industry from this otherwise rare type of liver tumor. Systematic tests carried out in an attempt to relate liver abnormality to VC exposure levels revealed two cases of angiosarcoma and nine cases of portal fibrosis in 274 PVC production workers, and two cases of portal fibrosis in 909 workers not associated with PVC production in a Louisville plant. (no refs)

239 AU - Andrews AW ; Zawistowski ES ; Valentine CR
AD - Frederick Cancer Res. Center, Frederick, MD 21701
TI - A COMPARISON OF THE MUTAGENIC PROPERTIES OF VINYL CHLORIDE AND METHYL CHLORIDE.
SI - ICDB/77/20359
SO - Mutat Res; 40(3):273-276 1976
LA - ENG
AB - The mutagenic properties of vinyl chloride and methyl chloride were compared in Salmonella typhimurium tester strain TA 1535. A level of 23% methyl chloride was toxic to the bacteria; an inhibitory level of vinyl chloride was not reached. With the exception of 0.5% methyl chloride, all concentrations of both chemicals (0.4-15.4% vinyl chloride and 0.5-23% methyl chloride) caused a significant number of revertants. Because of the similar properties of these gases and because vinyl chloride is a mutagen/carcinogen, methyl chloride should be considered and investigated as a possible carcinogen. (9 refs)

240 AU - Fishbein L
AD - Natl. Center Toxicological Res., Jefferson, AR 72079
TI - INDUSTRIAL MUTAGENS AND POTENTIAL MUTAGENS. I. HALOGENATED ALIPHATIC DERIVATIVES.
SI - ICDB/77/20357
SO - Mutat Res; 32(3/4):267-307 1976
LA - ENG
AB - Many industrially and environmentally significant halogenated aliphatic derivatives are discussed in terms of their use patterns, residue levels and distribution patterns, chemical and physical properties, and metabolism. Halogenated hydrocarbons are discussed in general, while mutagenic and potential mutagenic halogenated aliphatic derivatives are specifically discussed. These derivatives include vinyl chloride, vinylidene chloride, trichloroethylene, tetrachloroethylene, ethylene dichloride and dibromide, chloroprene, chloroform, carbon tetrachloride, fluorocarbons, epichlorohydrin, 2-chloroethanol, and haloethers. (242 refs)

241 AU - Maltoni C
AD - Inst. Oncology and Tumour Centre, Bologna, Italy
TI - PRECURSOR LESIONS IN EXPOSED POPULATIONS AS INDICATORS OF OCCUPATIONAL CANCER RISK.
SI - ICDB/77/20224
SO - Ann NY Acad Sci; 271:444-447 1976
LA - ENG
AB - Occupational cancer risk was monitored on two separate occasions by cytological examinations. The first involved three groups of workers who were known or suspected of being at risk for developing pulmonary cancer: chromium industry workers, vinyl chloride-polyvinyl chloride (VC-PVC) industry workers, and workers at different chemical factories not directly involved in the production or use of known carcinogens. The results of sputum cytology showed that the incidence of abnormal cases was higher than expected among chromium and VC-PVC workers, even when compared to populations of heavy smokers. The second occasion was the cytologic investigation of urinary sediments in a group of Italian dye stuff factory workers exposed to aromatic amines and, therefore, at risk for urinary tract tumors. A high incidence of 1% for Class III cytology and over was obtained. These results indicate both the value and need for cytologic examinations as preventive measures that can be taken to overcome occupational risks of carcinogenesis. (no Refs)

242 AU - Kappus H ; Bolt HM ; Buchter A ; Bolt W
AD - Inst. Toxicology, Univ. Tubingen, W. Germany
TI - LIVER MICROSOMAL UPTAKE OF [**14C] VINYL CHLORIDE AND TRANSFORMATION TO PROTEIN ALKYLATING METABOLITES IN VITRO.
SI - ICDB/77/20169
SO - Toxicol Appl Pharmacol; 37(3):461-471 1976
LA - ENG
AB - Microsomal uptake and irreversible binding of vinyl chloride (VC) radioactivity were determined in Wistar rat liver microsomes incubated with [1,2-**14C] vinyl chloride, gas in an all-glass vacuum system. Both the uptake of VC by microsomes and the alkylation of proteins by VC were dependent on incubation time, enzymatically active microsomes, NADPH, oxygen, and the partial pressure of VC in the atmosphere, and could be inhibited by carbon monoxide. Incubation in the presence of NADPH resulted in a 10-x increase in the amount of VC taken up by microsomes. Uptake of VC by albumin solutions and liposomal suspensions was one-third to one-fourth of the microsomal uptake in the absence of NADPH. Addition of glutathione and cytoplasmic fractions to microsomal incubations with NADPH resulted in an increase in VC uptake and a decrease in protein alkylation by VC metabolites. Trichloropropane oxide had no effect on microsomal VC uptake but caused a 2-fold increase in the amount of protein bound by VC metabolites. The results are consistent with the involvement of chloroethylene oxide as the primary microsomal metabolite of VC capable of reacting with proteins. (31 Refs)

243 AU - Duck BW ; Carter JT
AD - Occupational Health Unit, B.P. Res. Centre, Sunbury-on-Thames, Middlesex, England
TI - VINYL CHLORIDE AND MORTALITY? (LETTER TO EDITOR).
SI - ICDB/77/20159
SO - Lancet; 2(7978):195 1976
LA - ENG
AB - Dr. Joan Davis has pointed out the value of additional tabulation of deaths more than 15 yr after first exposure of vinyl chloride in those exposed for at least 15 yr. The observed vs expected deaths were 25:24.15 for all causes, 8:6.51 for all cancer, 4:1.98 for digestive system cancer, and 3:2.96 for lung cancer. An age-standardized death rate can be calculated only if the age structure of the population is known. (2 Refs)

244 AU - Kappus H ; Kaufmann R ; Appel KE ; Bolt HM
AD - Inst. Toxicology, Univ. Tubingen, Wilhelmstr. 56, Tubingen, W. Germany
TI - COVALENT BINDING OF **14C-VINYL CHLORIDE TO PROTEINS AND NUCLEIC ACIDS IN VITRO AND IN VIVO (MEETING ABSTRACT).
SI - ICDB/77/20020
SO - Arch Pharmacol; 293(Suppl): R 64 1976
LA - ENG
AB - When rat liver microsomes were incubated in atmospheric air containing C14-vinyl chloride (VC) gas, a max of 0.5 nanomoles of VC metabolites was covalently bound to microsomal protein. RNA and sulfhydryl-containing proteins bound VC metabolites when added to the incubation medium. All these microsome binding reactions could be inhibited by 1-naphthyl-4(5)-imidazole and CO. The addition of glutathione plus cytoplasmic fractions decreased the covalent binding of VC metabolites to microsomal proteins while the total metabolism of VC during incubation was enhanced. There was a two-fold increase in the covalent binding of VC metabolites to microsomal proteins when trichloropropene oxide was in the medium. The results support the concept that chloroethylene oxide formed by microsomal enzymes via an epoxidation step is involved in covalent binding of VC to proteins. After exposure of rats to C14-VC gas, VC-derived radioactivity incorporated into proteins was mostly detected in the liver, lung, kidney, and spleen. VC radioactivity was also incorporated into DNA and RNA isolated from rat liver. These results support the view that VC-induced carcinogenicity is caused by the alkylation of nucleic acids and/or proteins by a reactive metabolite of VC. (0 Refs)

245 AU - Wagoner JK ; Infante PF ; Saracci R
AD - Div. Surveillance, Hazard Evaluations and Field Studies, Natl. Inst. Occupational Safety and Health, Cincinnati, OH 45202
TI - VINYL CHLORIDE AND MORTALITY? (LETTER TO EDITOR).
SI - ICDB/77/19924
SO - Lancet; 2(7978):194-195 1976
LA - ENG
AB - The article by Duck on a decreased risk of death with increasing exposure to vinyl chloride is discussed. If, in this study, one selects a subgroup of workers by the fact that they have achieved 15 yr experience exposure, then none of these workers could have died before the 15th anniversary. Information on risk of dying can only come from the number of man years at risk and the number of deaths after 15 yr. When this factor is corrected, the death rate tends to increase with increasing duration of exposure. This example of misallocation of person years at risk, the resultant erroneous conclusions, and subsequent reference to these conclusions demonstrate the need for standardization of data handling techniques for cohort mortality studies. (13 Refs)

246 AU - Fishbein L
TI - ATMOSPHERIC MUTAGENS.
SI - CARC/77/04263
SO - Chemical Mutagens, Principles and Methods for Their Detection. Hollaender A, ed. New York, Plenum Press, vol. 4, 1976.
LA - ENG
AB - The source and effect of atmospheric mutagens on man are discussed. Various pollutants are the products of man's own waste: sulfur oxides, nitrogen oxides, polynuclear aromatic hydrocarbons, peroxyacyl nitrates and miscellaneous oxygenated derivatives. Many of these compounds, such as benzo(a)pyrene and dibenzanthracene, are mutagenic. Drastic disturbances in respiratory function have been attributed to ozone, and a variety of studies have indicated that it is a general mutagenic agent. Various halogenated hydrocarbons with mutagenic properties have now been located throughout the world. These hydrocarbons include fluorocarbons, vinyl chloride, trichloroethylene, tetrachloroethylene, carbon tetrachloride, miscellaneous halogenated hydrocarbons, and bromoalkanes. Fluorine, another mutagen that is worldwide in distribution, is prevalent in urban settings. Studies have shown the mutagenic potential of sodium fluoride in a variety of female mammalian germ cells. Other mutagenic compounds that are discussed are pesticides and related compounds (DDT and its metabolites, dichlorvos, formaldehyde and ethylene oxide) and polychlorinated biphenyls and aerosols (lead, mercury). Information is sparse or lacking on many of these mutagens and on aspects of their transport, residence times, and stability. The fate and mutagenic hazard to man of many of these compounds, particularly halogenated hydrocarbons, is speculative. (606 Refs)

247 AU - Hoffman D ; Wynder EL
TI - ENVIRONMENTAL RESPIRATORY CARCINOGENESIS.
SI - ICDB/77/19233
SO - Chemical Carcinogens. Searle CE, ed. Washington DC, American Chemical Society, American Chemical Society Monograph 173, 1976.
LA - ENG
AB - Environmental respiratory carcinogenesis is discussed. The topics include industrial carcinogens, radioactive aerosols, arsenicals, chromium, nickel, coke oven effluents, chloromethyl ethers, vinyl chloride, and nitrosamines. Air pollution is discussed in terms of epidemiological considerations, laboratory studies, sources for atmospheric carcinogens, indoor pollution, and reduction of atmospheric carcinogens. Tobacco smoke is discussed in terms of some epidemiological observations, characteristics of tobacco smoke, experimental tobacco carcinogenesis, and reduction of tumorigenicity. (148 refs)

248 AU - Shahin MM
AD - Dept. Genetics, Univ. Alberta, Edmonton, Alberta T6G 2E9, Canada
TI - THE NON-MUTAGENICITY AND -RECOMBINOGENICITY OF VINYL CHLORIDE IN THE ABSENCE OF METABOLIC ACTIVATION.
SI - ICDB/77/18892
SO - Mutat Res; 40(3):269-272 1976
LA - ENG
AB - The ability of vinyl chloride to induce reversion and mitotic recombination in the yeast Saccharomyces cerevisiae was investigated. Strain D5 was chosen for study of the induction of recombinational events and XV185-14C was chosen for reversion induction in mutants. Negative results were obtained for mutagenicity and recombinogenicity of vinyl chloride. Vinyl chloride had no effect on viability, even at a concentration as high as 0.55% and treatment up to 48 hr. The results demonstrate that vinyl chloride is not mutagenic or recombinogenic in yeast under these experimental conditions. (7 refs)

249 AU - Davis W ; Maltoni C
AD - International Agency for Research on Cancer, 150 cours Albert-Thomas, 6 9008 Nyon, France
TI - BIOLOGICAL CHARACTERIZATION OF HUMAN TUMORS.
SI - ICDB/77/18825
SO - Adv Tumor Prev Detect Charact; 3:1-424 1976
LA - ENG
AB - Lectures and papers presented at the Sixth International Symposium on the Biological Characterization of Human Tumors, Copenhagen, May 13-16, 1975, are grouped into chapters covering the biochemical guidelines in cancer chemotherapy (17 papers), comparisons of classical and modern techniques for the characterization of tumors (5), the carcinogenicity of vinyl chloride (4), malignant melanoma (6), hormones and cancer (4), and clinical and experimental studies (10). Epidemiologic studies indicate that the incidence of malignant melanoma is related to the amount of skin exposed to sunlight. Histologic classification

is discussed, particularly in relation to prognosis, and the possibilities for immunotherapy of this tumor are considered. The problems of surgery and application of hyperthermic treatment are also discussed. The role of hormones is considered in relation to cancer of the breast, cervix, and endometrium. (refs)

250 AU - Schaffner F ; Popper H ; Selikoff IJ
AD - Mount Sinai Sch. Medicine, City Univ. New York, New York, NY 10029
TI - INITIAL FEATURES OF VINYL CHLORIDE (VC) HEPATIC INJURY (MEETING ABSTRACT).
SI - ICDB/77/18775
SO - Gastroenterology; 71(5):A35/928 1976
LA - ENG
AB - An attempt was made to define the vinyl chloride (VC)-induced lesions in the livers of mice after exposure to gaseous VC 5 hr/day, 5 days/wk for 1, 3 and 6 mo at 2,500 and 6,000 ppm. Animals were also studied 1 mo after exposure ceased. Hepatocellular changes seen as early as 1 mo included hypertrophy of the <smooth endoplasmic reticulum, reflecting metabolism of VC and plasma membrane loss of microvilli and invagination. These findings reflected a movement of a possible injurious metabolite across the membrane. The sinusoidal reaction was multicellular. The size and number of lipocytes was increased with little fibrosis. These cells appeared normal except during recovery, when their fat content decreased in a patchy fashion. Macrophages were large and filled with phagosomes, some containing long needle-like crystals. Lymphocytes were numerous, but no plasma cells were seen. The main abnormality involved the endothelial lining cells. Early changes resembled swollen cells; later, the bulky, and, in places, multilayered cells contained more organelles, especially mitochondria and endoplasmic reticulum (ER) but no phagosomes. Discontinuities developed in the sinusoidal walls so that RBC were not only in but also around sinusoids dilated by beginning peliosis hepatis. Platelet thrombi were also seen in and around sinusoids. The lining cells, probably the precursors of angiosarcoma, resembled fibroblasts but nowhere did their ER contain fluffy collagen components. These observations suggest that VC is metabolized in hepatocytes, and that metabolites leave these cells through the plasma membrane to injure sinusoidal lining cells, eventually producing angiosarcomas. Attempts at screening for VC hepatic injury should be directed at endothelial cells and altered microcirculation rather than at hepatocytes, macrophages or fibroblasts. (no refs)

251 AU - Infante PF ; Wagoner JK ; Waxweiler RJ
AD - Division Surveillance, Natl. Inst. Occupational Safety and Health, Main Post Office Building, Cincinnati, OH 45202
TI - CARCINOGENIC, MUTAGENIC AND TERATOGENIC RISKS ASSOCIATED WITH VINYL CHLORIDE.
SI - ICDB/77/17043
SO - Mutat Res; 41(1):131-142 1976
LA - ENG
AB - Results of an epidemiological survey of cancer, birth defects and

fetal mortality in groups of people with some kind of exposure to vinyl chloride (VC) are presented. In a cohort of workers occupationally-exposed to VC for at least 5 yr and for whom at least 15 yr had elapsed since the time of initial exposure, observed/expected deaths from all cancers, brain and CNS cancers, respiratory system cancers, biliary and liver cancers, lymphatic and hematopoietic system cancers were 31/16.9, 3/0.6, communities with VC polymerization facilities, observed/expected deaths for CNS cancer, leukemia and aleukemia, and lymphomas were 38/24, 47/48.1 and 61/48.7 respectively, and observed/expected rate of congenital malformation (per 1000 live births) was 73/40.8. The fetal mortality rate among wives of workers exposed to VC was assessed by questionnaire and interview surveys to have been 10.1% prior to their husband's exposure to VC; after such exposure, the rate was increased to 16.5%, with the excess in fetal mortality being associated with younger-aged husbands. (30 refs)

252 AU - Szentesi I ; Hornyak E ; Ungvary G ; Czeizel A ; Bognar Z
AU - Timar N
AD - Lab. Human Genetics, Natl. Inst. Hygiene, H-1966 Budapest, Gyali ut 2-6, Hungary
TI - HIGH RATE OF CHROMOSOMAL ABERRATION IN PVC WORKERS.
SI - ICDB/77/16454
SO - Mutat Res; 37(2-3):313-316 1976
LA - ENG
AB - Chromosome examinations were performed on 45 polyvinyl chloride (PVC) workers exposed to vinyl chloride for 0.5 to 12 yr. Two control groups were used. The first was composed of 44 industrial workers who were not exposed to PVC and were only indirectly exposed to other chemicals. The second control group was composed of 49 individuals who had no occupational exposure to chemicals. The rate of numerical chromosome aberrations did not differ significantly between PVC workers and either control group. The frequency of chromatid-type aberrations was higher in PVC workers than in either control group. Unstable chromosome-type aberrations were also significantly higher in PVC workers. The PVC workers who showed a significantly higher frequency of chromatid -type abberations or unstable chromosome-type aberrations had been exposed to the compound for longer periods than other PVC workers. They are to undergo a clinical check-up to determine whether they can continue in their present occupations. (17 refs)

253 AU - Salmon AG
AD - Central Toxicology Lab., Imperial Chemical Industries Limited, Alderley Park, North Macclesfield, Cheshire SK10 4TJ, UK
TI - CYTOCHROME P-450 AND THE METABOLISM OF VINYL CHLORIDE.
SI - ICDB/77/15198
SO - Cancer Lett (Amsterdam); 2(2):109-114 1976
LA - ENG
AB - The involvement of cytochrome P-450 in vinyl chloride metabolism was studied. Rat liver microsomes were obtained from male Alderly

Park strain SPF albino rats (weighing 150-200 g), and [U-C14]vinyl chloride (1 mCi/millimole) was utilized. Enzymic oxidation of vinyl chloride was assayed by the formation of nonvolatile products. There was a time-dependent increase in the amount of label incorporated into nonvolatile water-soluble material. The reaction rate remained constant for 15 min but decreased later, possibly due to exhaustion of substrates and further metabolism of products. Label was not incorporated into either the soluble or solid fractions in the absence of microsomes or NADPH or in the presence of microsomes previously heated to 100 C for 5 min. Addition of 1 mM reduced glutathione to the reaction mixture increased the microsome-catalyzed formation of nonvolatile water-soluble products. In the absence of active enzymes, there was no reaction of vinyl chloride with glutathione. The concentration of cytochrome P-450 was found to be 0.6 nanoM/mg protein. Addition of 100 microM phenobarbital to a microsome suspension increased absorbance at 390 nanometers and decreased it at 420 nanometers (a typical type 1 difference spectrum). A similar difference spectrum was demonstrated after saturation of a microsomal suspension with vinyl chloride. The type 1 difference spectrum suggests an interaction with a cytochrome P-450 present in liver microsomes without induction. (12 refs)

254 AU - Anderson D ; Hodge MC ; Purchase IF
AD - Imperial Chemical Industries Ltd., Central Toxicology Lab., Alderley Park, North Macclesfield, Cheshire SK10 4TJ, England
TI - VINYL CHLORIDE: DOMINANT LETHAL STUDIES IN MALE CD-1 MICE.
SI - ICOB/77/13863
SO - Mutat Res ; 40(4):359-370 1976
LA - ENG
AB - The mutagenic activity of vinyl chloride (VC) was investigated in CD-1 mice by the dominant lethal test at inhalation exposure levels of 30,000, 10,000 and 3,000 ppm (6 hr/day for 5 days). The only significant mortality occurred in the groups exposed to the highest level of VC. Mice were also given ethyl methanesulfonate (200 mg/kg/day x 5, po) or cyclophosphamide (200 mg/kg on day 5, ip). Cyclophosphamide or methanesulfonate treatment increased the number of pregnancies with early deaths. The effect was significant in weeks 1 and 2 for the cyclophosphamide-treated group and week 2 for the methanesulfonate-treated group. No differences from controls were observed in the VC-treated group. As indicated by the total implants per pregnant female, VC caused no preimplantation egg losses. As demonstrated by the number of females with one or more early deaths, the number of early deaths/pregnancy, or the number of early deaths/total implants/pregnancy, VC caused no significant increase in the number of postimplantational early fetal deaths. It is concluded that, although mutagenic effects of VC have been reported, no such effects, as determined in the present study, occur in the germ cells of CD-1 mice. (14 refs)

255 AU - Douglas DB ; Owen R
TI - OCCUPATIONAL CANCER.
SI - CARC/77/03201
SO - The Physiopathology of Cancer. Homburger F, Brennan MJ, Krakoff I, ed. Basel, S Karger, Diagnosis, Treatment, Prevention, vol 2, 1976.
LA - ENG
AB - Occupational carcinogens, an agent or substance which induces cancer as a result of occupation, are reviewed, as are the prevention and control of occupational cancer. Most occupational cancers develop in the skin, upper and lower respiratory tracts, and urinary bladder. A recent epidemic of cases of epithelioma of the scrotum has been seen among workers exposed to mineral oils. Gases emitted from various coal carbonization processes may induce lung cancer. The relationship between 2-naphthylamine, benzidine, and human cancer is well-established but the association between human bladder cancer and other aromatic amines, such as 4-aminobiphenyl, 4-nitrobiphenyl, auramine, and magenta, is equivocal. Occupational exposure to benzene has caused leukemia. Isopropyl oil had been responsible for an increased risk of paranasal, laryngeal, and pulmonary cancer, but the hazard no longer exists because of changes in production. Exposure to leather dust in footwear manufacture and to wood dust in furniture manufacture has been linked to cancer of the nasal cavity and paranasal sinus. Workers engaged in mustard gas production have an increased risk of cancer of the paranasal sinus, larynx, and lung. The association between exposure to vinyl chloride monomer in the plastics industry and the development of a rare liver cancer has been recognized recently. Arsenic exposure has been associated with skin cancer; its association with lung cancer is less well-established, though not disproved. Exposure to asbestos has been linked with cancer of the lung, pleura, and peritoneum. In the chromate industry, workers have a risk of lung cancer 15 times that of the general population; the insoluble chromium compounds, e.g., chromate dust and chromic oxides, are the active carcinogens. Exposure to nickel compounds during refining is associated with a higher risk of cancer of the nasal sinus and lung. Exposure to UV and ionizing radiation may cause skin cancer; in addition, ionizing radiation has been linked to cancer of the hemopoietic tissues, bone, and lung. Potential occupational carcinogens include alkylating agents, such as chloromethyl methyl ether and bis (chloromethyl ether); 4,4'-methylenebis-ortho-chloroaniline; N-nitrosamine; and some compounds of nickel and beryllium. Recognized carcinogens should be replaced by less harmful agents, but where this is not practicable, environmental and personal monitoring must be carried out. (97 refs)

256 AU - Whelan JG ; Creech JL ; Tamburro CH
AD - St. Anthony Hosp., 1313 St. Anthony Place, Louisville, KY 40204
TI - ANGIOGRAPHIC AND RADIONUCLIDE CHARACTERISTICS OF HEPATIC ANGIOSARCOMA FOUND IN VINYL CHLORIDE WORKERS.
SI - CARC/77/03042
SO - Diagn Radiol; 118(3):549-558 1976
LA - ENG
AB - The angiographic and radionuclide changes associated with hepatic angiosarcoma, recently discovered in a large series of vinyl chloride workers, were illustrated. All 1,180 workers at a Louisville, KY, vinyl chloride polymerization plant were given liver scans; 50 were subsequently followed with hepatic and splenic angiography, transjugular hepatic venography, venous pressure studies, and liver biopsies. Four cases of hepatic angiosarcoma were found, and there was one false-positive case. Of the screening procedures used, the liver scan was the most useful in detecting tumors. No single biochemical liver test was consistently abnormal in these patients. The characteristic angiographic features of the angiosarcoma are peripheral tumor stain, puddling of contrast agent extending from the midarterial phase up to 34 sec, and some degree of central hypovascularity within the tumor. Transjugular hepatic pressures and biopsies are essential procedures, since systemic venous hypertension seems to develop in some workers. Subcapsular fibrosis, portal fibrosis, sinusoidal dilatation, and endothelial lining cell hyperplasia are associated with the tumors. (32 refs)

257 AU - Maltoni C
AD - Inst. Oncology and Bologna Tumour Centre, Bologna, Italy
TI - CARCINOGENICITY OF VINYL CHLORIDE: CURRENT RESULTS. EXPERIMENTAL EVIDENCE.
SI - CARC/77/02911
SO - Adv Tumor Prev Detect Charact; 3:216-237 1976
LA - ENG
AB - Partial results are presented from a series of experiments designed to study the effect of vinyl chloride (VC) administered through different routes at different concentrations, for varying periods of time, by continuous or intermittent treatment, on animals of different species (rats, mice, hamsters), strains (Sprague-Dawley and Wistar rats), sex, and age (adults, newborns, embryos). A complete autopsy was made on each animal, which was kept under observation until spontaneous death. Histological examinations were performed on Zymbal glands, interscapular brown fat, salivary glands, tongue, lungs, liver, kidneys, spleen, stomach, different segments of the intestine, bladder, brain, bones of the legs and feet, and any other organ with pathological lesions. Animals exposed to the highest doses (30,000 and 10,000 ppm), with or without tumors, were examined radiologically. When given by inhalation, VC produced the following tumors: in rats, Zymbal gland carcinomas, nephroblastomas, angiosarcomas, mammary carcinomas, and forestomach papillomas; in mice, lung adenomas, mammary carcinomas, angiosarcomas and angiomas of the liver and

other sites, skin epithelial tumors, and forestomach papillomas; and in hamsters, liver angiosarcomas, skin trichoepitheliomas, melanomas, forestomach papillomas, acanthomas, hepatomas, and lymphomas. The response was affected by the length of exposure and by the strain. The onset of tumors in the offspring of breeders exposed during pregnancy for 7 days suggests a transplacental effect. When given by stomach tube at high doses, VC induced angiosarcomas of liver and other sites and Zymbal gland carcinomas in rats. The doses producing these tumors, however, were extremely high when compared to possible human exposure. Thirty cases of liver angiosarcoma have been identified among workers of VC-PCV (polyvinyl chloride) industries in the US and several European countries. The majority of cases did not occur until 15 yr or more after the first exposure to VC. An excess mortality for cancers of the respiratory tract, blood-forming tissues, and brain has also been observed among workers of VC polymerization plants in the US. It is concluded that VC carcinogenesis has shown the value of experimental bioassays in predicting oncogenic risks. (7 refs)

258 AU - De Serres FJ
AD - Natl. Inst. Environmental Health Sciences, Research Triangle Park, NC
TI - PROSPECTS FOR A REVOLUTION IN THE METHODS OF TOXICOLOGICAL EVALUATION.
SI - CARC/77/02908
SO - Mutat Res; 38:165-176 1976
LA - ENG
AB - The impact of research programs to develop efficient assay systems for mutagenic activity to screen untested environmental chemicals and to develop better methods to determine their effect on man is considered. Food and feed additives in widespread use such as sodium nitrite, sodium bisulfite and other nitrofuran derivatives are mutagenic in experimental organisms. A nitrofuran derivative called AF-2, which was used widely as a food preservative in Japan for 10 yr, was found to be a potent mutagen and its use as a food preservative was banned. Most pesticides are also potent mutagens in experimental organisms, and ethylene dibromide, heptachlor, and chlordane are also carcinogenic in mice and rats. Atrazine, a herbicide used widely on most commercially grown corn, is converted to a potent mutagen. Hycanthone, a drug used to treat schistosomiasis, is a supermutagen in experimental organisms. Its long-term genetic effects on treated populations have not been evaluated adequately. The majority of commercial hair dyes available in the United States, England, and Japan are potent mutagens in various short-term tests for mutagenicity. Industrial chemicals that are mutagenic in experimental organisms and have been associated with occupational carcinogenesis include b-propriolactone, ethyleneimine, 4-aminobiphenyl, 4-nitrobiphenyl, bis(chloromethyl) ether, benzidine, and vinyl chloride. Vinyl chloride has produced significant levels of chromosome damage in somatic cells of exposed workers. The primary concern over the

effects of environmental mutagens on man is that exposure may produce damage in germ cells that will be transmitted to future generations. Newly developed short-term tests for mutation induction include assays for both forward and reverse mutation at specific loci and tests for inhibition of DNA repair. In the assays for mutation induction, the best correlation between carcinogenic and mutagenic activity is with Salmonella; at least 70%-75% of the carcinogens tested with this system show mutagenic activity. It is generally agreed that these short-term tests provide a mechanism for identifying potential mutagenic and carcinogenic agents and that they are most effectively used to establish priorities for testing in higher organisms. (39 refs)

259 AU - Hutt MS ; Anthony PP
TI - EPIDEMIOLOGY OF SOME HUMAN CANCERS: (3) LIVER.
SI - CARC/77/02793
SO - Scientific Foundations of Oncology. Symington T, Carter RL, ed. London, William Heinemann Medical Books Ltd, 1976.
LA - ENG
AB - A discussion is presented of the epidemiology and possible etiology of liver cancers, in particular, of hepatocellular carcinoma. Cirrhosis is a common precursor to hepatocellular carcinoma, but not to cholangiocarcinoma (bile duct carcinoma). Animal experiments indicate that the increased cell turnover associated with cirrhotic regeneration leads to a higher risk of malignant transformation. a-Fetoprotein production is seen in hepatocellular carcinoma but not in cholangiocarcinoma. The following possible etiological factors in hepatocellular carcinoma are briefly considered: parasitic infections, malnutrition, natural carcinogens, drugs, vinyl chloride, and mycotoxins (particularly, aflatoxin B1). A more detailed consideration is given to the frequent association of hepatitis B antigen (HBAg) with cirrhosis and hepatocellular carcinoma: in Uganda, 27% of patients with cirrhosis and 40% with hepatocellular carcinoma possessed HBAg compared to 3% of control subjects. It was also shown that younger persons and men were more commonly positive and that macronodular types of cirrhosis, which predominate in Uganda, were particularly associated with the presence of HBAg. (95 refs)

260 AU - Watanabe PG ; McGowan GR ; Gehring PJ
AD - Toxicology Res. Lab., Dow Chemical Co., Midland, MI 48640
TI - FATE OF (**14 C)VINYL CHLORIDE AFTER SINGLE ORAL ADMINISTRATION IN RATS.
SI - CARC/77/02613
SO - Toxicol Appl Pharmacol; 36(2):339-352 1976
LA - ENG
AB - Male Sprague-Dawley rats were given single doses of 0.05, 1, and 100 mg/kg po of **14 C-vinyl chloride (VC), and the routes and rates of elimination of **14 C activity were followed for 72 hr. Following 0.05 and 1 mg/kg, excretion in the urine as nonvolatile metabolites and as **14 CO2 in expired air accounted for 59%-68% and 9%-13%, respectively, of the administered dose. Only 1%-2% of

the dose was expired by the lungs as VC. Conversely, after 100 mg/Kg, 67% of the dose was eliminated by the lungs as VC, and urinary nonvolatile metabolites and **14 CO2 comprised 11% and 3%, respectively. Pulmonary elimination after 100 mg/kg showed an apparent biphasic clearance with half-times (t1 /2) of 14.4 and 40.8 min for the respective fast and slow phases. Following 0.05 and 1 mg/Kg, the pulmonary clearance of VC was monophasic, with t1 /2 of 53.3 and 57.8 min. The percentage of the dose remaining in the carcass after 72 hr was 10%, 11%, and 2% of the 0.05-, 1-, and 100-mg/kg doses, respectively. The urinary radioactivity was separated by high-pressure liquid chromatography into three major metabolites. Two of the three major urinary metabolites were identified as N-acetyl-S-(2-hydroxyethyl)cysteine and thiodiglycolic acid by gas chromatography-mass spectrometry. The proportions of the urinary metabolites were not influenced by dose. The fate of doses of 1-100 mg/kg VC was clearly dose-dependent. The results suggest that the metabolism of VC is a saturable process. (20 refs)

261 AU - Couderc P ; Panh MH ; Pasquier B ; Pasquier D ; N'Golet A
AU - Faure H
AD - Laboratorie d'Anatomie Pathologique, C.H.U., 38043 Grenoble Cedex, France
TI - ANGIOSARCOMA OF THE BONE REVEALING A HEPATIC TUMOR IN A VINYL CHLORIDE WORKER.
SI - CARC/77/02358
SO - Sem Hop Paris; 52(31/32):1721-1722 1976
LA - FRE
AB - A case history is presented of a vinyl chloride-induced angiosarcoma of the liver in a 38-yr-old man occupationally exposed to the chemical for 10 yr. The liver neoplasm was asymptomatic and was discovered when the patient was hospitalized for dorsal and lumbar pain increasing in intensity after a fall 5 mo previously. X-ray studies revealed osteolysis and compression of the lumbar vertebrae and a portion of the 5th rib missing. Myeloma and thyroid, kidney, and prostate neoplasms were ruled out by diagnostic studies. A costal tumor was removed and diagnosed as an angiosarcoma, rare in bones, particularly costal and vertebral bones. Subsequently, the hepatic tumor was diagnosed by scintigraphy, arteriography, etc. A spontaneous rupture of the hepatic tumor required emergency intervention; however, the patient died. Multiple bone tumors as well as a subcapsular angiosarcoma occupying the right lobe of the liver were found at autopsy. It was not determined whether the multiple tumors were primary multifocal neoplasms or metastases of the hepatic tumor. (5 refs)

262 AU - Preussmann R
AD - Deutsches Krebsforschungszentrum, Institut fur Toxikologie und Chemotherapie, Im Neuenheimer Feld 280, D-6900 Heidelberg, West Germany
TI - CHEMICAL CARCINOGENS IN THE HUMAN ENVIPONMENT: PROBLEMS AND QUANTITATIVE ASPECTS.
SI - CARC/77/02335
SO - Oncology; 33(2):51-57 1976
LA - ENG
AB - A review is given of the concept of environmental causation of human cancer. The problem of determining risk evaluations and preventive measures involves determination of a chemical's carcinogenicity and the monitoring and quantification of environmental carcinogens. Although some chemicals are clearly carcinogenic, others such as cyclamates are questionable. Currently environmental carcinogens are not being monitored regularly, partly because determination of trace quantities is analytically difficult and standardized reference methods have not been adopted. Problems that enter into quantification of environmental carcinogens and risk evaluation are discussed. Environmental levels of polycyclic aromatic hydrocarbons (PAH), aflatoxins, vinyl chloride (VC), and N-nitroso compounds are compared to the doses necessary to experimentally induce tumors. Exposure to PAH, the best representative of which is benz(a)pyrene (BP), is mainly via ingestion and inhalation. Among aflatoxins, which grow well in food products under certain conditions, aflatoxin B is the most potent hepatocarcinogen known. Occupational exposure to VC is causally connected with the induction of human angiosarcoma of the liver. Industrial discharge of VC and the use of PVC as a packaging material for food are sources of exposure of the general population. Several aspects of carcinogenic N-nitroso compounds are reviewed, including their content in food products. With the exception of aflatoxins, quantities of single carcinogens may be subthreshold. In view of syncarcinogenic and other enhancing and/or modifying effects, however, the probability of multifactorial cause of human cancer does not allow the definition of safe levels. (28 refs)

263 AU - VomBruck CG ; Eckert WR ; Rudolph FB
AD - Unilever Gesellschaft mbH, Hamburg, West Germany
TI - MIGRATION OF VINYL CHLORIDE FROM PVC PACKAGINGS.
SI - CARC/77/02186
SO - Fette Siefen Anstrichm; 78(8):334-337 1976
LA - GER
AB - Gas chromatographic assay of vinyl chloride (VC) migration in polyvinyl chloride (PVC) or fat simulant HB 307 was made by Puschmann's method with a sensitivity of 0.00001% (0.1 mg/kg) for PVC and 0.000001% (0.01 mg/kg) for HB 307. VC migration from PVC was directly proportional to the initial VC concentration. In two separate PVC samples the VC level fell from 0.006% to 0.002% and from 0.0017% to 0.0006% after 35 days. At 20 C a linear relation

was also obtained for the VC flow into HB 307 for 100 days. At 40 C a max VC concentration was reached in HB 307 in 50-60 days, after which the level gradually fell. The appearance of a max suggests a reflux from HB 307 through PVC into the ambient atmosphere. On the average, an adult will consume about 1 kg of packaged food per day. Since only a small fraction of that kilogram is in PVC packaging, the threat of VC contamination, even at a 0.006% concentration in PVC, is very small. (4 refs)

264 AU - French JE ; Andersen ME ; Jenkins LJ
AD - Experimental Pathology Dept., AFRRI-NNMC, Bethesda, MS 20014
TI - VINYLIDENE CHLORIDE-INDUCED ULTRASTRUCTURAL CHANGES IN RAT LIVER (MEETING ABSTRACT).
SI - CARC/77/01991
SO - J Cell Biol; 70(2/Part2):361a 1976
LA - ENG
AB - Vinyl chloride and vinylidene chloride(1,1-dichloroethylene, DCE) are closely related chemicals and are known occupational and environmental contaminants. The pathobiological effects after oral administration of DCE (in corn oil) to fasted male Holtzman rats was determined by correlating the ultrastructural damage to the liver with changes in the serum levels of glutamic-pyruvic transaminase (SGPT) and glutamic-oxaloacetic transaminase (SGOT). In a completely randomized study, fasted rats received a single oral dose of 40 to 80 mg DCE/kg of body wt. After 0, 1, 2, 4, and 8 hr, SGPT and SGOT values were determined and liver tissue samples were immersion fixed in 3% cacodylate buffered glutaraldehyde, post-fixed in osmium tetroxide and prepared by conventional EM methods. SGPT and SGOT values increased dramatically according to dosage and time of exposure in a linear manner, which indicated significant hepatic damage. The appearance of myelin-like bodies occurred at a similar frequency in both control and treated rats. Control rats were also characterized by slightly dilated rough endoplasmic reticulum(RER) and perinuclear cisternae. However, DCE-exposed rats showed significant dilation of the RER, loss of ribosomes, mitochondrial swelling, loss of cristae and chromatinolysis in a dose and time related manner. Margination of the chromatin along the nuclear envelope (chromatinorrhexis) did not occur within this time period of exposure and dosage of DCE. DCE is a very hepatoxic xenobiotic and its pathobiology may be different according to the route of administration. (No refs)

265 AU - Watanabe PG ; McGowan GR ; Madrid EO ; Gehring PJ
AD - Toxicology Res. Lab., Dow Chemical Co., Midland, MI
TI - FATE OF (**14 C)VINYL CHLORIDE FOLLOWING INHALATION EXPOSURE IN RATS (MEETING ABSTRACT).
SI - CARC/77/01962
SO - Toxicol Appl Pharmacol; 37(1):93-94 1976
LA - ENG
AB - The objective of the present study was to determine the rate of inhaled (**14 C)vinyl chloride (**14 C-VC) at different exposure concentrations in rats. Male rats were exposed to 10 or 1000

ppm(**14 C)VC for 6 hr and the routes and rates of elimination of **14 C activity were followed for 72 hr after termination of exposure. Following exposure to 10 ppm VC, urinary **14 C activity and expired VC comprised 68 and 2% respectively, of the recovered radioactivity. After exposure to 1000 ppm VC, the proportion of the radioactivity in the urine decreased while that expired as VC increased, representing 56 and 12% respectively. The pattern of pulmonary elimination of VC per se was prescribed by similar monoexponential processes following 10 or 1000 ppm with respective half-lives of 20.4 and 22.4 min. The elimination of **14 C in the urine was described by a biexponential process; the half-lives for the initial phase of excretion were 4.6 and 4.1 hr following 10 and 1000 ppm, respectively. The percentage of the recovered **14 C remaining in the carcass after 72 hr was 14 and 15% at the respective low and high exposure levels. The **14 C remaining in the tissues was comprised primarily of nonvolatile metabolites of VC rather than VC per se. The urinary **14 C was separated by high-pressure liquid chromatography into three major metabolites corresponding to N-acetyl-S-(2-hydroxyethyl)cysteine, thiodiglycolic acid, and a third unidentified metabolite. The proportions of the urinary metabolites were not markedly influenced by the exposure magnitude. The fate of inhaled (**14 C)VC was shown to be dose-dependent and this is consistent with previous studies on the fate of VC following ingestion.

266 AU - Kraybill HF
AD - NCI, NIH, Bethesda, MD 20014
TI - DISTRIBUTION OF CHEMICAL CARCINOGENS IN AQUATIC ENVIRONMENTS.
SI - CARC/77/01664
SO - Prog Exp Tumor Res ; 20:3-34 1976
LA - ENG
AB - Various contaminants in raw and finished water supplies that may have impact on the health of marine animals and man are reviewed, and specific categories of pollutants are considered. The organochlorine insecticides appear to demonstrate the greatest potential for a tumorigenic response. From bioassay data, DDT and chlordane could be classified as suspect carcinogens. A polychlorinated biphenyl (Aroclor 1260) has induced hyperplastic nodules with histological evidence for carcinomas in female rat livers. Polycyclic aromatic hydrocarbons are ubiquitous in the aquatic environment and may present the greatest carcinogenic insult. If these chemicals are discharged into waterways solubilized in solvents, there may be some miscibility or they may precipitate out of the solution. A few of the compounds are: auramine, benzidine, o-tolidine, 3,3'-dimethylbenzidine, and 2-naphthylamine. The effect of benzene on marine animals should be observed especially since it is a leukemogenic agent. It may occur at low concentrations as a contaminant in water from refinery wastes or intentional dumping. A systematic monitoring of aerial discharge and water effluents around plants producing vinyl chloride and polyvinyl chloride showed that values could range from 0.15-327 ppm. The fact that vinyl chloride has been detected and concentrations have been measured in waterways

suggests that marine animals could be adversely affected and that vinyl chloride might be included in marine foods taken from contaminated waters. Some correlations have been found between levels of carcinogenic metals in certain river basins in the US and cancer mortalities in the region. Nickel concentration seemed to correlate with mouth and intestinal cancer death rates and arsenic with eye and larynx cancers and myeloid leukemia. Beryllium was correlated with bone cancer and mortalities from breast and uterine cancer. Lead was associated with kidney cancer, leukemias, lymphomas, and stomach, intestinal, and ovarian cancers. (70 refs)

267 AU - Stafford J
AD - Plastics Div., ICI, PO Box 6, Bessemer Road, Welwyn Garden City, Hertfordshire AL7 1HD, England
TI - THE VINYL CHLORIDE MONOMER HEALTH PROBLEM.
SI - CARC/77/01663
SO - Chem Ind ; 5(11):466-470 1976
LA - ENG
AB - Proceedings of the British Plastics Federation conference on 'Vinyl Chloride and Safety at Work' of May 18, 1975 and the conference of the Occupational Health Section of the Royal Society of Medicine of September 12, 1975, were reviewed, as were recent developments on the vinyl chloride health problem in the UK, Europe, and the US. The health hazards associated with polyvinyl chloride manufacture seem to be entirely related to the vinyl chloride monomer (VCM). During 1969-71 the first fibrosarcoma due to VCM was produced in experimental animals. Soon after, another investigator found that VCM exposure produced a considerable yield of tumors of many types in the glands and liver of rats exposed to varying dosages, with a linear relationship between the log concentration and the number of tumors. Numerous epidemiological surveys have turned up over 40 cases of angiosarcomas connected with VCM in the world. Nearly all of these cases were autoclave cleaners who experienced high exposures to VCM. Much more statistical data will be necessary to assess the threshold for plant exposure so that a proper perspective can be placed on those standards now being used by manufacturers. (No refs)

268 AU - Berk PD ; Martin JF ; Young RS ; Creech J ; Selikoff IJ ; Falk H
AU - Watanabe P ; Popper H ; Thomas L
AD - Room 4D-52, Building 10, Section on Diseases of the Liver, Digestive Diseases Branch, Natl. Inst. Arthritis, Metabolism, and Digestive Diseases, NIH, Bethesda, MD 20014
TI - VINYL CHLORIDE-ASSOCIATED LIVER DISEASE.
SI - CARC/77/01512
SO - Ann Intern Med; 84(6):717-731 1976
LA - ENG
AB - The association of vinyl chloride exposure and liver diseases is reviewed. Polyvinyl chloride has been produced from vinyl chloride monomer for over 40 yr, but recognition of toxicity among vinyl chloride polymerization workers is more recent. In

the mid 1960's, acro-osteolysis was found in workers involved in cleaning polymerization tanks. In 1974, the same population of workers was found to be at risk for an unusual type of hepatic fibrosis and angiosarcoma of the liver. Two cases of vinyl chloride-associated liver injury, one of hepatic fibrosis and one of angiosarcoma, are presented. The histologic features of these lesions are similar to the hepatic fibrosis and angiosarcomas resulting from chronic exposure to inorganic arsenicals. Preliminary studies suggest that the toxicity of vinyl chloride may result from formation, during high-dose exposure, of active metabolites by mixed function oxidases of the liver. Epidemiologic studies indicate an increased incidence not only of liver disease, but also of cancers of the brain, lung, and possibly other organs. (51 refs)

269 AU - Gamble J ; Liu S ; McMichael AJ ; Waxweiler RJ
AD - NCNB Plaza, Suite 32, Chapel Hill, NC 27514
TI - EFFECT OF OCCUPATIONAL AND NONOCCUPATIONAL FACTORS ON THE RESPIRATORY SYSTEM OF VINYL CHLORIDE AND OTHER WORKERS.
SI - ICDB/77/09719
SO - J Occup Med; 18(10):659-670 1976
LA - ENG
AB - The respiratory function and symptoms in 174 vinyl chloride workers, 81 polyvinyl chloride workers, 72 former vinyl chloride workers, 136 rubber workers and 68 maintenance workers with exposure to vinyl chloride, polyvinyl chloride and rubber at the same plant were investigated. Respiratory questionnaires and lung function tests were administered to all workers. Except for small airway obstruction associated with rubber, increased respiratory symptoms and decreased pulmonary function were not associated with working in chemicals, plastics, or rubber. Some increases in baseline pulmonary function were associated with vinyl chloride exposure. Acute reductions in pulmonary function were observed in smokers working in chemicals, plastics, and rubber. Heavier cigarette smokers over 40 yr of age had the most adversely affected respiratory system. Work was not associated with chronic respiratory effects, but all exposure groups experienced some acute respiratory insult. The literature on this subject is reviewed. (34 refs)

270 AU - Anonymous
AD - No affiliation given
TI - PREDICTIVE ONCOLOGY: FOLLOWING PATIENTS AT HIGH CA RISK.
SI - ICDB/77/06647
SO - Patient Care; 10(6):56-70 1976
LA - ENG
AB - The factors that directly relate to tumor developments, and the management of high risk cancer patients is discussed. An estimated 65-85% of all cancers are environmentally related. The patient's total environmental exposure to or ingestion of implicated substances such as vinyl chloride, asbestos, aflatoxins, and overuse of alcohol should be determined. Chloromycetin and other antibiotics with DNA inhibiting qualities

should be avoided. When possible, immunosuppressants, hematodepressants, and antihistamines, and the use of cyclophosphamide, methotrexate, or tetracycline for skin disorders or protection should be avoided. Benign skin lesions or bursitis should not be irradiated. The patient should check any drug, even nonprescription, with his physician. High risk women should not be given estrogens, and if undergoing hysterectomy, the ovaries should be removed at the same time. Cancer risk factors are less decisive than heart disease factors, so enthusiastic recommendations are necessary. Patients must be educated before significant changes occur in morbidity and mortality. Community resources are available, and detection clinics can be organized to work in league with rehabilitation facilities. (no refs)

271 AU - Hoffmann D ; Wynder EL
AD - Naylor Dana Inst. Disease Prevention, American Health Foundation, Valhalla, NY 10595
TI - SMOKING AND OCCUPATIONAL CANCERS.
SI - CARC/77/00959
SO - Prev Med; 5(2):245-261 1976
LA - ENG
AB - Epidemiological evidence that tobacco use has an added effect to that of occupational carcinogens is reviewed. There is a lack of epidemiological data for the joint reaction of occupational carcinogens and tobacco smoke. This applies particularly to workers in nickel refineries, coke oven and gas workers, and for workers in the chemical industries related to halo ethers and vinyl chloride and certain urinary carcinogens. Synergistic and/or additive effects of occupational carcinogens and tobacco smoke are epidemiologically established in the areas of exposure to radon daughters and to some types of asbestos. Experimental evidence of syncarcinogenic and/or cocarcinogenic effects of tobacco smoke and occupational carcinogens is needed in the areas of carcinogenesis of nickel, chromium, arsenicals, vinyl chloride, and halo ethers. The latter, however, are very potent respiratory carcinogens by themselves. Similarly, the aromatic amines as potent industrial bladder carcinogens may be studied for cocarcinogenic mechanisms with tobacco smoke constituents. Epidemiological studies in occupational cancer must include the smoking histories in order to determine the relative contribution of causative factors. Furthermore, it is the heavy cigarette smoker who is most likely to be the first affected by traces of carcinogens. (105 refs)

272 AU - Watanabe PG ; McGowan GR ; Madrid EO ; Gehring PJ
AD - Toxicology Res. Lab., Health and Environmental Res., Midland, MI 48640
TI - FATE OF [**14 C] VINYL CHLORIDE FOLLOWING INHALATION EXPOSURE IN RATS.
SI - CARC/77/00949
SO - Toxicol Appl Pharmacol; 37(1):49-59 1976
LA - ENG

AB - The fate of inhaled **14 C-vinyl chloride (VC) at different exposure concentrations was studied in rats. Male rats were exposed to 10 or 1,000 ppm **14 C-VC for 6 hr, and the routes and rates of elimination of **14 C activity were followed for 72 hr after termination of exposure. Following exposure to 10 ppm of VC, urinary **14 C activity and expired VC comprised 68% and 2%, respectively, of the recovered radioactivity. After exposure to 1,000 ppm of VC, the proportion of the radioactivity in the urine decreased and that expired as VC increased, representing 56% and 12%, respectively. The pattern of pulmonary elimination of VC per se was described by similar apparent first-order kinetics following 10, or 1,000 ppm with respective half-lives of 20.4 and 22.4 min. **14 C activity in the urine was eliminated in accordance with a two-exponential equation; the half-lives for the initial phase of excretion were 4.6 and 4.1 hr following 10 and 1,000 ppm, respectively. Recovered **14 C activity remaining in the carcass after 72 hr was 14% and 15%. VC per se was not found in tissues. The urinary **14 C activity was separated by high-pressure liquid chromatography into three major metabolites corresponding to N-acetyl-S-(2-hydroxyethyl)cysteine, thiodiglycolic acid, and a third unidentified metabolite. The proportions of the urinary metabolites were not markedly influenced by the exposure magnitude. The fate of inhaled **14 C-VC was dose-dependent; this is consistent with previous studies on the fate of VC following ingestion as well as inhalation. (13 refs)

273 AU - Magnusson J ; Ramel C
AD - Wallenberg Lab., Univ. Stockholm, Stockholm, Sweden
TI - MUTAGENIC EFFECTS OF VINYL CHLORIDE IN DROSOPHILA MELANOGASTER (MEETING ABSTRACT).
SI - CARC/77/00859
SO - Mutat Res; 38(2):115 1976
LA - ENG
AB - Genetic investigations on Salmonella have shown that vinyl chloride is converted to a mutagenic metabolite in liver microsomes. To study the effect of vinyl chloride in the gonads and the transmission of mutations to the next generation, tests with sex-linked recessive lethals in Drosophila were performed by the Muller 5 method. Males were treated with doses of vinyl chloride in the air for 3 hr and mated to Muller 5 females. A significant increase in recessive lethals was obtained both in the first and second generations; this indicated that the induction of recessive lethal mosaics took place. These results are in accordance with previous findings that Drosophila exhibits a metabolic conversion of indirect carcinogens, resembling the metabolic activation in mammals. (No refs)

274 AU - Loprieno N ; Abbondandolo A ; Barale R ; Baroncelli S ; Bonatti S
AU - Bronzetti G ; Cammellini A ; Corsi C ; Corti G ; Frezza D
AU - Leporini C ; Mazzaccaro A ; Nieri R ; Rosellini D ; Rossi A
AD - Laboratorio di Mutagenesi e Differenziamento, CNR e Istituto di Genetica dell'Universita, Pisa, Italy
TI - MUTAGENICITY OF INDUSTRIAL COMPOUNDS: VINYL CHLORIDE, STYRENE AND THEIR POSSIBLE METABOLITES (MEETING ABSTRACT).
SI - CARC/77/00858
SO - Mutat Res; 38(2):114-115 1976
LA - ENG
AB - Mutagenicity methodologies were applied to the study of vinyl chloride, styrene, and their metabolities (2-chloroethylene oxide, 2-chloroethanol, 2-chloroacetaldehyde, and styrene oxide) to correlate the mammalian metabolic fate of the compounds with their biological activity. The compounds were studied by liver microsomal assay and host-mediated assay with the yeast S pombe and S cerevisiae. Preliminary experiments were also done with somatic mammalian cells (V79 chinese hamster), on which the induction of 8-azaguanine resistant clones was assessed. Vinyl chloride was found to be mutagenic in the presence of liver microsomal preparations and in the host-mediated assay; moreover, the possible in vivo metabolite, 2-chloroethylene oxide, was responsible for mutagenic activity. Styrene was found to be inactive on yeast (+- microsomes) or slightly active on hamster cells; styrene oxide was found to be active in different biological systems. (No refs)

275 AU - Maricq HR ; Johnson MN ; Whetstone CL ; LeRoy EC
AD - Div. Rheumatology Immunology, Dept. Medicine, Medical Univ. South Carolina, 80 Barre St., Charleston, SC 29401
TI - CAPILLARY ABNORMALITIES IN POLYVINYL CHLORIDE PRODUCTION WORKERS. EXAMINATION BY IN VIVO MICROSCOPY.
SI - ICDB/77/02755
SO - JAMA; 236(12):1368-1371 1976
LA - ENG
AB - To determine whether symptomatic vinyl chloride (VC) workers have finger-skin-capillary abnormalities, whether the abnormalities are similar or different from those in patients with idiopathic scleroderma and Raynaud syndrome, whether microvascular abnormalities are related to the type of VC associated abnormalities (especially liver), whether microvascular abnormalities are related to the nature and duration of VC exposure, and whether microvascular abnormalities are found in workers not exposed to VC, the hands of 152 VC-exposed workers were examined by wide-field capillary microscopy. Examination revealed scattered scleroderma-like microvascular abnormalities in 21 workers and isolated capillary abnormalities in another 27, as compared with only three isolated abnormalities in 50 manual workers not exposed to VC. Thirteen of 17 VC workers with objective evidence of VC-associated abnormalities (angiosarcoma or fibrosis of liver, acroosteolysis, or scleroderma-like skin lesions) also had microvascular abnormalities. Since

microvascular changes occur more frequently than overt VC-associated pathologic conditions, they may represent an early manifestation of the VC effect. Thus, capillary microscopy may become a useful mass-screening procedure in the early detection and prevention of VC-associated disease.

276 AU - Rannug U ; Ramel C
AD - Environmental Toxicology Unit, Wallenberg Lab., Stockholm, Sweden
TI - THE MUTAGENICITY OF WASTE PRODUCTS FROM THE VINYL CHLORIDE INDUSTRIES (MEETING ABSTRACT).
SI - ICDB/77/01850
SO - Mutat Res; 38(2):113 1976
LA - ENG
AB - Vinyl chloride has been shown to possess carcinogenic and mutagenic properties. There is a risk that byproducts also possessing these properties may be formed in industrial processes involving this compound. The manufacture of vinyl chloride from acetylene and/or ethylene has given rise to a waste product, the EDC tar that contains ethylene dichloride as one of its main components. (This waste product has been dumped into the sea in large quantities.) It was tested for mutagenicity with one of the strains in the Salmonella test system (TA1535), which responded to base-pair substitutions in DNA. Ethanol, dimethyl sulfoxide, and Tween 80 were used to dissolve or emulsify the tar. They produced a mutagenic effect which was approximately of the same magnitude. However, when a microsomal fraction from rat liver plus an NADPH-generating system was added, the EDC tar exhibited a considerably stronger mutagenic effect. These results suggest that there are direct as well as indirect mutagenic components in the EDC tar.

277 AU - Robinson JS ; Thompson JM ; Belcher R ; Stephen WI
AD - Dept. Anaesthetics, Univ. Birmingham, Birmingham, England
TI - VINYL CHLORIDE: THE CARCINOGENIC RISK (LETTER TO EDITOR).
SI - ICDB/77/01742
SO - Br Med J; 2(6039):815 1976
LA - ENG
AB - Vinyl chloride behaves as a non-ideal gas at room temperature and, as such, a given mass occupies less vol at any particular temperature and partial pressure than predicted by the ideal gas laws. Although the resultant error arising from the use of parts per million (ppm) as opposed to the ideal v/v may be small, precision is essential in establishing the threshold and ceiling limits. It is simpler to use microg/liter for air pollution thresholds because the monitoring instruments are most easily and reliably calibrated in mass/vol units.

278 AU - Schlatter CH
AD - Institut fur Toxikologie, Schorenstrasse 16, CH-8603 Schwerzenbach bei Zurich
TI - THE RISK OF CONSUMERS AND PVC WORKERS TO VINYL CHLORIDE.
SI - CARC/77/00617
SO - Schweiz Med Wochenschr; 106(19):647-650 1976
LA - GER
AB - The signs and symptoms of vinyl chloride intoxication, the epidemiology of hepatic hemangiosarcoma, the results of animal experimentation, current estimates of occupational risk, and the danger of polyvinyl chloride packaging to the general population are topically reviewed.

279 AU - Lloyd JW
AD - NIOSH Center for Disease Control, 5500 Fishers Lane, Rockville, MD 20852
TI - OCCUPATIONAL CANCER.
SI - CARC/77/00366
SO - Proceedings of the Eleventh Canadian Cancer Research Conference. Natl Cancer Inst Canada Toronto Ontario 6-8 May 1976, 1976.
LA - ENG
AB - There is usually an exceedingly long delay before the first indications of an occupational cancer hazard and the definitive analysis of excess risk that is required before the institution of workplace controls. Brief discussion is given of the excesses of: bladder cancers in dye and rubber workers and in workers exposed to 4-aminobiphenyl, a rubber antioxidant; skin cancer among workers in copper smelters and tin refineries and among persons exposed to arsenic, such as sheep dip workers; lung and nasal sinus cancers among nickel and chromium workers; lung and digestive tract cancers and pleural and peritoneal mesotheliomas among workers in the asbestos industry; leukemias among radiologists; lung cancers among uranium millers; bone cancers among radium dial painters; cancer of the nasal sinuses in woodworkers; and angiosarcomas of the liver in workers exposed to vinyl chloride.

280 AU - Fox AJ
AD - Medical Statistics Div., St. Catherines House, 10 Kingsway, London WC2B 6JP, England
TI - VINYL CHLORIDE AND MORTALITY? (LETTER TO EDITOR).
SI - ICOB/77/00227
SO - Lancet; 2(7982):416-417 1976
LA - ENG
AB - An analysis of the data on workers exposed to vinyl chloride indicated that an unbiased measure can only be obtained from studies of men who had left the industry during a fixing period and were still alive at the end of that period. These calculations provided little evidence to support the suggestion of an excess risk of lung and brain cancer in workers exposed to vinyl chloride. However, there was an excess of deaths due to cancer of the liver, particularly angiosarcoma.

281 AU - Berry G ; Rossiter CE
AD - Llandough Hosp., Penarth, Glamorgan CF6 1XW, United Kingdom
TI - VINYL CHLORIDE AND MORTALITY? (LETTER TO EDITOR).
SI - ICDB/77/00226
SO - Lancet; 2(7982):416 1976
LA - ENG
AB - Analysis of the results provided in an article and the followup letters and replies indicates that there is little evidence of excess mortality, either overall or from cancer, in workers exposed to vinyl chloride. Furthermore, there does not appear to be a trend corresponding to increasing duration of exposure. These findings are in contrast to the inverse and exaggerated trends given in previous articles.

282 AU - Muller KT ; Buchter A ; Gross R ; Bolt W
AD - Med. Univ.-Klinik, 5 Koln 41, Joseph-Stelzmann-Str. 9, West Germany
TI - RESULTS OF A STUDY OF 17 CASES OF LONG-TERM EXPOSURE TO VINYL CHLORIDE.
SI - CARC/77/00312
SO - Med Welt; 27(1):21-24 1976
LA - GER
AB - A discussion of the physicochemical properties of vinyl chloride (VC) and its toxicology precedes a review of 17 patients with VC intoxication. Liver pathology and positive Raynaud signs occurred in 11/17, esophageal or fundic varices in 8/17, splenomegaly in 8/17, thrombocytopenia in 10/17, and acro-osteolysis in 8/17. Six probands presented with granulo cytopoiesis and marrow stimulation by sternal puncture. Five patients had various changes in antibody composition, and six were leukopenic. All patients were otolaryngologically negative. A suspicion of hepatic hemangioendothelioma in one subject was disconfirmed on laparoscopy, although the patient had elevated serum iron and distal hypalgesia. The subjects were men, with a mean 9-yr VC exposure.

283 AU - Corbett TH
AD - US Veterans Admin. Hosp., Ann Arbor, MI 48105
TI - CANCER AND CONGENITAL ANOMALIES ASSOCIATED WITH ANESTHETICS.
SI - CARC/77/00158
SO - Ann NY Acad Sci; 271:58-66 1976
LA - ENG
AB - Certain anesthetics in general use may be carcinogenic, embryolethal, teratogenic, and/or mutagenic. Spontaneous abortion rates as high as 38% have been reported among nurse anesthetists, compared to a rate of 9% among general duty nurses, and 16.4% of 434 children born to nurse anesthetists who had worked during pregnancy had birth defects, compared to only 5.7% of 261 children born to nurse anesthetists who had not worked while pregnant. Three studies have indicated an increased cancer risk in operating-room personnel; a recent survey involving 50,000 such personnel and 30,000 non-operating room female medical

personnel controls revealed an increased prevalence of cancer in the former, ranging from 1.3 to 2 times the control rate. Halogen ether anesthetics such as isoflurane, methoxyflurane, and enflurane are similar in chemical structure to the proved carcinogen bis(chloromethyl) ether, and trichloroethylene is likewise similar to the carcinogen vinyl chloride. Isoflurane has been shown to be carcinogenic in mice. When pregnant Swiss/ICR mice were exposed to 0.5% isoflurane for 2 hr on days 12, 14, 16, and 18 of pregnancy and the offspring were exposed to 0.1% isoflurane every other day from age 5 days for 25 exposures, 10/37 male offspring killed after 15 mo had hepatic neoplasms, with three animals having multiple tumors. No neoplasms were observed among 23 control animals. Isoflurane, and the structurally similar halogenated ether and alkane anesthetic agents, must be regarded with suspicion and studied for carcinogenic properties as soon as possible.

284 AU - Kotin P
AD - Health, Safety & Environment Dept., Johns-Manville Corp., Denver, CO 80217
TI - DOSE-RESPONSE RELATIONSHIP AND THRESHOLD CONCEPTS.
SI - CARC/77/00144
SO - Ann NY Acad Sci; 271:22-28 1976
LA - ENG
AB - The author examines the concepts of dose-response and threshold levels in cancer induction. The applicability of the dose-response concept has been clearly demonstrated for the tumorigenic effects of carcinogenic agents in animal models over certain concentration ranges. This has been verified in man, and dose-response data and no-effect levels have been determined for carcinogenic organic and inorganic chemicals (specifically for vinyl chloride and asbestos), metals, and for non-ionizing and ionizing radiation. In the absence of evidance to the contrary, the applicability of the threshold concept in considerations of acceptable levels of carcinogens within the environment cannot be denied.

285 AU - Maltoni C
AD - Inst. Oncology and Tumour Centre, Bologna, Italy
TI - PREDICTIVE VALUE OF CARCINOGENESIS BIOASSAYS.
SI - CARC/77/00123
SO - Ann NY Acad Sci; 271:431-443 1976
LA - ENG
AB - Bioassays provide an important means of predicting the oncogenic risk of particular occupational and environmental agents to man. In fact, the three most important occurrences of environmental and occupational tumors discovered after 1970 were directly or indirectly predicted by animal studies. The first was the adolescent clear-cell vaginal adenocarcinoma found in girls born to mothers treated during pregnancy with synthetic nonsteroid estrogen therapy. As long ago as 1938, it was demonstrated that stilbestrol had carcinogenic properties, with mammary tumors arising in male mice treated with the compound; several years

later, the same hormone was shown to produce a variety of tumors among different animal species. The second occurrence was that of pulmonary carcinoma among workers exposed to bis(chloromethyl) ether, which had previously been shown to produce sc fibrosarcomas and skin carcinomas when injected sc into rats or applied topically to mice. When the compound was inhaled by rats, it induced squamous cell carcinomas of the lung. The third example was provided by the identification of liver angiosarcomas in workers occupationally exposed to vinyl chloride (VC), after the carcinogenicity of the compound had been demonstrated in rats. Data from inhalation experiments with VC in rats, mice, and hamsters and from ingestion experiments in rats are reported in detail. Sixty Swiss mice of both sexes were treated by inhalation of VC in air at 10,000 ppm for 4 hr/day, 5 days weekly for 30 wk. After 81 wk 55 developed pulmonary tumors, 13 had mammary carcinomas, 8 had liver angiosarcomas, 9 had vascular tumors, and 3 had epithelial tumors of the skin; of 150 untreated mice, 8 developed pulmonary tumors and 1 a vascular tumor after the same length of time. Bioassays can also be used to predict the carcinogenicity of inorganic substances. Various inorganic materials were tested by sc injection of 30-mg quantities into Sprague-Dawley rats. Of 40 animals in each group, 9 developed rhabdomyosarcomas and fibrosarcomas with neochromium, 8 with chromium allumen, 26 with chromium yellow, 27 with molybdenum orange, 16 with cadmium yellow, and 1 with iron yellow, after 125-150 wk. None of 140 control animals developed neoplasms. Of 49 male and 48 female Sprague-Dawley rats, 34 and 31 developed peritoneal mesotheliomas following the endoperitoneal injection of 25 mg of crocidolite.

286 AU - Lilis R ; Anderson H ; Miller A ; Selikoff IJ
AD - Mount Sinai Sch. Medicine, New York, NY
TI - PULMONARY CHANGES AMONG VINYL CHLORIDE POLYMERIZATION WORKERS.
SI - CARC/77/00015
SO - Chest; 69(2):299-303 1976
LA - ENG
AB - Pulmonary changes uncovered during clinical examinations of three groups of exposed vinyl chloride (VC) polymerization workers are discussed. The examination included chest x-rays, smoking history, a chronic bronchitis questionnaire, and pulmonary function tests. The first group was from a plant known to have high exposure levels to VC and polyvinyl chloride (PVC). The second plant was the first PVC polymerization facility, so that long exposure effects could be expected. The third plant had a relatively low exposure level. In the first group, the overall prevalence of small linear reticular and/or rounded opacities was 22.7%; x-ray changes increased with length of exposure. In the second group the prevalence of chest x-ray changes was 19.4%. The third group had a much lower prevalence of chest x-ray abnormalities (4.3%). The prevalence of positive smoking history was higher in workers with abnormal chest x-ray films in the first two groups, perhaps indicating a multiple factor effect of smoking and VC-PVC exposure. No significant differences were

found between the groups with abnormal and normal chest x-rays with respect to chronic bronchitis or age. Pulmonary function tests showed a relatively high prevalence of obstructive changes, but there was no consistent correlation between abnormal chest x-ray and pulmonary function abnormalities. It is possible that chest x-ray changes and obstructive pulmonary function abnormalities reflect different pathologic processes, the chest x-ray changes being mainly related to parenchymal damage, while the obstructive pulmonary function changes reflect airway changes.

287 AU - Owen R
AD - London, England
TI - VINYL CHLORIDE: EPIDEMIOLOGICAL STUDIES AND PREVENTIVE MEASURES.
SI - CARC/76/04520
SO - Adv Tumor Prev Detect Charact; 3:238-241 1976
LA - ENG
AB - Epidemiological studies are being made to assess the effects of occupational exposure to vinyl chloride in Great Britain. Cancer and mortality rates of 6,000-8,000 past and present workers in five polyvinyl chloride plants are being related to vinyl chloride exposure in terms of time and concentration. A retrospective study of cases of angiosarcoma of the liver is underway to evaluate the association between this disease and occupation. The medical and social histories of these cases are also being compiled. The United Kingdom has lowered its interim standards for vinyl chloride exposure to a ceiling value of 30 ppm and a time-weighted average of 10 ppm.

288 AU - Montesano R ; Bartsch H
AD - Unit Chemical Carcinogenesis, International Agency Res. Cancer, Lyon, France
TI - MUTAGENICITY AND METABOLISM OF VINYL CHLORIDE.
SI - CARC/76/04519
SO - Adv Tumor Prev Detect Charact; 3:242-245 1976
LA - ENG
AB - Studies on the mutagenicity and metabolism of vinyl chloride are reviewed. The mutagenic and/or carcinogenic effect of vinyl chloride appears to be mediated through the formation of electrophilic metabolites by microsomal mixed-function oxidase. The pretreatment of rats with drugs that modify the activity of the enzyme results in changes in the in vitro mutagenicity of vinyl chloride. This supports the hypothesis that the carcinogen has to be converted into electrophilic and mutagenic metabolites. Pretreatment of rats with phenobarbitone increases the mutagenic response, whereas the administration of pregnenolone-16a-carbonitrile and aminoacetonitrile reduces the liver-mediated mutagenicity of vinyl chloride. Experiments involving the trapping of chloroethylene oxide in vitro by 4-nitrobenzylpyridine, following activation of vinyl chloride in the presence of mouse liver microsomal enzymes, an NADPH generating system, and oxygen, support the hypothesis that monochloroethylene oxide is a primary reactive and mutagenic metabolite of vinyl chloride.

289 AU - Pregaglia GF
AD - Dept. Res. and Technology, Petrochemical Div., Montedison, Milan, Italy
TI - PRODUCTION AND USE OF VINYL CHLORIDE: IMPACT OF THE LINK BETWEEN VINYL CHLORIDE MONOMER AND CANCER.
SI - CARC/76/04518
SO - Adv Tumor Prev Detect Charact; 3:209-215 1976
LA - ENG
AB - Exposure hazards associated with the production and use of vinyl chloride monomer (VCM) are reviewed along with some possible solutions. VCM has recently been associated with the cancer deaths of production workers exposed to the compound, and the Occupational Safety and Health Administration has recommended that the exposure level be reduced to 1 ppm (averaged over an 8-hr period) starting in 1976. Exposure hazards to VCM in polyvinyl chloride manufacturing plants include: VCM loss from valves and pumps to the ambient air at concentrations ranging from a few to a few dozen parts per million; the need for workers to enter reactor vessels periodically for cleaning; monomer escape from the polymer during storage and processing of the latter; and monomer losses through vent gas streams. Possible means of reducing VCM exposure include: the scale-up to larger reactors, resulting in fewer leaks and easier cleaning; remote control operation and the use of highly sensitive vapor detectors; and new processes for the removal of VCM from vent gases, such as the adsorption of VCM on activated carbon and its regeneration with steam.

290 AU - Anonymous
AD - No affiliation given
TI - VINYL CHLORIDE: THE CARCINOGENIC RISK.
SI - ICDB/76/24393
SO - Br Med J; 2(6028):134-135 1976
LA - ENG
AB - Previous studies have indicated the carcinogenicity of vinyl chloride monomer in workers exposed to the gas. It appears that 12-29 yr latent interval exists between the exposure and the onset of symptoms, with a mean duration of exposure of 18 yr. The threshold value for exposure has recently been lowered to 10 ppm. It will take future studies to decide whether this threshold value will have eliminated the risk of cancer.

291 AU - Loprieno N ; Barale R ; Baroncelli S ; Bronzetti G ; Cammellini A
AU - Corsi G ; Leporini C ; Nieri R ; Rossi AM
TI - THE MUTAGENICITY OF THE CARCINOGEN VINYL CHLORIDE AND ITS COMPARISON WITH A KNOWN ALKYLATING MUTAGEN.
SI - CARC/76/04106
SO - Screening Tests In Chemical Carcinogenesis; International Agency for Res. on Cancer. (Brussels, Belgium, 9-12 June 1975, no. 12, 1976.
LA - ENG
AB - The authors compared the mutagenic activity of methyl

methanesulfonate (MMS), used as a reference chemical, with that of vinyl chloride (VCM). The mutagenic activities were determined by use of the genetic systems of two eukaryotic yeast cells (Schizosaccharomyces pombe and Saccharomyces cerevisiae), which allow the evaluation of forward mutations on the five-loci system of S pombe and mitotic gene conversions on the two-loci system of S cerevisiae or the one-locus system of S pombe. From the experimental data available, the biological effect of VCM has been attributed mainly to its conversion by microsomal enzymes to reactive metabolites of the alkylating type. For this reason, the alkylating compound MMS was chosen for comparison. In the present experiments, it was found that 1 mmol of MMS is equivalent to 41.7 mmol of VCM. Mitotic gene-conversion data gave a similar ratio: VCM is 10 to 40 times less effective than MMS. The values of the specific mutation rates and of the dose required for doubling the spontaneous mutation frequency indicated that VCM is converted to a highly reactive mutagenic metabolite.

292 AU - Bolt HM ; Kaepus H ; Buchter A ; Bolt W
AD - Institut fur Toxikologie der Universitat, Wilhelmstr. 56, D-7400 Tubingen, West Germany
TI - DISPOSITION OF [1,2**-14 C] VINYL CHLORIDE IN THE RAT.
SI - CARC/76/04103
SO - Arch Toxicol (Berl); 35(3):153-162 1976
LA - ENG
AB - Three male Wistar rats, 200-250 g, were exposed to (1,2**-14 C)-vinyl chloride in an all-glass closed system of 10.3 l volume. To avoid saturation of the metabolizing enzymes, concentrations below 100 ppm were applied. In preliminary experiments, it was found that only about 40% of inspired vinyl chloride is absorbed by the lungs. Uptake of vinyl chloride by the rats was completely blocked by acute pretreatment with potent inhibitors of cytochrome P-450-dependent microsomal drug metabolism (i.e, by 35 mg/kg 3-bromophenyl-4(5)-imidazole or 50 mg/kg 6-nitro-1,2,3-benzothiadiazole in 0.6 ml/kg dimethyl sulfoxide, DMSO). A weaker inhibition was observed after pretreatment with 2-diethylaminoethyl-2,2-diphenylvalerate;HCl (SKF-525A) or 5,6-dimethyl-1,2,3-benzothiadiazole (50 mg/kg in 0.6 ml/kg DMSO). Metyrapone did not cause inhibition. Uptake of vinyl chloride was increased by pretreatment with 1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane (DDT) and, to a lesser extent, with clotrimazole. No significant stimulation of uptake was observed after pretreatment with phenobarbital, 3-methylcholanthrene, rifampicin, or chronic ethanol treatment. Immediately after exposure, highest radioactivity levels were observed in liver and kidney; the radioactive metabolites were rapidly excreted, mainly in the urine (69.4% 6 2.6% within 24 hr).

293 AU - Van Duuren BL ; Banerjee S
AD - New York Univ. Medical Center, New York, NY 10016
TI - COVALENT INTERACTION OF METABOLITES OF THE CARCINOGEN TRICHLOROETHYLENE IN RAT HEPATIC MICROSOMES.
SI - CARC/76/04102
SO - Cancer Res; 36(7):2419-2422 1976
LA - ENG
AB - Trichloroethylene (TCE), a structural analog of vinyl chloride, induces hepatocellular carcinoma and other tumors in B6C3F1 hybrid mice. TCE epoxide, a possible metabolite, is expected to be highly reactive toward cellular nucleophiles; e.g, proteins and nucleic acids. Hence, the microsomal metabolism of TCE and its covalent binding to microsomal protein were examined. Rat liver microsomes from male Sprague-Dawley rats were incubated in vitro with **14 C-TCE. The results showed that TCE binds covalently to microsomal protein, since extensive organic extractions and Pronase digestion do not dissociate the TCE-protein complex. The binding was decreased by 7,8-benzoflavone, blocked by 2-diethylaminoethyl-2,2-diphenylvalerate;HCl (SKF-525A), and enhanced by ip administration of phenobarbital. The possibility that TCE epoxide, once formed, could be converted to water-soluble products through enzymatic hydrolysis by epoxide hydrase was also investigated. Addition of 3,3,3-trichloropropene oxide, a potent inhibitor of epoxide hydrase, to the incubation system markedly enhanced TCE binding. These observations support the view that, in order to bind to protein, it is necessary for TCE to be metabolized to its epoxide, a reactive intermediate that is most likely involved in TCE carcinogenesis and toxicity.

294 AU - Wegman DH ; Peters JM ; Jaeger RJ ; Burgess WA ; Boden LI
AD - 665 Huntington Ave., Boston, MA 02115
TI - PUBLIC-HEALTH ROUNDS AT THE HARVARD SCHOOL OF PUBLIC HEALTH. VINYL CHLORIDE: CAN THE WORKER BE PROTECTED?
SI - CARC/76/03840
SO - N Engl J Med; 294(12):653-675 1976
LA - ENG
AB - The toxicology, economic and engineering aspects, and regulation of occupational exposure to vinyl chloride are reviewed. Well before 1974, when three cases of a rare neoplasm, angiosarcoma of the liver, were reported in workers exposed to vinyl chloride over a 20-yr period, there was sufficient evidence to support the presumption of a serious occupational hazard. Toxicological studies as early as 1938 indicated that vinyl chloride has little acute lethal action and negligible short-term toxicity but is a potent carcinogen in rodents under work-like exposure of 50 ppm and less. Useful toxicologic screening should be carried out in locations other than the workplace and in species other than man. The manner in which workers are exposed to vinyl chloride varies greatly, depending on their occupation in one of three stages: (a) production of vinyl chloride monomer (VCM); (b) reaction of VCM to form polyvinyl chloride (PVC); and (c) the fabrication of

plastic products from PVC. Major exposure and the cases of angiosarcoma of the liver occur in the second industrial stage. The most common exposure in the first stage occurs from leaks and faulty equipment maintenance. In the third stage, exposure (1,000 ppm) occurs when workers periodically crawl into the reactor to clean the inside surface. The federal occupational standard for vinyl chloride exposure (issued in October 1974), although accepting in principle 1 ppm as the maximum possible exposure, permits temporary exposures of up to 25 ppm without respiratory protection.

295 AU - Pelfrene AF
AD - Univ. Nebraska Medical Center, 42nd and Dewey Ave., Omaha, NB 68105
TI - CARCINOGENIC ROLE OF VINYL CHLORIDE (LETTER TO EDITOR).
SI - CARC/76/03813
SO - Nouv Presse Med; 5(15):999-1000 1976
LA - FRE
AB - The author disagrees with the interpretation of current vinyl chloride data given in an earlier review. The carcinogenicity of this gas is well-documented, in man as well as in laboratory animals. Since January 1, 1975, the maximum permissible limit in American industry has been 1 ppm (a time-related average value for an 8-hr day, 5-day work week). There is also a ceiling of 5 ppm for a maximum of 15 min exposure. The 1-ppm value is well above the capacity of present detection techniques with a sensitivity of 0.1 ppm. Reduction and control of exposure thresholds are therefore possible. It is an exaggeration to assert that American vinyl chloride workers are generally exposed to concentrations of 600 to 1,000 ppm. Only some (in the polymerization units) run the risk of overexposure. The figures quoted seem abnormally high if one recalls that, in 1958, the discovery of neurotoxic and angiotoxic effects in vinyl workers led to the lowering of the highest permissible limit to 500 ppm. Laboratory animals not only develop ecto- and mesodermic tumors after exposure to 50 to 200 ppm, they do so at lesser doses, and also after inhalation and ingestion. Extrapolation from rat to man is difficult, but one should not ignore laboratory results. It is preferable to limit human exposure to toxic products on the strength of animal experiments than to wait for the same conclusions from studies of human epidemiology.

296 AU - Smith PM ; Williams DM ; Evans DM
AD - Llandough Hosp., B.P. Chemicals International Ltd., Penarth, Glamorgan, Wales
TI - HEPATIC ANGIOSARCOMA IN A VINYL CHLORIDE WORKER.
SI - CARC/76/03453
SO - Bull NY Acad Med; 52(4):447-452 1976
LA - ENG
AB - An unusual case is presented of a 36-yr-old man who developed angiosarcoma of the liver after exposure to vinyl chloride monomer gas (VCM) for only 3 1/2 yr. The mean duration of exposure for previously reported cases of angiosarcoma was 16 yr.

The latent period from the first exposure to VCM to diagnosis was 8 yr, contrasting to the previous mean interval of 17 yr. A liver biopsy 15 mo prior to death showed striking focal dilation of the sinusoids. There is some evidence that this may be a precursor to tumor formation.

297 AU - Milvy P ; Garro AJ
AD - Mount Sinai Sch. Medicine, Fifth Ave. and 100th St., New York, NY 10029
TI - MUTAGENIC ACTIVITY OF STYRENE OXIDE (1,2-EPOXYETHYLBENZENE), A PRESUMED STYRENE METABOLITE.
SI - CARC/76/03446
SO - Mutat Res; 40(1):15-18 1976
LA - ENG
AB - The possible mutagenic effects of styrene and some of its metabolites were studied in various strains of Salmonella typhimurium. Only styrene oxide induced mutations in strains TA1535 and TA100, showing an activity similar to vinyl chloride and its presumed metabolites. The mutants were not clustered around the zone of inhibited growth, but randomly distributed, suggesting that the styrene oxide was dispersed by vaporization rather than by diffusion through the agar. It is concluded that styrene vapor may metabolize to a potentially carcinogenic compound, and current acceptable levels may pose a health threat to workers.

298 AU - Barnes AW
AD - ICI Plastics Div., Welwyn Garden City, Hertfordshire, England
TI - VINYL CHLORIDE AND THE PRODUCTION OF PVC (MEETING ABSTRACT).
SI - CARC/76/03008
SO - Proc R Soc Med; 69(4):277-281 1976
LA - ENG
AB - The polymerization characteristics of vinyl chloride are described, and the process for producing polyvinyl chloride (PVC) is outlined. Interfaces of exposure of humans to PVC are outlined, and theoretical exposure levels for workers at various stages in the production process and for the average U.K civilian are calculated. Average annual dietary ingestion is calculated as 0.0001 g/yr. Atmospheric exposure for polymerization workers has decreased from approximately 1,000 ppm in 1940 to approximately 5 ppm in 1975, although certain workers might have been exposed to as much as 3,000 ppm in 1940. The daily dose of the polymerization plant worker who had been exposed to 1,000 ppm is calculated at 0.36 g/kg, the dose for the polymerization plant worker presently exposed to 5 ppm is 0.0018 g/kg, and that of the average citizen 0.000000004 g/kg.

299 AU - Loprieno N ; Barale R ; Baroncelli S ; Bauer C ; Bronzetti G
AU - Cammellini A ; Cercignani G ; Corsi C ; Gervasi G ; Leporini C
AU - Nieri R ; Rossi AM ; Stretti G ; Turchi G
AD - Istituto di Genetica, University, Pisa, Italy
TI - EVALUATION OF THE GENETIC EFFECTS INDUCED BY VINYL CHLORIDE MONOMER (VCM) UNDER MAMMALIAN METABOLIC ACTIVATION: STUDIES IN VITRO AND IN VIVO.
SI - CARC/76/03349
SO - Mutat Res; 40:85-95 1976
LA - ENG
AB - The mutagenic activity of vinyl chloride monomer (VCM) was observed on yeast in the presence of a pure preparation of mouse (Swiss albino) liver microsomes and in the ''host-mediated assay''; the gene conversion inducible by Saccharomyces cerevisiae was also observed. VCM in the presence of purified microsomes (sedimented at 105,000 g) was converted into an active metabolite(s) that produced gene mutations in the yeast S pombe (forward mutation) and gene conversions in two loci of diploid S cerevisiae. No mutagenic activity was found when yeast cells were treated with VCM, a phosphate buffer, or microsomes alone; this demonstrates that the enzyme necessary to metabolize VCM into a biologically reactive compound is not present in the yeast. Moreover, the compound was active in the host-mediated assay, when mice were treated with an oral dose of 700 mg/kg of VCM. These results have demonstrated that VCM is mutagenic for eukaryotic organisms and that it produces other genetic changes; this activity is liver-microsome dependent and dose dependent. It is recommended that reliable methodologies, like this mammalian metabolic activation one, for assessing the toxicological values of many industrial compounds before they reach production, be made available.

300 AU - Wainbren K
AD - Royal Postgraduate Medical Sch., Du Cane Road, London W12 OHS, England
TI - HISTOPATHOLOGY OF LIVER LESIONS ASSOCIATED WITH EXPOSURE TO VINYL CHLORIDE MONOMER (MEETING ABSTRACT).
SI - CARC/76/03503
SO - Proc R Soc Med; 69(4):299-303 1976
LA - ENG
AB - An outline of the cell characteristics of angiosarcoma of the liver and changes that have occurred, with and without tumor development, in patients exposed to vinyl chloride monomer are presented. The tumors appear as dark hemorrhagic nodules with distortion and fibrosis in the intervening tissue; frank necrosis is often present. There are three types of involvement: the sinusoidal pattern, the papillary type, and the cavernous type. The cells are usually associated with vessel walls and vascular spaces. Near the tumor and sometimes in the absence of tumors, perisinusoidal reticular fibers are prominent and fibrosis in the portal tracts is often reported. Subcapsular fibrosis may also occur. The relevance of these nontumorous changes to the

subsequent development of angiosarcoma is unknown at this time.

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