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MIDLAND, MICHIGAN, 48640

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VINYL CHLORIDE

PAGE 1

- 1 AU - Baxter PJ
AD - Employment Medical Advisory Service, Baynards House, 1 Chepstow Place, London W2 4TF, England
TI - EPIDEMIOLOGICAL STUDIES OF PVC MANUFACTURERS AND FABRICATORS, AND PRIMARY ANGIOSARCOMA OF THE LIVER (MEETING ABSTRACT).
SI - CARC/76/03502
SO - Proc R Soc Med; 69(4):297-299 1976
LA - ENG
AB - Prospective studies of polyvinyl chloride manufacturers and fabricators and retrospective studies of primary angiosarcoma of the liver are being set up in England to assess the risk of occupational exposure to vinyl chloride. These studies will also permit the testing of hypotheses concerning the carcinogenicity of vinyl chloride in other areas of the body.
- 2 AU - Duck BW
AD - Occupational Health Unit, BP Research Centre, Sunbury on Thames, TW167LN, England
TI - MEDICAL SURVEILLANCE OF VINYL CHLORIDE WORKERS (MEETING ABSTRACT).
SI - CARC/76/03409
SO - Proc R Soc Med; 4(69):307-309 1976
LA - ENG
AB - The progress of teams set up in England to study workers exposed to vinyl chloride and polyvinyl chloride is reviewed. Although all the results are not yet in, the low incidence of liver disorders in these workers does not seem to warrant the mass screening that was initially undertaken. With stringent environmental standards now in force, future efforts will concentrate on the evaluation of specific hypotheses.
- 3 AU - Williamson KS
AD - ICI Ltd., Central Medical Group, Fulshaw Hall, Wilmslow, Cheshire, SK9 10B, England
TI - REVIEW OF ANIMAL STUDIES (MEETING ABSTRACT).
SI - CARC/76/03405
SO - Proc R Soc Med; 69(4):281-283 1976
LA - ENG
AB - The author reviews several studies that have been conducted on animals exposed to vinyl chloride gas. It appears that the proportion of the dose retained and metabolized is greater following small doses than large ones. The amount that is inhaled is eliminated in three ways: unchanged from the lungs, in the carbon dioxide from the lungs, and by the excretion of metabolites in the urine. Although many studies are incomplete, there is substantial evidence to indicate that vinyl chloride is oncogenic.

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- 4 AU - Kobayashi Y
AD - Engineering Faculty, Yokohama Natl. Univ., Yokohama, Japan
TI - CASE STUDY OF VINYL CHLORIDE AS A CARCINOGEN.
SI - CARC/76/03379
SO - J Jpn Soc Saf Eng; 15(2):101-104 1975
LA - JPN
AB - Cases of hepatic angiosarcoma associated with vinyl chloride monomer (VCM) and various facets of the VCM problem are summarized. VCM production in Japan began in the 1950's, and, in the United States, in the 1930's. In Japan, since 1975, recommended VCM concentrations in the factory atmosphere range from 2 to 5 ppm, and provisions have been made for adequate ventilation. Governmental surveys of 10 representative Japanese factories from 1974 to 1975 showed that 97.3% of the work areas had atmospheric VCM concentrations of less than 3 ppm. Other factories had atmospheric VCM concentrations greater than 5-10 ppm. One case of hepatic angiosarcoma was recently reported among retired Japanese factory workers. According to the National Institute of Occupational Safety and Health (NIOSH, United States), 38 cases of hepatic angiosarcoma worldwide (United States, Canada, Europe) occurred since 1975 among workers exposed to VCM from 4 to 30 yr.
- 5 AU - Taylor KJ ; Barrett JJ ; Williams DM ; Smith PM ; Duck BW
AD - Yale Univ. Sch. Medicine, New Haven, CT
TI - PRELIMINARY RESULTS OF GREY-SCALE ULTRASONOGRAPHY IN THE DETECTION OF VINYL CHLORIDE RELATED LIVER AND SPLEEN DISEASE (MEETING ABSTRACT).
SI - CARC/76/03376
SO - Proc R Soc Med; 69(4):292-295 1976
LA - ENG
AB - In an attempt to devise a method for mass examination of vinyl chloride-exposed workers, a pilot project was carried out with grey-scale ultrasonography, a technique that allows normal tissue parenchyma to be displayed. Results of tests with 19 volunteers exposed to vinyl chloride suggest that this method is a complement to rather than a replacement for current techniques. The main advantage is that it is a noninvasive method of monitoring populations without exposing them to ionizing radiation.
- 6 AU - Falk H ; Waxweiler RJ
AD - Center for Disease Control, United States Public Health Service, Dept. Health, Education, and Welfare, Atlanta, GA 30333
TI - EPIDEMIOLOGICAL STUDIES OF VINYL CHLORIDE HEALTH EFFECTS IN THE UNITED STATES (MEETING ABSTRACT).
SI - CARC/76/03367
SO - Proc R Soc Med; 69(4):303-305 1976
LA - ENG
AB - The high incidence of hepatic angiosarcoma in the vinyl chloride industry in the United States has prompted a large number of surveys; the results of three of these are examined. A review of

death certificates indicated that angiosarcoma comprised 35% of all hepatic sarcomas between 1966-1973; there was also a 2:1 male:female ratio, suggesting that occupational exposure was important in the etiology. A study of polyvinyl chloride workers and controls showed no significant differences between the groups in six liver function tests but these tests are not totally reliable for vinyl chloride-induced disease. In the third study, 12 lung cancer cases were identified in vinyl chloride-exposed workers, but the correlation was not as close here as it was with hepatic angiosarcoma.

- 7 AU - Hills JP
AD - Messenger, Lynch, Hills and Miller, Attorneys and Counselors at Law, Beltsville, MD 20705
TI - LEGAL DECISIONS AND OPINIONS IN POLLUTION CASES.
SI - CARC/76/02330
SO - Environ Sci Technol; 10(3):234-238 1976
LA - ENG
AB - A review is presented of the court histories of a number of legal actions involving the dumping of asbestos-containing waste into Lake Superior, the orders of the Environmental Protection Agency (EPA) to reduce the level of lead in gasoline and ban the pesticide aldrin/dieldrin, and the vinyl chloride standard set by the Secretary of Labor. The indications are that the courts, rather than demanding scientific proof when hearing scientific evidence, are in fact applying a more lenient standard than the traditional legal one: Is it more likely than not that the proposition asserted is true? Thus, in the case of asbestos dumping, the court eventually took action to require the manufacturing company concerned to dispose of the asbestos-containing waste in an alternative fashion, even though it found the possibility of risk to health from dumping to reside only in the realm of respectable medical opinion and not to be an established likelihood. However, because the actual risk to health could not be ascertained, it declined to take drastic or immediate action, but stipulated that the company be given a period of years in which to change its practices. Similarly, the U.S. Court of Appeals for the District of Columbia rejected an appeal of the EPA's ban on aldrin/dieldrin which was based on the argument that there was no proof that the pesticide presented a hazard to human health, since the finding that the material was carcinogenic in several mouse strains could not be extrapolated to humans. The Court noted that certain proof was impossible to obtain, that the burden of proof regarding the safety of the pesticide rested with the manufacturer, and that a total ban was justified because the concept of threshold levels has no practical significance when carcinogens are involved. The courts seem to be coming to accept that when the risk of harm to large populations is at stake, the risk might be very small, and yet justify action.

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- 8 AU - Harnden DG
AD - Medical Sch., Univ. Birmingham, Birmingham B15 2TJ, England
TI - CHROMOSOME ABNORMALITIES AND PREDISPOSITION TOWARDS CANCER (MEETING ABSTRACT).
SI - CARC/76/02305
SO - Proc R Soc Med; 69(1):41-43 1976
LA - ENG
AB - The available evidence supports the idea that chromosome changes are important as predisposing factors for the initiation of malignancy, and may also be important for the progression of tumors. Predisposition to malignancy is observed in patients with chromosome breakage syndromes such as Fanconi's anemia, in which breakage occurs at random, Bloom's syndrome, in which there are frequent chromatid exchanges between identical loci on homologous chromosomes, and ataxia telangiectasia, in which chromosomal rearrangements occur as the result of breakage throughout the karyotype but with particular frequency at locus 14q13. Ataxia telangiectasia is characterized by the appearance of clones of cytogenetically distinct lymphoid cells that have a rearrangement involving at least one chromosome no. 14. Malignancies may arise from within pre-existing clones that already have proliferative advantages. Similar clones of lymphocytes with abnormal chromosomes have been reported in subjects exposed to ionizing radiations, and clones of abnormal fibroblasts have been observed both in patients with chromosome-breakage syndromes and in apparently normal individuals. Furthermore, chromosome rearrangement, as opposed to chromosome breakage, is a characteristic of virus-cell interactions that frequently lead to cellular transformation, and chemical carcinogens may also induce chromosomal aberrations. Such aberrations have been shown in lymphocytes from workers exposed to vinyl chloride. Chromosomal damage, whether elicited by chemical, physical, viral, or inherited genetic factors, may predispose to malignancy, but the induction of damage does not mean that malignancy will necessarily ensue.
- 9 AU - Moria DF ; Ritchie S ; Silver MD
AD - Central Hosp., Toronto, M5A 2S5 Canada
TI - ANGIOSARCOMA OF THE LIVER AFTER VINYL CHLORIDE EXPOSURE: REPORT OF A CASE AND REVIEW OF THE LITERATURE.
SI - CARC/76/02408
SO - Lab Invest; 34(3):346 1976
LA - ENG
AB - An 88-yr-old man died of angiosarcoma of the liver--an extremely uncommon primary liver tumor. He had a brief 6-mo history of diarrhea, ascites and edema, and died of hepatic failure. At autopsy, the liver showed a diffuse honeycombed appearance which is characteristic of these tumors. Histologically the patterns seen were sinusoidal, cavernous, papillary, and anaplastic types. In the areas of liver uninvolved by the tumor, there was cirrhosis with marked perisinusoidal and portal fibrosis. For 50 years the man had been a sales manager in an automobile tire

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manufacturing plant where vinyl chloride monomer is polymerized into poly vinyl chloride. The apparent rarity of angiosarcoma in vinyl chloride workers is noted by the fact that only 26 cases are reported from various parts of the world, and as far as is known this is the only case from Canada. Vinyl chloride is a new industrial carcinogen and the reactor cleaners in the polymerization plant are at the highest risk. The other toxic effects and the literature are briefly reviewed.

- 10 AU - Ward AM ; Udnoon S ; Watkins J ; Walker AE ; Darke CS
AD - Hallamshire Hosp. Medical Sch., Sheffield S10 2RX, England
TI - IMMUNOLOGICAL MECHANISMS IN THE PATHOGENESIS OF VINYL CHLORIDE DISEASE.
SI - ICDB/76/18263
SO - Br Med J; 1(6015):936-938 1976
LA - ENG
AB - To determine the etiology and pathogenesis of vinyl chloride (VC) disease, immunological and immunochemical investigations performed on 58 workers from a VC polymerization plant showed the presence of circulating immune complexes in 19 out of 28 patients with the disease and in 2 of 30 workers exposed to VC. The immunological data were reviewed in relation to the clinical picture of the disease and to the available evidence on the metabolism of VC. The results suggest that VC disease is an immune complex disorder and that the immune response is initiated by the adsorption of VC or a metabolite, presumably the dioxide, onto tissue or plasma protein, producing either a haptenic group or a conformational change within the protein molecule that escapes tolerance and stimulates B cell proliferation.
- 11 AU - Withey JR
AD - Bureau Chemical Safety -5(-1Foods-5)-1, Health Protection Branch, Ottawa, Canada
TI - PHARMACODYNAMICS AND UPTAKE OF VINYL CHLORIDE MONOMER ADMINISTERED BY VARIOUS ROUTES TO RATS.
SI - CARC/76/00916
SO - J Toxicol Environ Health; 1(3):381-394 1976
LA - ENG
AB - To assess the hazard presented by the oral ingestion of vinyl chloride monomer, rats that had been surgically prepared with an indwelling jugular cannula were dosed by intragastric intubation with aqueous solutions containing up to 2.0 mg/ml vinyl chloride. Time-concentration curves were obtained from sequential samples of blood. The uptake of vinyl chloride by this route was found to be extremely rapid; peak concentrations were achieved less than 10 min after administration of the dose. Elimination from the blood compartment appeared to be bi-exponential. The distribution and elimination rates of vinyl chloride from the blood were also determined from the blood concentration data after the administration of an intravenous dose of aqueous or vegetable oil solution. Studies with the same animal model in a single restraint cage that allowed a "head only" exposure to concentrations of vinyl chloride up to 7,000 ppm in the gas phase

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have shown a similar rapid uptake followed by a plateau blood concentration during several hours of exposure. On removal from the vinyl chloride atmosphere, blood levels fell rapidly to barely detectable concentrations after 2 hr. Thus subsequent monitoring would not be a reliable indicator of exposure. Uptake profiles after oral dosage were extremely variable.

- 12 AU - Rannug U ; Gothe R ; Wachtmeister CA
 AD - Wallenberg Lab., Univ. Stockholm, S-104 05 Stockholm, Sweden
 TI - THE MUTAGENICITY OF CHLOROETHYLENE OXIDE, CHLOROACETALDEHYDE, 2-CHLOROETHANOL AND CHLOROACETIC ACID, CONCEIVABLE METABOLITES OF VINYL CHLORIDE.
 SI - CARC/76/00697
 SO - Chem Biol Interact; 12(3-4):251-263 1976
 LA - ENG
 AB - The ability of four conceivable metabolites of vinyl chloride - chloroethylene oxide, chloroacetaldehyde, 2-chloroethanol and chloroacetic acid - to cause base-pair substitution directly in *Salmonella typhimurium* TA1535 was compared. The main comparison was performed at initial concentrations from 0.1-1.5 mM. In this region, however, a mutagenic effect was observed only with chloroethylene oxide and chloroacetaldehyde, the former being approximately 20 times more effective than the aldehyde when compared on a molar basis. 2-Chloroethanol and chloroacetic acid were also studied at higher concentration (1 mM-1 M), and a weak mutagenic response was found with a 1 M 2-chloroethanol solution. With chloroacetic acid no enhancement of the mutation frequency could be detected. Chloroethylene oxide was found to be approximately 450 times more effective as a mutagen than chloroacetaldehyde when the comparison was based on exposure doses, defined as the time-dependent concentrations of the compounds in the treatment solutions, integrated between the times of onset and termination of treatment. Similarly, chloroethylene oxide was 10,000-15,000 times more effective as a mutagen than ethylene oxide, used as a positive control. Although chloroethylene oxide might play a part in the previously reported mutagenicity of vinyl chloride, it is more likely that it is the active metabolite of major importance, as this substance has the most pronounced property of producing a high number of mutants at low doses without causing a toxic effect.
- 13 AU - Baxter PJ ; Fox AJ
 AD - Employment Medical Advisory Service, 1 Chapstow Place, London W2 4TF, England
 TI - ANGIOSARCOMA OF THE LIVER IN P.V.C. FABRICATORS (LETTER TO EDITOR).
 SI - CARC/76/00535
 SO - Lancet; 1(7953):245-246 1976
 LA - ENG
 AB - A proportional-mortality study using death certificates for 1970-1972 was undertaken to detect any recent change in the pattern of mortality that may have occurred ascribable to vinyl chloride exposure. The only statistically significant excesses

for the causes of death were stomach cancer and diseases of the urogenital system.

- 14 AU - Dalderup LM ; Freni SC ; Bras G ; Bronckhorst FB
AD - Factory Inspectorate (DGA), Voorburg, P.B. 69, Holland
TI - ANGIOSARCOMA OF THE LIVER (LETTER TO EDITOR).
SI - CARC/76/00530
SO - Lancet; 1(7953):246 1976
LA - ENG
AB - Angiosarcoma of the liver in Holland was studied, particularly to determine an association with exposure to vinyl chloride. Twenty-seven patients were diagnosed as having angiosarcoma out of at least 40,000 necropsies since 1950. Of these, there were only eight definite (seven men) and one possible liver angiosarcoma. Although two cases were related to long-term arsenic or zinc chromate exposure, none of the 27 cases was associated with vinyl chloride exposure.
- 15 AU - Hussain S ; Osterman-Golkar S
AD - Wallenberg Lab., Univ. Stockholm, S-104 05 Stockholm, Sweden
TI - COMMENT ON THE MUTAGENIC EFFECTIVENESS OF VINYL CHLORIDE METABOLITES.
SI - CARC/76/00527
SO - Chem Biol Interact; 12(3-4):265-267 1976
LA - ENG
AB - In the region of low doses on dose-response curves, the mutagenic effectiveness per unit dose, determined as the time integral of concentration, was found for several alkylating agents to be approximately proportional to the calculated rate of reaction at a certain low nucleophilic strength, n approximately equal to 2. This proportionality appears to be independent of the nature of the alkyl introduced, and for this reason the computed degree of alkylation at n equal to 2, and at a given tissue dose, may be used tentatively to estimate genetic risk. The mutagenic effectiveness of chloroethylene oxide was found to be higher than the values obtained for two standard compounds, ethylene oxide and methyl methanesulfonate.
- 16 AU - Makk L ; Dalmore F ; Creech JL ; Ogden LL ; Fadell EH
AU - Songster CL ; Clanton J ; Johnson MH ; Christopherson WM
AD - Saint Anthony Hosp., Louisville, KY 40204
TI - CLINICAL AND MORPHOLOGICAL FEATURES OF HEPATIC ANGIOSARCOMA IN VINYL CHLORIDE WORKERS.
SI - CARC/76/00479
SO - Cancer; 37(1):149-163 1976
LA - ENG
AB - Fifteen male workers exposed to vinyl chloride developed angiosarcoma of the liver. Thirteen died of disease and two are currently living for short periods after diagnosis. Their ages ranged from 36-58 yr and their exposure time ranged from 4-27.8 yr. The most common presenting symptoms were fatigue, weight loss, and abdominal pain. Hepatomegaly followed by splenomegaly were the most common physical findings. Biochemical profiles

proved to be of little value in detection or diagnosis. Of eight patients autopsied, distant organ involvement was present in two cases, duodenal involvement in one, and direct extension of tumor to adjacent organs or tissues in four additional ones. The remainder, diagnosed by open liver biopsy, revealed no tumor extension. The gross features of the tumors were hemorrhagic necrosis, cystic degeneration, fibrosis, and apparent multicentricity. The histologic features were those of the typical angiosarcoma found in a variety of sites with a wide range of cellular differentiation. The histologic diagnosis was often impaired by the extensive tumor necrosis. Elsewhere in the liver subcapsular fibrosis, a distinct type of portal fibrosis and endothelial cell hyperplasia with or without sinusoidal dilatation were noted.

- 17 AU - Bartsch H ; Montesano R
AD - International Agency for Res. on Cancer, Unit Chemical Carcinogenesis, 150 cours Albert Thomas, 69008 Lyon, France
TI - MUTAGENIC AND CARCINOGENIC EFFECTS OF VINYL CHLORIDE.
SI - ICDB/77/15680
SO - Mutat Res; 32(2):93-113 1975
LA - ENG
AB - The carcinogenic and mutagenic effects of vinyl chloride (VC) are described. VC administered by inhalation is carcinogenic in rats, mice, and hamsters, producing angiosarcoma of the liver and other tissues in all three. In addition, in rats, VC induces tumors of the Zymbal glands and of the skin, nephroblastomas, hepatomas, and neuroblastomas. In mice, tumors of the lung and skin are also observed. The mutagenic activity of VC has been demonstrated by an in vitro technique utilizing the reverse mutation system of *Salmonella typhimurium*, in which the genetic indicator reverts to histidine prototrophy by single base-pair substitutions or by base-pair insertions or deletions. The carcinogenicity of VC in man and animals and its mutagenic action after metabolic conversion by microsomal enzymes from humans and rodents into electrophilic derivatives strengthen the relationship between mutagenesis and carcinogenesis. Despite the fact that there is no direct proof that chloroethylene oxide is the metabolite of VC primarily responsible for its biological effects in vivo, the biological importance of this compound is stressed by circumstantial evidence. The available data concerning the biological hazards of VC demonstrate that it is toxic, carcinogenic, and mutagenic in animals and man. (100 refs)
- 18 AU - De Serres FJ
AD - Environmental Mutagenesis Branch, Natl. Inst. Environmental Health Sciences, P.O. Box 12233, Research Triangle Park, NC 27709
TI - THE UTILITY OF SHORT-TERM TESTS FOR MUTAGENICITY IN THE TOXICOLOGICAL EVALUATION OF ENVIRONMENTAL AGENTS.
SI - ICDB/77/15113
SO - Mutat Res; 33(1):11-15 1975
LA - ENG
AB - Data from recent studies have demonstrated the utility of

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short-term tests for mutagenicity in the toxicological evaluation of numerous environmental chemicals. A correlation between carcinogenic and mutagenic activity has been found by using in-vitro techniques for metabolic activation in combination with sensitive microbial assay systems for detecting genetic alterations and measuring inhibition of enzymes responsible for DNA repair in *Salmonella typhimurium*, *Escherichia coli* and *Bacillus subtilis*. Generally, these assays have been able to distinguish between chemical carcinogens and noncarcinogenic structural analogs. Compounds which give positive mutagenicity results must be tested further for carcinogenicity. The combined use of these three tests, although they are not definitive, may serve as a method for prescreening chemicals in the development of a meaningful data base for benefit-risk evaluation. In short-term tests using *Salmonella*, many chemicals involved in occupational carcinogenesis, including vinyl chloride, benzidine, 4-nitrobiphenyl, and others, have all been shown to be active. Therefore, such assays could be an efficient, qualitative means of testing and controlling the use of potentially hazardous industrial chemicals. (no refs)

- 19 AU - Muller G ; Norpoth K
AD - Institut für Staublungenforschung und Arbeitsmedizin, Universität
Münster, Münster, West Germany
TI - DETERMINATION OF TWO VINYL CHLORIDE METABOLITES IN URINE (MEETING
ABSTRACT).
SI - CARC/77/02541
SO - Naturwissenschaften; 62(11):541 1975
LA - GER
AB - A ninhydrin-positive compound was detected in the urine of female
Wistar rats following the inhalation of vinyl chloride. The
retention time of this compound corresponded to that of
S-carboxymethylcysteine. Thiodiacetic acid was determined by
capillary gas chromatography after its conversion to the dimethyl
derivative. The findings indicate the value of determining the
urinary thiodiacetic acid concentration in vinyl chloride-exposed
subjects. (4 refs)
- 20 AU - Schlipkoter HW
AD - No affiliation given
TI - EFFECT OF AIR POLLUTANTS ON HUMANS WITH SPECIAL REFERENCE TO
ORGANIC COMPOUNDS (MEETING ABSTRACT).
SI - CARC/77/02428
SO - Lufthyg Silikoseforsch; 8:218-220 1975
LA - GER
AB - General data on the biological and toxic effects of hydrocarbon
air pollutants are reviewed. Polycyclic aromatic hydrocarbons,
such as benzo(a)pyrene, dibenz(a,h)anthracene, and benzo(b)fluoranthene,
induce sarcoma or carcinoma in experimental animals, depending on
the route of administration. There is an increasing amount of
evidence on the induction of angiosarcoma in workers exposed to
vinyl chloride. (No refs)

- 21 AU - Kilian DJ ; Picciano DJ ; Jacobson CB
AD - Dept. Industrial Medicine and Biomedical Res., Dow Chemical
U.S.A., Texas Div., Freeport, TX 77541
TI - INDUSTRIAL MONITORING: A CYTOGENETIC APPROACH.
SI - CARC/77/01118
SO - Ann NY Acad Sci; 269:4-11 1975
LA - ENG
AB - The authors describe the use of cytogenetic monitoring to detect changes induced by occupational exposures to chemicals, particularly to vinyl chloride. During a 10-yr period, 43,044 shorthand and conventional karyotypes of 1,689 production workers were studied by chromosome analysis correlated with a standardized medical history. Blood samples were drawn from each individual, slides were prepared, and a metaphase spread was located. The selected cells were photographed, the metaphase spread photographs were evaluated, and anomalous chromosomes were classified and tabulated according to the type of structural aberration. Chromosomes were karyotyped to permit detection of aberrations such as small deletions, translocations, and pericentric inversions. Preliminary data from the cytogenetic analysis of blood samples from 121 vinyl chloride workers were compared with preemployment examination records from 75 individuals who served as controls. The following three differences were seen: vinyl chloride workers showed less chromatid breakage, a greater frequency of dicentric chromosomes, and a lower percentage of abnormal cells than the preemployment comparison group. It is concluded that chromosome analysis is the procedure of choice for objective observation and measurement of possible insults to human genetic material and that the techniques described are the best for the detection of genetic injury at a stage when corrective action can be taken. (8 refs)
- 22 AU - International Agency for Research on Cancer
TI - EVALUATION OF CARCINOGENIC RISK OF CHEMICALS TO MAN. SOME ANTI-THYROID AND RELATED SUBSTANCES, NITROFURANS AND INDUSTRIAL CHEMICALS.
SI - ICDB/77/06781
SO - IARC Monogr; 7:326 1974
LA - ENG
AB - The carcinogenic risk of some anti-thyroid and related substances, nitrofurans, and industrial chemicals is discussed. The anti-thyroid and related substances consist of amitrole, ethylmethiourea, methylthiouacil, propylthiouacil, thioacetamide, thiouacil, thiourea, and urethane. The nitrofurans include 2-amino-5-(5-nitro-2-furyl)-1,3,4-thiadiazole, trans-2-[(dimethylamino)methyliminol-5-(2-(5-nitro-2-furyl)-vinyl)-1,3,4-oxadiazole, 2-(2-formylhydrazino)-4-(5-nitro-2-furyl)thiazole, 2-(morpholinomethyl)-3-[(5-nitrofurfuryl)idene]amino]-2-oxazolidinone, 5-nitro-2-furaldehyde semicarbazone, 1-[(5-nitrofurfuryl)idene]amino]-2-imidazolidinone, and

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N-[4-(5-nitro-2-furyl)-2-thiazolyli]acetamide. The industrial chemicals consist of acetamide, benzene, diazomethane, ortho-dichlorobenzene, para-dichlorobenzene, ethyl methanesulfonate, methyl methanesulfonate, polychlorinated biphenyls, and vinyl chloride. (refs)

- 23 AU - Fumes-Carvioto F ; Lambert B ; Lindsten J ; Ehrenberg L
AU - Natarajan AT ; Osterman-Golkar S
AD - Dept. Clinical Genetics, Karolinska Hosp., Stockholm, Sweden
TI - CHROMOSOME ABERRATIONS IN WORKERS EXPOSED TO VINYL CHLORIDE (LETTER TO EDITOR).
SI - CARC/77/00939
SO - Lancet; 1(7904):459 1975
LA - ENG
AB - Conventional lymphocyte cultures from seven workers occupationally exposed to vinyl chloride and three non-exposed controls were given chromosomal analysis. The level of exposure to vinyl chloride had continuously decreased during the past years; at the time of the study, the air concentration was 20 to 30 ppm. Of 566 control cells, 11 had chromosomal aberrations which were the result of previous diagnostic x-rays. Of the experimental cells, 9.52% were aberrant; this is statistically significant in comparison to the controls. The highest frequency of abnormal cells was in those subjects who had the shortest amount of exposure. (11 refs)
- 24 AU - Bartsch H ; Malaveille C ; Montesano R
TI - THE PREDICTIVE VALUE OF TISSUE-MEDIATED MUTAGENICITY ASSAYS TO ASSESS THE CARCINOGENIC RISK OF CHEMICALS.
SI - CARC/77/00992
SO - Screening Tests in Chemical Carcinogenesis Proceedings of a workshop organized by IARC and the Commission of the European Communities and held in Brussels, Belgium, 9-12 June 1975. Montesano R, Bartsch H, Tomatis L, Davis W, ed., International Agency for Research on Cancer. (Lyon, France); IARC Scientific Publications No. 12, 1975.
LA - ENG
AB - The Salmonella microsome system was used to assess the in vitro Salmonella mutagenicity assay for predicting possible carcinogenic effects of chemicals, to compare the capacity of different tissues and different species to convert chemical substances into mutagens, and, in particular, to investigate the metabolic activation of nitrosamines and chlorinated olefinic hydrocarbons. The mutagenicity of a series of cyclic nitrosamines in S typhimurium strain TA 1538 was similar in liquid suspension and in soft agar, but discrepancies arose when a series of dialkyl nitrosamines (of the form $(C_nH_{2n+1})_2N-N=O$) with different chain lengths were considered. The dialkyl nitrosamines with $n > 3$ did not show an enzyme-mediated response in the liquid incubation system, and in the soft agar metabolically activated dimethylnitrosamine and diethylnitrosamine exhibited negligible mutagenic activity. These findings reflect false negatives from both systems, perhaps brought about by the deterioration of

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microsomal enzymes by lipid peroxidation in the liquid system and by the trapping of short-lived alkylating molecular species by nucleophilic components of the agar. When the mutagenicity of a series of propylated nitrosamine derivatives was studied with microsomes from hamster and rat tissues, there was not a good correlation between tissue-specific activation to mutagenic intermediates and the known susceptibility of different tissues to carcinogenesis. A better correlation was seen when the activation to mutagenic metabolites of vinyl chloride by microsomes derived from rat and mouse liver, kidney, and lung tissues was studied. The major enzymic activities were located in both liver and kidney, sites where angiosarcoma and nephroblastoma are induced in animals exposed to vinyl chloride. No tissues studied exhibited a higher enzymic capacity than the liver to bring about the production of mutagenic metabolites. Microsomes from human livers were capable of generating mutagenic metabolites from N-nitrosomorpholine and vinyl chloride. Some aspects of the metabolism of chlorinated olefinic hydrocarbons are discussed further. (56 refs)

- 25 AU - Makk L ; Delorme F ; Creech JL
 AD - St. Anthony Hosp., Louisville, KY
 TI - HEPATIC ANGIOSARCOMA IN WORKERS FOLLOWING CHRONIC EXPOSURE TO VINYL CHLORIDE. EPIDEMIOLOGY AND RESEARCH PROGRAM IN WORKERS.
 SI - CARC/77/00503
 SO - Union Med Can; 104(12):1833-1835 1975
 LA - FRE
 AB - Several cases of hepatic angiosarcoma were found in two factories (one in Louisville, Kentucky, and one in Quebec, Canada), involved in the production of polyvinyl chloride from vinyl chloride. As a result, a survey was made of all 1103 employees of the Kentucky plant to detect other cases of angiosarcoma and to find early signs of benign liver damage. Three new cases were found in three men, aged 36-58, who had been exposed to the compounds for a period ranging from 4 yr to 27 yr, 10 mo. They survived from 2 to 22 mo after the appearance of the first symptoms. Although no test is specific for angiosarcoma of the liver, abnormalities in tests for hepatic function may be directly proportional to the extent of the lesions.
- 26 AU - Horbach L ; Koller S ; Loskant H
 AD - Institut für Medizinische Statistik und Dokumentation, Universität Erlangen-Nürnberg, 8520 Erlangen, Waldstrasse 6, West Germany
 TI - ANALYSIS OF CANCER MORTALITY FROM 1950 TO 1968 IN LARGE PREDOMINANTLY CHEMICAL INDUSTRIAL PLANTS WITH RESPECT TO INDUSTRIAL EXPOSURE.
 SI - CARC/77/00313
 SO - Zentralbl Arbeitsmed; 25(8):225-241 1975
 LA - GER
 AB - A comprehensive retrospective survey of cancer mortality in 10 large industrial facilities during 1950-1968 is discussed. Three chemical plants, a pharmaceutical house, a large automobile

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factory, three rubber plants, and two petroleum refineries were canvassed. Detailed data from questionnaires, medical reports, etc., about exposures, work habits, and type of cancer were matched with exhaustive classifications of chemical compounds. Mortality for the period included 4,445 men. The incidence of oropharyngeal carcinoma was higher and that of esophageal and gastric cancer lower than in the general population. Colon and rectal carcinomas, especially in nonexposed groups, were much higher than expected. Despite vinyl chloride exposure in the sample population, the occurrence of portal and biliary cancer was less than expected. Pancreatic tumors were also elevated. Striking increases in both urinary tract and respiratory cancer were established; bronchopulmonary involvement was especially high in workers exposed to both organic and inorganic chemicals. Skin cancer was slightly higher than expected. The incidences of cancer of the bone, connective tissue, endocrine glands, and prostate were similar to general population rates.

- 27 AU - Muller R ; Bechtelshaimen H ; Gadiqk P ; Marsteller HJ
 AU - Leibach HK
 AD - Pathologisches Institut der Universität, D-5300 Bonn-Venusberg, West Germany
 TI - MORPHOLOGICAL CHANGES OF THE LIVER AFTER CHRONIC VINYL CHLORIDE INTOXICATION.
 SI - CARC/77/00299
 SO - Leber Magen Darm; 5(5):204-209 1975
 LA - GER
 AB - The liver histopathology of 50 workers exposed to vinyl chloride was examined from biopsy material. Three of the probands presented with polycentric hemangioendothelial sarcoma extending along the ectatic sinusoids into the parenchyma. In border areas a transition between proliferating atypical sinusoid cells and tumor cells was apparent, typical of the angiosarcomas reported after chronic arsenic and thorium dioxide exposure. Septal fibrosis of the portal fields and collagenization of sinusoid walls, chainlike proliferation of sinusoid endothelial cells with nuclear polymorphism, hepatocytic hyperplasia with nuclear polyploidy, and focal adaptation of the hepatocytic cytoplasm (with hyperplasia of the smooth endoplasmic reticulum) to hydropic swelling, fat vacuolization, and cell necrosis were signs of generalized hepatotoxicity. Hepatocytic hyperplasia was most pronounced in the areas of the reactive sinusoid endothelium and at tumor interfaces.
- 28 AU - Marsteller HJ ; Leibach HK ; Muller R ; Gadiqk P ; Lange CE
 AD - Medizinische Universitätsklinik, D-5300 Bonn-Venusberg, West Germany
 TI - LIVER DISEASE IN POLYVINYL CHLORIDE PRODUCTION WORKERS--CLINICAL AND LAPAROSCOPIC ASPECTS.
 SI - CARC/77/00298
 SO - Leber Magen Darm; 5(5):196-202 1975
 LA - GER
 AB - Clinical and histopathological findings in suspected

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occupationally induced liver and spleen disease among 44 workers engaged in vinyl chloride polymerization are presented. Palpable hepatomegaly and splenomegaly were found in 28 and 16 patients, respectively. A considerable BSP retention, low grade hyperbilirubinemia, and transient elevation in SGOT, SGPT, and alkaline phosphatase were the only remarkable biochemical variables. The majority had pronounced thrombocytopenia, with platelet dysfunction. Hepatic fibrosis with encapsulated vascularization was conspicuous in 35 probands; a nodular liver surface and portal hypertension were also present. Liver histopathology was not conspicuous. Adaptive hepatocyte focalization, nuclear polymorphism and polyploidy, septal fibrosis, focal collagenization of sinusoid walls, and sinusoid endothelial proliferation and atypia were identified. No angiosarcomatous areas were found in laparotomies of the patients with noncirrhotic portal fibrosis after vinyl chloride exposures ranging between 9 mo and 21-3/4 yr.

- 29 AU - Rademacher P
 AD - Organisch-Chemisches Institut, Universität Munster, Munster, West Germany
 TI - CHEMICAL CARCINOGENS.
 SI - CARC/76/04467
 SO - Chemie in unserer Zeit; 9(3):79-84 1975
 LA - GER
 AB - The roster of known chemical carcinogens, demonstrations of their properties, and their mechanistic development in host cells are reviewed with special attention to occupational exposure. If 90% of all cancers result exogenously, then 60% are attributed to chemical hazards; cancer mortality is 25% higher among chemists than the general population. The conventional biphasic schedule of cell transformation is adopted. During an initial phase of chemical attack, a normal cell becomes precancerous; during a subsequent promotional phase, cocarcinogens shift the atypical cell into the malignant state. Experimental evidence fitting various chemical carcinogens into this scheme is cited. Inorganic compounds, aromatic hydrocarbons and their N, O, and S analogs, aromatic amines, nitro and azo compounds, aliphatic hydrazines, azo and azoxy compounds, N-nitroso compounds, alkylating agents, naturally occurring products (especially bacterial, fungal, or faunal metabolic products), and routine laboratory reagents are implicated. Based on the recent vinyl chloride episode, maximum allowable occupational concentrations are discussed in connection with instrumentation and procedures designed to minimize vulnerability to carcinogenic hazards.

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- 30 AU - Englund A ; Holmberg B
AD - Landsorganisationen, Sweden
TI - OCCUPATIONAL CANCER DISCUSSED AT NEW YORK CONFERENCE.
SI - ICD8/75/05500
SO - Lakartidningen; 72(38):3487-3488 1975
LA - SWE
AB - The proceedings of a conference on occupational cancer organized by the New York Academy of Sciences in cooperation with National Cancer Institute and NIOSH (held on March 24-27, 1975, New York) are reviewed. Increased incidence of lung cancer was found among workers exposed to very small glass-fibers in glass-fiber manufacturing plants. A suspected relationship between asbestos exposure and cancer of the larynx was verified. Increased incidence of skin and lung cancer was found among workers exposed to chloroprene (Neoprene). Vinyl chloride, trichlorobenzene, and benzoyl chloride were found to be carcinogens. Increased incidence of lung and kidney cancer was observed among coke oven operators. The high time requirements and the high expenses involved in carcinogenicity testing, and the correlation existing between carcinogenic and mutagenic properties justifies short-term mutagenicity tests for screening for carcinogenic substances. Because of the many factors involved in the carcinogenic response, a zero exposure to carcinogenic substances is recommended.
- 31 AU - Carter RL ; Roe FJ
AD - Inst. Cancer Res., Royal Cancer Hosp., London, England
TI - CHEMICAL CARCINOGENS IN INDUSTRY.
SI - CARC/76/03623
SO - J Soc Occup Med; 25(3):86-94 1975
LA - ENG
AB - Occupational hygiene programs and industrial plant designs must be improved to reduce the hazards of known industrial carcinogens. Polycyclic aromatic hydrocarbons, specifically, mineral oils and coal gas, have been linked with scrotal and skin cancers in industrial workers. A more refined cutting oil may reduce the risk of scrotal cancer. The incidence of deaths from lung cancer in England was found to be almost double the normal rate for workers exposed to coal and tar gas. An enhanced risk for bladder cancer was noted in workers exposed to benzidine, b-naphthylamine, and a-naphthylamine. The incidence was dose-related, with the highest rate in workers who distilled b-naphthylamine. Exposure to the alkylating agent mustard gas was associated with a marked increase in deaths from respiratory tract carcinoma in Japanese workers. Bis(chloromethyl)ether (BCME) exposure for 6 to 9 yr in 68 production workers (31-65 yr) was followed by lung cancer in 8/68; 5 tumors were oat-cell carcinoma. An increased incidence of hepatic angiosarcoma was noted for workers involved in polymerizing vinyl chloride to poly(vinyl chloride) (PVC); there was also an excess of neoplasms of the biliary system, lung, and brain in vinyl chloride workers who died before age 60. An increased risk for respiratory cancer

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has been established in workers involved in mining or milling asbestos products; the basis for carcinogenicity is still uncertain, but studies indicate that there may be an optimal size of the fiber for carcinogenic activity. Computerized industrial epidemiology may help to determine cancers of occupational origin that have been overlooked and help to protect workers from known hazards.

- 32 AU - Hublet P
AD - Ecole de Sante publique de la Faculte de medecine, Universite libre de Bruxelles, rue Belliard 100, 1040 Brussels, Belgium
TI - INDUSTRIAL HAZARDS DUE TO VINYL CHLORIDE.
SI - CARC/76/02991
SO - Arch Belg Med Soc; 33(2):73-89 1975
LA - FRE
AB - Various aspects of vinyl chloride are reviewed: its physical and chemical properties, methods of synthesis, means of identification, uses, evidence of toxic effects, and industrial risks due to exposure. Because of its toxicity, greater efforts should be made to reduce the concentration in factory air, and workers exposed to the chemical should be examined often. More detailed studies of vinyl chloride and other toxic chemicals should be undertaken.
- 33 AU - Delorme F ; Makk L
AD - Centre hospitalier regional de la Mauricie, C.P. 1130, Shawinigan-Sud, Quebec, Canada
TI - HEPATIC ANGIOSARCOMA IN WORKERS FOLLOWING CHRONIC EXPOSURE TO VINYL CHLORIDE. MORPHOLOGICAL DESCRIPTION OF THE LESIONS.
SI - CARC/76/02914
SO - Union Med Can; 104(12):1836-1844 1975
LA - FRE
AB - The histological characteristics of liver angiosarcomas (2 metastases) in 18 men (36 to 58 yr; mean age 46.7) who had prolonged exposure to vinyl chloride (4 yr to 27 yr 10 mo; mean time 17 yr 4 mo) are presented. Various benign lesions were noted not only in the angiosarcoma cases but also in noncancerous cases who also had prolonged exposure. Many of the perisinusoidal cells of the angiosarcomas resembled, with their elongated nuclei, the small mesenchymatous cells of the benign tumors. The angiosarcomas had different forms: sinusoidal, sarcomatous, nodulopapillary, and cavernous. These cancers are generally preceded by the appearance of ten benign lesions induced by the vinyl chloride. They appear simultaneously in many places and apparently are multifocal. The numerous nodules are not intraparenchymal metastases from a primary tumor but are themselves primary tumors.

- 34 AU - Ravier E ; Diter JM ; Pialat J
AD - Societe des Usines chimiques Rhone-Poulenc, Usine de Roussillon
38, Roussillon, France
TI - A CASE OF LIVER ANGIOSARCOMA IN A WORKER EXPOSED TO MONOMERIC
VINYL CHLORIDE.
SI - CARC/76/02906
SO - Arch Mal Prof; 36(3):171-177 1975
LA - FRE
AB - The authors present the case history of 43-yr-old man with
prolonged industrial exposure to monomeric vinyl chloride who was
admitted to the hospital for acute abdominal bleeding. The right
hepatic lobe was excised; a hemangioendotheliosarcoma of the
liver was histopathologically diagnosed. The patient died
following surgery. The cancer was probably the result of exposure
to the carcinogen.
- 35 AU - Duport J ; Andlauer P ; Gattelet M ; Chalabreysse J ; Archimbaud M
AU - Teulon F ; Bertrand R
AD - Centre de Recherches de l'I.N.R.S., B.P. 27, 54500
Vandœuvre-lès-Nancy, France
TI - OCCUPATIONAL DISEASES IN CONNECTION WITH THE MANUFACTURE OF
PLASTIC BOTTLES FROM POLYVINYL CHLORIDE.
SI - CARC/76/02949
SO - Arch Mal Prof; 36(4-5):225-241 1975
LA - FRE
AB - Because of an outbreak of eczema, the blood and urine from
workers in a factory that manufactures plastic bottles from vinyl
chloride were examined. The chemical pollutants of the
surrounding area, all industrial chemicals and cleansing
solvents, and the heat decomposition of the polyvinyl chloride
(PVC) bottles were studied. Over a 6-mo period, 677 blood samples
from 159 workers revealed depressed levels of RBC and polynuclear
neutrophils, elevated levels of HSC, and variable levels of
polynuclear eosinophils. It is concluded that the manufacture of
vinyl chloride bottles causes dermatitis and hematological
abnormalities characterized by leukocytosis with relative
lymphocytosis. Analysis of the air by gas phase chromatography
and mass spectrometry revealed only slight traces of aromatic
hydrocarbons. No aromatic hydrocarbons were found in the
cleansing solvents. Industrial forms of PVC began to decompose
slowly between 215 and 220 C; benzene was one of the byproducts
of decomposition. Because this temperature is reached for short
periods only and because decomposition is slow, it is unlikely
that it is a major factor. Neither benzene nor phenol were found
in the blood or urine, respectively. There were significant
levels of hippuric acid, a possible metabolite of organic toxins,
in the urine. Since none of these compounds was considered the
cause of the dermatitis or hematological abnormalities,
a-phenylindole, the only compound detected in high concentrations
in the air, will be studied.

- 36 AU - Ott MG ; Langner RR ; Holder BB
AD - Dow Chemical Co., Corporate Medical Dept., 2030 Dow Center,
Midland, Mich. 48640
TI - VINYL CHLORIDE EXPOSURE IN A CONTROLLED INDUSTRIAL ENVIRONMENT: A
LONG-TERM MORTALITY EXPERIENCE IN 594 EMPLOYEES
SI - CARC/75/01145
SO - Arch Environ Health; 30(7):333-339 1975
LA - ENG
AB - The relation between tumor incidence and the highest levels of
vinyl chloride exposure was examined. Measurements of the work
environment began in 1950 by collecting breathing zone samples on
silica gel and measuring chlorides by the Volhard method to
calculate vinyl chloride. More recently, a combination of gas
chromatography and mass spectrometry has been used to identify
airborne material. The study population included production
employees who worked between 1942 and 1960 in areas of potential
vinyl chloride exposure. Each job was classified according to
time-weighted average (TWA) concentration of vinyl chloride for
an eight-hr day. The high level concentration was defined as
over 200 ppm vinyl chloride, and the low level was below 25 ppm.
Observed deaths among vinyl chloride workers were 91% of the
expected deaths based on the U.S. white male population.
Distribution of malignant neoplasms suggests a possible
dose-response relationship, since nine of 13 malignancies were
observed in the high exposure group. The Chi 2 comparison of the
distribution of malignancy deaths between high and all other
exposure groups was significant (P is less than 0.01). No
adverse malignancy effects are demonstrated in the lower exposure
categories.
- 37 AU - Nisbet IC
AD - No Affiliation Given
TI - THE COSTS OF CANCER.
SI - CARC/76/00515
SO - Technol Rev; 78(3):8-9 1975
LA - ENG
AB - Social and economic problems arising when a cancer-causing
substance is identified are discussed, with particular emphasis
on the case of vinyl chloride. Prior to the discovery of its
hazards, an estimated 100 million pounds a year were lost to the
environment during manufacture and a further 40-50 million pounds
were released through deliberate dispersive uses. Although the
most hazardous of these uses--as a propellant in spray cans--was
banned in 1974, and although attempts are being made to reduce
manufacturing losses, human exposure continues. The most serious
problem is that trace quantities of unpolymersized vinyl chloride
are found in polyvinyl chloride. Both nonoccupational and
occupational exposure can be hazardous. Although federal law
requires strict regulation of occupational exposure to
carcinogens, the proposed standard for vinyl chloride offers
little or no assurance of safety.

- 38 AU - Chabalko JJ ; Fraumeni JF
AD - Natl. Cancer Inst., Bethesda, Md. 20014
TI - BLOOD-VESSEL NEOPLASMS IN CHILDREN: EPIDEMIOLOGIC ASPECTS.
SI - CARC/75/05748
SO - Med Pediatr Oncol; 1(2):135-141 1975
LA - ENG
AB - In a search for etiologic leads to blood-vessel neoplasms, 111 death certificates of U.S. children who died between 1960 and 1968 of angiosarcoma, hemangioendothelioma, and hemangiopericytoma and 127 medical records of similar cases from 12 institutes were examined. The available data provided no leads to environmental agents (vinyl chloride , thorotrast , arsenic) that can produce vascular liver tumors in adults; however, one infant, who died from a hepatic tumor, lived within a mile of an industrial source of polyvinyl chloride . About half of the children with hepatic hemangioendotheliomas had associated skin hemangiomas, which may aid in the differential diagnosis of liver tumors in infancy. Hepatic hemangioendotheliomas also predominated in girls, a possible clue to the origin of the tumor. A familial influence was suggested by one sibling aggregation of cutaneous hemangioendotheliomas.
- 39 AU - Schmidt AM
AD - No affiliation given
TI - VINYL CHLORIDE POLYMERS IN CONTACT WITH FOOD.
SI - CARC/75/05081
SO - Fed Regist; 40(171):40529-40537 1975
LA - ENG
AB - Proposed regulations restricting the uses of vinyl chloride (VC) polymers in contact with food, as suggested by the Food and Drug Administration, are reviewed. In general, the proposal permits the continued use of VC polymers in food packaging when the migration potential of VC is diminished, includes an interim regulation for the use of water pipes made from VC polymers, and prohibits all other use of VC polymers in food-contact articles. The chemical structure and properties of CC and VC homopolymers and copolymers are described. Earlier studies have indicated that polyvinyl chloride (PVC) is insoluble in various solvent systems used to simulate food. However, later migration studies have revealed residual VC from PVC bottles in distilled spirits and wines. No animal feeding studies have established a safe level of consumption when VC is extracted from containers into food. The existence of residual VC in articles made from VC polymers has been found to be related to the manufacturing process and the physical structure of the polymers; a model explaining the VC migration phenomenon is presented. Viewed as a simple diffusion phenomenon, experimental data indicate that while no VC is extractable from packaging materials, the greatest likelihood for migration of VC appears to be from PVC articles intended for one-time use. However, there is little likelihood that residual VC from PVC water pipes will become a component of potable water. Considerable data exist concerning the toxic

effects of VC from atmospheric exposures, especially by inhalation and occupational contact; it is also suggested that VC is carcinogenic when ingested. Although a variety of uses of VC polymers in food-contact articles was previously approved, it is now suggested that widespread use be prohibited. It is concluded that no migration of VC from thin plasticized film is expected, nor is any migration expected from jar and bottle cap liners and gaskets. No residual VC reported in beer and soft drink can linings, but VC polymers used as coatings for fresh citrus fruits present the possibility of ingestion. Data also indicate that rigid and semirigid PVC articles intended to contact food may transmit VC to the food they contact. Proposed federal regulations and amendments are presented.

- 40 AU - Janerich DT ; Lawrence CE
AD - Cancer Control Bureau, New York State Dept. Health, New York, N.Y.
TI - EPIDEMIOLOGICAL STRATEGIES FOR IDENTIFYING CARCINOGENS.
SI - CARC/75/04383
SO - Mutat Res; 33(1):55-63 1975
LA - ENG
AB - Two situations in which epidemiologic studies were used to identify carcinogens are reviewed and efforts to use New York State Cancer Control Bureau data for systematic surveillance of reported cancer incidence are discussed. The association between diethylstilbestrol and vaginal cancer in young women and between vinyl chloride and angiosarcoma of the liver was confirmed by epidemiological evidence, although in both cases the association was initially suggested by clinical observations. In the case of diethylstilbestrol, epidemiologic studies indicated the limits of the risk associated with intrauterine exposure; it is suggested that age limits will be identified for the carcinogenic potential of intrauterine exposure to diethylstilbestrol, just as intrauterine exposure to X-rays causes an increased risk of leukemia only during the first decade of life. In the case of vinyl chloride, its connection with angiosarcoma of the liver was first based on clinical observations and the rare nature of the disorder. Both of these situations indicate that present methods of detection are crude, and that a large number of people are exposed to chemicals before their carcinogenic potential is recognized. Preliminary efforts to develop a systematic cancer monitoring methodology in New York State involved analysis of cancer data from three anatomical sites: colon, pancreas, and gall bladder. These efforts yielded one instance in which an unquestionably high cancer incidence was suggestive of some environmental etiological agent. In two years, a single county showed unusual rates of pancreatic cancer. However, preliminary investigation showed no obvious environmental exposure associated with the cluster, and in subsequent years the incidence rate returned to within expected limits. Two alternatives in devising an epidemiological strategy are considered: the cohort study and the case history study. The case history study sometimes runs the risk of failing to detect a disease risk when one is actually present. Even when a properly structured cohort study is done,

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it is only as precise as the sample size used in the study. It is concluded, however, that epidemiologic studies together with laboratory and clinical disciplines, can produce a reasonable degree of assurance about the absolute limits of the risk associated with the use of suspected environmental hazards.

- 41 AU - Swaffield L
AD - no affiliation given
TI - ANOTHER CARCINOGEN?
SI - ICDB/75/07385
SO - Nature (Lond); 258(5532):190 1975
LA - ENG
AB - Trichloroethylene, used as a degreaser and chemically similar to vinyl chloride monomer (VCM), is implicated as a carcinogen.
- 42 AU - Spirtas R ; McMichael AJ ; Gamble J ; Van Ert M
AD - Occupational Health Studies Group, Univ. North Carolina, Chapel Hill, N.C.
TI - THE ASSOCIATION OF VINYL CHLORIDE EXPOSURES WITH MORBIDITY SYMPTOMS.
SI - CARC/75/03951
SO - Am Ind Hyg Assoc J; 36(10):779-789 1975
LA - ENG
AB - A population of vinyl chloride (VC) polymerization and rubber workers were questioned about job-related illness. Of the workers responding to a mail questionnaire, 200 were current VC workers and 89 were current workers in the rubber industry. The individual jobs were grouped according to VC exposure (i.e. high, low, and essentially no exposure to VC). As the symptoms under consideration were all transitory and reversible, an acute effects model was employed. Thus, the job was treated as the unit of observation. For the 255 high-exposure group jobs, 37% reported symptoms of dizziness or light-headedness at least once; 12% of the low-exposure group experienced such symptoms. Ten percent of the rubber workers reported these symptoms. Using a series of statistical analyses, the differential exposures to VC among the three study groups accounted for only one of the many possible hazards. A clear dose-response relationship indicated with the symptoms of dizziness, nausea, headache, 'pins and needles', and general fatigue. There were also some indications of a dose-response to fainting and eye, nose or throat irritation. It thus appears that a dose-response relationship exists between certain acute predominantly neurological symptoms and vinyl chloride exposure.
- 43 AU - Bartsch H ; Malaveille C ; Montesano R
AD - Int. Agency Res. Cancer, Lyons, France
TI - HUMAN, RAT AND MOUSE-LIVER MEDIATED MUTAGENICITY OF VINYL CHLORIDE IN S. TYPHIMURIUM STRAINS.
SI - CARC/75/00668
SO - Int J Cancer; 15(3):429-437 1975
LA - ENG
AB - The mutagenicity of vinyl chloride monomer (VCM) and its presumed

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metabolites in *Salmonella typhimurium* strains as mediated by tissue fractions of mouse, rat, and human origin were studied. The male BD-IV rats (100-130 g) and male OF-1 mice (30-35 g) used were fed a Charles River CRF diet. After six hours of exposure to 20% VCM in air (vol/vol) strain TA 1530 was specifically reverted to His prototrophy. This mutagenic response was increased to 283% of the control value by mouse liver postmitochondrial fraction (9,000 x g supernatant); to 345% of the control by rat liver postmitochondrial fraction; and from 270-700% of the control value by four samples of this fraction from four biopsies of human livers. Phenobarbital sodium (PB) was added to the animals' drinking water (1 mg/ml) for seven days before tissue fractionation in some experiments. This treatment increased the above mutagenic response to 457% for mouse liver fractions and to 383% for rat liver fractions. No cytotoxic effects of VCM were seen. Chloroacetic acid (a urinary metabolite of VCM) and chloroacetaldehyde were toxic, while chloroethanol was weakly mutagenic for TA 1530. The effects of subcellular fractions from mouse liver on the mutagenic response after six hours of exposure to 20% VCM at 37 C were: postmitochondrial fraction, 323% of control; microsomal fraction, 132%; cytosol (supernatant after 100,000 x g) 144%; and microsomal fraction plus cytosol, 522% of control. The number of His+ revertants minus the number of spontaneous mutations found when no tissue fraction was added was used as the control value. A casual relationship between VCM exposure and angiosarcoma of the liver in man has been established.

- 44 AU - Nicholson WJ ; Hammond EC ; Seidman H ; Selikoff IJ
 AD - Mt. Sinai Sch. Med., City Univ. New York, N.Y.
 TI - MORTALITY EXPERIENCE OF A COHORT OF VINYL CHLORIDE-POLYVINYL CHLORIDE WORKERS.
 SI - CARC/75/00597
 SO - Ann NY Acad Sci; 246:225-230 1975
 LA - ENG
 AB - The medical histories and current health status were obtained from 255 of 257 Goodyear Tire and Rubber Company employees who had been exposed to polyvinyl chloride (PVC) and vinyl chloride (VC) for a minimum of five yr subsequent to 1946. Observation began ten yr after the onset of exposure. The individuals worked in PVC production majority, maintenance, shipping, and in the laboratory. These workers may often have been exposed to peak VC concentrations exceeding 1,000 ppm. Over 50% of the employees were under age 37 as they entered the cohort. Twenty-four individuals were deceased and three of these deaths were due to liver hemangiosarcoma. One glioblastoma, two lymphomas, and one liver cirrhosis with associated bleeding esophageal varices accounted for other deaths. All of these conditions appear to be associated with VC. The three hemangiosarcomas occurred in individuals exposed prior to 1951. Longer periods of observation are thus needed to study the full spectrum of VC-induced malignancies and their incidence among exposed workers.

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- 45 AU - Schweitzer GE
AD - Off. Toxic Subst., Environ. Prot. Agency, Wash., D.C.
TI - ENVIRONMENTAL CONCERNS BEYOND THE WORKPLACE.
SI - CARC/75/00596
SO - Ann NY Acad Sci; 246:296-302 1975
LA - ENG
AB - Preliminary investigations were undertaken by the Environmental Protection Agency on vinyl chloride monomer (VCM) and polyvinyl chloride (PVC) activities, especially their migration beyond the manufacturing plants. A nationwide sampling program to determine VCM levels in ambient areas was initiated at ten PVC plants. The need for the proposed Toxic Substances Control Act which would require reporting of industrial data is emphasized. Over 200 million and 50 million pounds of VCM and PVC, respectively, are estimated to be discharged into the air, water, effluents and sludge annually. A materials loss of 6% in the PVC production process was reported. Leakage typically occurs during opening of polymerization kettles, transfer, drying and disposal of oversize polymer particles. Increased maintenance has reduced loss to 4% in some plants. Many compounding and fabrication plants are attempting to reduce the amount of monomer associated with the polymer following polymerization since monomer concentration ranges between 500-1,000 ppm and may reach 7,000 ppm. Epidemiological studies of populations near PVC plants and toxicological tests in vivo are necessary in assessing effects of VCM exposure on the nonworker population. In vitro experiments on the significance of impurities in VCM, synergistic effects due to exposure to other chemicals, and metabolic reactions induced by VCM are necessary. The persistence and migration of VCM in the environment should also be studied. Physical properties of PVC must be considered with regard to disposal. Landfill disposal presents problems because long-term PVC stability cannot be guaranteed and HCl is produced when it is incinerated.
- 46 AU - Rowe VK
AD - Dow Chem. U.S.A., Health Environ. Res., Midland, Mich
TI - EXPERIENCE IN INDUSTRIAL EXPOSURE CONTROL.
SI - CARC/75/00594
SO - Ann NY Acad Sci; 246:306-310 1975
LA - ENG
AB - Industrial hygiene methods employed by the Dow Chemical Company provide a model upon which future environmental control systems can be based. The results of toxicological studies of vinyl chloride and vinylidene chloride since 1959 indicated an increased need for monitoring of these substances in the air. Dow widely uses combustion-conductivity analysis but gas chromatography and infrared spectrophotometry have also been recently employed. Time-weighted averages of vinyl chloride exposure that an employee would have in a given job can be computed. In 1959, it was established that this average exposure should not exceed 50 ppm vinyl chloride or 25 ppm vinylidene chloride for an eight-hour five-day week. Exposure was 1-10.4

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ppm for most employees in three monomer plants, but laboratory personnel were exposed to 30 ppm. While levels were only 1-5 ppm for most employees in the polymer plant, some areas showed as high as 150 ppm. Safe levels of any hazardous material must be established and maintained through appropriate engineering and monitoring. Corrective measures should be taken when breakdowns occur and a medical surveillance program must be supported. Vinyl chloride is processed in closed vessels with maximum ventilation, and process automation and remote operation are emphasized. The number of samples for control analysis is minimized, manual collection is reduced by using on-line gas chromatography, and a closed-loop sampling system is used. Polymerization vessels must contain vinyl chloride concentrations of less than 50 ppm before entry for cleaning and air purge must be maintained during the operation.

- 47 AU - Thomassen MJ ; Buoan LC ; Brand KG
 AD - Univ. Hosp. Cleveland, Ohio
 TI - FOREIGN-BODY TUMORIGENESIS: NUMBER, DISTRIBUTION, AND CELL DENSITY OF PRENEOPLASTIC CLONES.
 SI - CARC/75/00280
 SO - JNCI; 54(1):203-207 1975
 LA - ENG
 AB - The number of preneoplastic clones was calculated in foreign body tumorigenesis and their distribution patterns on foreign body surfaces were analyzed in an investigation which was undertaken primarily to determine how many different preneoplastic parent cells are mobilized in an animal responding to foreign body implantation. Double 15 x 22 mm plastic films (rigid and unplasticized vinyl chloride acetate copolymer; two films on top of each other) were implanted sc in CBA/H-T6 mice. After 7.5 (group 1), 8.5 (group 2), and 9.5 (group 3) months, the films were removed and each interior film covered by a cell monolayer on one side only was cut in four 7 x 10 mm segments. The film segments were then transferred to (CBA/H CBA/Br)F1, or (CBA/H-T6 CBA/Br)F1, recipient mice which carried preformed foreign body-reactive tissue capsules, induced two months earlier by implantation of glass coverslips. Each segment was placed in the preformed tissue capsule with the cell area pointing toward the body wall of the animal. Tumors arising from segments of the same implant and from the corresponding original capsule were examined for possible homology by: in vitro culture and chromosomal analysis; preparation of histologic sections stained with hematoxylin and eosin for determination of the histopathologic sarcoma type and the grade of anaplasticity; tumor growth characteristics and growth rate in vivo on transplantation of 1-mm³ tumor specimens to histocompatible recipients and in vitro; and evaluation of tumor latencies. Definite homology was established in 2/9 tumor-positive donor animals in group 1 and in 2/9 tumor-positive animals in group 2. Five tumors of definite homology were seen among 11 positive donors in group 3. It is concluded that preneoplastic clones were present in limited numbers and that they were either widely

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disseminated or spatially restricted on the implant surfaces. It is further concluded that for clone dissemination, the clonal cells must reach a crucial stage of preneoplastic maturity and/or the foreign body-reactive capsule must be in a condition permitting cells to complete preneoplastic maturation and achieve neoplastic autonomy.

- 48 AU - Brand KG ; Buoen LC ; Johnson KH ; Brand I
AD - Med. Sch., Univ. Minnesota, Minneapolis
TI - ETIOLOGICAL FACTORS, STAGES, AND THE ROLE OF THE FOREIGN BODY IN FOREIGN BODY TUMORIGENESIS: A REVIEW
SI - CARC/75/00276
SO - Cancer Res; 35(2):279-286 1975
LA - ENG
AB - Attempts were made to correlate previously published data and observations on the process of foreign body tumorigenesis with the course of the tumorigenic foreign body reaction as studied histologically and by electron microscopy. Plastic films (unplasticized vinyl chloride acetate copolymer, 15x22x0.2 mm) were implanted in CBA/H or CBA/H-T6 mice. After various time periods, the implants were excised, cut into smaller segments, and transferred separately into recipient mice which were fully histocompatible, yet distinguishable from the donor mouse. Sarcomas of donor origin developed in the recipients up to two yr later. Tumors that arose from segments of the same original implant were often homologous. Similar experiments were conducted to determine appearance time and location of preneoplastic cells relative to the course of foreign body reaction. The earliest successful demonstration of preneoplastic cells on the foreign body surface was accomplished at 11 weeks postimplantation. From these observations it seems that the process of foreign body tumorigenesis proceeds through several stages, each seemingly providing specific conditions required sequentially for preneoplastic maturation as expressed by the following criteria: cellular proliferation and tissue infiltration during acute foreign body reaction; fibrosis of the tissue capsule surrounding the foreign body; quiescence of the tissue reaction; and availability of a foreign body surface for direct contact with clonal preneoplastic cells. There is no indication that the initial acquisition of neoplastic potential and the determination of specific tumor characteristics are based on direct physical or chemical reactions between cells and the foreign body. These key etiological events presumably occur in mesenchymal stem cells associated with the microvasculature no later than during the acute stage of foreign body reaction and long before clonal descendants of these cells are first found in contact with the foreign body surface. It is suggested that cells with neoplastic determination may be present in normal tissue prior to the introduction of a foreign body and that the foreign body only creates the conditions required for step-wise preneoplastic maturation.

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- 49 AU - McCann J ; Simmon V ; Streitwieser D ; Ames BN
AD - Biochemistry Dept., Univ. California, Berkeley, Calif. 94720
TI - MUTAGENICITY OF CHLOROACETALDEHYDE, A POSSIBLE METABOLIC PRODUCT OF 1,2-DICHLOROETHANE (ETHYLENE DICHLORIDE), CHLOROETHANOL (ETHYLENE CHLOROHYDRIN), VINYL CHLORIDE AND CYCLOPHOSPHAMIDE (MEETING ABSTRACT).
SI - CARC/75/03179
SO - Proc Natl Acad Sci USA; 72(8):3190-3193 1975
LA - ENG
AB - A rapid, sensitive bacterial test to detect chemical carcinogens as mutants utilizes a special set of histidine mutants of *Salmonella typhimurium* for reversion, and a rat (or human) microsomal system for metabolic conversion of carcinogens to their active forms. The mutagenicity of chloroacetaldehyde was tested in this system because the compound is a possible metabolite in mammals of the large-volume industrial chemicals 1,2-dichloroethane (ethylene dichloride; 3.5 billion kg/yr, U.S.) and vinyl chloride (2.5 billion kg/yr, U.S.), and of the antineoplastic agent, cyclophosphamide. Chloroacetaldehyde effectively reverted a new *Salmonella* bacterial tester strain (TA100) at all levels tested (1-5 mg). Chloroacetaldehyde was hundreds of times more effective in reverting TA100 than was chloroethanol (ethylene chlorohydrin), a known metabolic precursor of chloroacetaldehyde and a possible metabolite of dichloroethane and vinyl chloride; or vinyl chloride, which is itself mutagenic for TA100. Chloroethanol was activated by rat and human liver homogenates to a more highly mutagenic form with reversion properties similar to chloroacetaldehyde. Reversion properties of cyclophosphamide after in vitro metabolic activation suggests that chloroacetaldehyde is not the active mutagenic form of this antineoplastic drug. The likely involvement of chloroacetaldehyde in the metabolism of dichloroethane and chloroethanol indicates that the carcinogenicity of these industrial chemicals should be thoroughly examined.
- 50 AU - Drew RT ; Harper C ; Gupta BN ; Tallev FA
AD - Natl. Inst. Environmental Health Sciences, P.O. Box 12233, Res. Triangle Park, N.C. 27709
TI - EFFECTS OF VINYL CHLORIDE EXPOSURES TO RATS PRETREATED WITH PHENOBARBITAL.
SI - CARC/75/03679
SO - Environ Health Perspect; 11:235-242 1975
LA - ENG
AB - Male Charles River CD-1 rats were exposed to ten consecutive days, 6 hours/day, to vinyl chloride vapors at an average concentration of 13,500 ppm. The exposed rats were divided into three groups of eight rats each: each group was pretreated with 3-methylcholanthrene; (15 mg/kg, ip for two days prior to first exposure); one group was pretreated with phenobarbital (1 mg/ml in drinking water for three days prior to exposure and during exposure); and the third group received no treatment. Half the

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animals in each group were sacrificed 18 hr after the last exposure and half were sacrificed four days later. In a second experiment, four rats pretreated with phenobarbital were exposed to vinyl chloride vapors at a concentration of 17,300 ppm for two days and sacrificed on the third day. In both experiments control animals, also treated with phenobarbital or 3-methylcholanthrene, were exposed to air only. At the time of sacrifice, lungs, kidneys, spleen, heart, and a small piece of the liver from each animal were preserved for histological examination. The remainder of the liver was processed for assay of microsomal enzyme activity. The following parameters were investigated: growth rate, organ weights, morphological changes, and both benzphetamine-N-demethylase activity and cytochrome P-450 content of microsomes prepared from the livers. In both experiments the only marked difference noted in any group was a decrease in the growth rate of the animals exposed to vinyl chloride and treated with phenobarbital. This decreased growth rate was particularly apparent on the third day of the vinyl chloride exposures. Occasional morphological changes were also seen in the livers of the animals treated with phenobarbital and exposed to vinyl chloride. Although changes resulting from exposure to VC and phenobarbital have been demonstrated, these changes have not been shown to be preneoplastic.

- 51 AU - Hafner RE ; Watanabe PG ; Gehring PJ
 AD - Health and Environmental Res., Dow Chemical U.S.A., Midland, Mich. 48640
 TI - PRELIMINARY STUDIES OF THE FATE OF INHALED VINYL CHLORIDE MONOMER (VCM) IN RATS.
 SI - CARC/75/03678
 SO - Environ Health Perspect; 11:235-242 1975
 LA - ENG
 AB - Male Sprague-Dawley were exposed to vinyl chloride monomer gas (VCM) in a closed recirculating system. The rate at which VCM was removed from the system via metabolism was determined for rats exposed to initial concentrations of VCM ranging from 50-1167 ppm. Upon exposure to initial concentrations of 50-105 ppm, the rate of metabolism was $8.04 \pm 3.40 \times 10^{-3} \text{ min}^{-1}$. Upon exposure to initial concentration ranging from 220 to 1167 ppm, the rate constants were less; the mean value being $2.65 \pm 1.35 \times 10^{-3} \text{ min}^{-1}$. Regardless of concentration, the disappearance followed apparent first order kinetics. Pretreatment of rats with pyrazole (320 mg/kg) prior to exposure to 65 and 1234 ppm VCM caused 71 and 87% reductions, respectively, in the rate of metabolism. Ethanol (5 ml/kg, 95%) caused 96% and 83% reductions in the rate of VCM metabolism by rats exposed to 56 and 97 ppm VCM, respectively. Ethanol was less effective in blocking the rate of metabolism by rats exposed to high concentrations of VCM; 46 and 36% in rats exposed to 1025 and 1034 ppm VCM. In rats exposed to 65 ppm VCM, SKF-525-A (75 mg/kg) administration caused no inhibition of the rate of VCM metabolism; however, a 19% inhibition was seen in rats exposed to 1038 ppm. The nonprotein sulphhydryl content of the liver

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(glutathione and cysteine) of rats exposed to 50-15,000 ppm VCM was reduced without a relationship to dose. With repeated daily exposure, the degree of reduction was reduced. Preliminary results indicate that the primary metabolites of VCM react with the non-protein sulfhydryl. Final metabolic products excreted in the urine appear to be S-(2-hydroxyethyl)cysteine and S-(2-carboxymethyl)cysteine and the respective N-acetyl derivatives. Monochloroacetic acid was identified as another potential metabolite. The results suggest that VCM is readily and extensively metabolized. Metabolism via the primary pathway, postulated to involve alcohol dehydrogenase, is swamped by exposures to concentrations exceeding 220 ppm. In rats exposed to concentrations at and exceeding this level, metabolism occurs via a secondary pathway(s), postulated to be epoxidation and/or peroxidation. These results are considered pertinent in assessing the potential hazard at low-level exposures to VCM.

- 52 AU - Creech JL ; Makk L
 AD - Dep. Surg., Univ. Louisville, Ky.
 TI - LIVER DISEASE AMONG POLYVINYL CHLORIDE PRODUCTION WORKERS.
 SI - CARC/75/00577
 SO - Ann NY Acad Sci; 246:88-94 1975
 LA - ENG
 AB - A protocol for systematic testing of all employees of a chemical plant producing polyvinyl chloride (PVC), ABS resins, and specialty synthetic rubber is presented. An attempt to relate liver abnormality to the degree of vinyl chloride exposure resulted in the determination of five categories of work areas; the highest exposure was in the area of PVC production, followed sequentially by other areas of production, PVC maintenance personnel, other maintenance employees, and all other employees. A standard sequential multiple analysis (SMA-12) was the initial test used, repeated at a maximum of every six mo. On the presentation of elevated liver function tests, consequent special procedures included fractionation of lactate dehydrogenase (LDH) determination of alkaline phosphatase activity, total bilirubin, complete blood count, chest x-rays, a liver spleen scan, plus liver biopsies when indicated. On original examination of 1183 employees, 26.6% had one abnormal test, 3.5% had two or more abnormal tests; abnormalities persisted in 24% of those retested. Results of scans of 116 employees indicated patchy uptake, enlarged liver, enlarged spleen, and/or cold spot in 50.8 of those tested. While a correlation of abnormal SMA-12 examinations with the various areas of production was obscure, 10% of the workers in PVC production exhibited abnormal tests, as compared to 4.1% abnormal for other areas of production. Whereas the alkaline phosphatase test was found the most frequently elevated, there was no single outstandingly abnormal test. Results of 17 liver biopsies revealed two angiosarcomas and five normal reports; periportal fibrosis was otherwise found most common. Fractionation of LDH showed isolated factor four elevations in 66% of the employees. A very high incidence of creatine phosphokinase was found in 75% of the Negro workers, as

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compared to 12% of the Caucasians. It was concluded that no one isolated test provided an adequate evaluation, that the special procedures appeared quite accurate, and that such studies should be continued through the years and beyond retirement.

- 53 AU - Lloyd JW
 AD - Natl. Inst. Occup. Saf. Health, Rockville, Md.
 TI - ANGIOSARCOMA OF THE LIVER IN VINYL CHLORIDE/POLYVINYL CHLORIDE WORKERS.
 SI - CARC/75/00873
 SO - J Occup Med; 17(5):333-334 1975
 LA - ENG
 AB - Review of recent data on cases of liver angiosarcoma illustrated a clustering within recent years. Although the high risk of the disease for polymerization workers had previously gone unnoticed, an exact estimate of the incidence of liver angiosarcoma among the workers could not yet be determined, pending exposed-to-risk figures. Approximately 5,600 men are currently employed in 36 U.S. facilities, with 15 cases of liver angiosarcoma reported to date. Greater than 70% of the cases were initially employed in polymerization work more than 20 yr ago, setting an average latent period of 19 yr. The age at diagnosis of angiosarcoma among both vinyl chloride workers and polymerization workers was considerably lower than that of the general population, suggesting the possibility of a common etiology. Preliminary findings from continuing epidemiologic investigations indicated that polymerization workers may also be at high risk for other malignant neoplasms, particularly of the brain. It remains to be determined whether exposure to lower levels of vinyl chloride also represents excessive risk for liver angiosarcoma or other malignancies.
- 54 AU - Lange CE ; Juhe S ; Stein G ; Veltman G
 AD - Dep. Dermatol., Univ. Bonn, West Germany
 TI - FURTHER RESULTS IN POLYVINYL CHLORIDE PRODUCTION WORKERS.
 SI - CARC/75/00588
 SO - Ann NY Acad Sci; 246:18-21 1975
 LA - ENG
 AB - The possible nature and extent of occupational damage in 15 employees of polyvinyl chloride (PVC)-processing industries was investigated. In addition, case studies of two former workers of a PVC-producing plant, who had died of malignant tumors, are presented. Dermatological examinations and the following laboratory tests were performed on all 15 workers: complete blood cell platelet count, RBC sedimentation rate, serum electrophoresis, blood urea nitrogen, and Australia antigen. Employed for an average of five years, the workers had complained of sensations of pressure and/or pain in the upper abdomen, frequent dizziness, cold hands and feet, and increasing weakness in the legs. Clinical changes of Raynaud's syndrome were not observed. Slight to moderate thrombocytopenia (63,000-139,000/microl) was observed in seven patients; increased bromsulphalein retention of 5.2-15.1% at 45 min was noted in

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another seven patients. Reticulosis of 1.7-4.4% was seen in six patients. Leukopenia (3,250/microl) was seen in one patient, and slight splenomegaly was observed in another patient. Laparoscopy and biopsy results were less distinct, though similar to those observed in PVC-production workers. Despite the small number of workers examined, an increased number of findings were made of a combination of symptoms believed characteristic of vinyl chloride disease. A 38-yr-old man, employed for 12 yr, had a large tumor assigned to the liver and spleen, increased ESR, anemia, and other abnormal laboratory findings; surgical laparotomy and biopsies revealed a hemangioendothelial sarcoma of the liver, and increasing cachexia resulted in death. A 39-yr-old man, employed for 11 yr, had a tumor on the epigastric angle, abnormal laboratory results, a histological diagnosis of hemangioendothelial liver sarcoma, and resulting death.

- 55 AU - Van Esch GJ ; Van Logten MJ
AD - Natl. Inst. Public Health, Bilthoven, Netherlands
TI - VINYL CHLORIDE: A REPORT OF A EUROPEAN ASSESSMENT.
SI - CARC/75/00004
SO - Toxicology; 4(1):1-4 1975
LA - ENG
AB - A meeting of European toxicologists was held to assess the available toxicological and migration data on vinyl chloride, with special reference to its carcinogenic potential. Because of indications that vinyl chloride induces angiosarcomas in exposed workers, it is considered that 50 ppm vinyl chloride in inspired air is too high to adopt as a Threshold Limit Value. Present industrial exposure levels should be reduced as far as possible, and efforts should be made to eliminate the hazard to operatives of exposure to high vinyl chloride levels during the cleaning of polymerization vessels. Data on the migration of vinyl chloride from polyvinyl chloride (PVC) indicate that PVC used for food and drink containers and wrappings should contain less than 20 ppm vinyl chloride. This is necessary to maintain very low levels of contamination of food. The final solution of the vinyl chloride problem will depend on the evaluation of further data, including (a) epidemiologic studies on vinyl chloride-linked diseases in man, (b) levels of industrial and environmental exposure, (c) effects of po vinyl chloride in animals, (d) investigations to determine if induction of liver tumors by vinyl chloride is preceded by liver dysfunction and cirrhosis, (e) metabolism of vinyl chloride, (f) percutaneous migration of vinyl chloride, (g) estimated daily dietary intake of vinyl chloride in children and adults, (h) interaction of vinyl chloride with food and drink components, (i) vinyl chloride levels in PVC products, and (j) vinyl chloride levels in potable water and PVC tubing. (9 refs)

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- 56 AU - Buoen LC ; Brand I ; Brand KG
AD - Univ. Minnesota Medical Sch., Minneapolis, Minn. 55455
TI - FOREIGN-BODY TUMORIGENESIS: IN VITRO ISOLATION AND EXPANSION OF PRENEOPLASTIC CLONAL CELL POPULATIONS.
SI - CARC/75/03742
SO - JNCI; 55(3):721-723 1975
LA - ENG
AB - The intracellular aberrations connected with the preneoplastic stages of cells acquiring neoplastic autonomy were studied in foreign-body reactive tissues in vitro. Foreign-body reactions were induced in coisogenic CBA/H and CBA/H-T6 mice by sc implantation of 15 x 22 x 0.2 mm unplasticized vinyl chloride vinyl acetate copolymer films. At six mo post implantation, implants and unopened tissue capsules were transferred to recipient animals of the T6-different partner strain. After another three mo, part of the film/capsule complex was transferred to (C57BL/10ScSn x CBA/H-T6)F1 mice for tumor development. Capsule-derived and film-attached cells of the other part were separately cultured. Cultures consisting initially of euploid cells were often gradually replaced by different cells with specific aneuploid karyotypes which were identical with, or closely related to, those of the corresponding tumors. The cultured cells implanted in hybrid recipients at different passage numbers frequently gave rise to homologous tumors. Hence, it was possible to prepare in vitro cells with prefixed specific tumor determinants at different stages of preneoplastic maturation. It is concluded that analytic studies on foreign-body induced preneoplastic cell populations can be expected to complement findings on chemically or virus-transformed cells.
- 57 AU - Williams DM ; Taylor KJ ; Crossley IR ; Smith FM
AD - Royal Marsden Hosp., Sutton, England
TI - SCREENING VINYL CHLORIDE MONOMER WORKERS FOR LIVER DISEASE (MEETING ABSTRACT).
SI - ICRB/75/06901
SO - Gut; 16(10):839 1975
LA - ENG
AB - A study of workers to determine whether changes had been induced by past exposure to vinyl chloride was carried out by means of a clinical examination and standard hematology and liver function tests. Of 487 workers examined, 102 had abnormalities on initial testing, but only 2 were finally shown to have portal hypertension. Both had been 1st identified through thrombocytopenia, having normal liver function tests. The remainder were either normal on repeat testing or had minor changes attributable to alcohol (10 cases) or Gilbert's disease (6 cases). In comparison, 44 of 112 control subjects had initial test abnormalities. A test sample of 19 workers was therefore chosen at random and examined blind by Gray scale ultrasonography. Four with minimal or no exposure were confirmed as normal, but 11 of the remainder had abnormalities consisting

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of an enlarged portal vein in 7, splenomegally in 8, and changes in hepatic texture in 7.

- 58 AU - Sharma RA ; Bobek M
 AD - Roswell Park Memorial Inst., Buffalo, N.Y. 14263
 TI - SYNTHESIS OF 5-VINYLRIDINE AND 5-VINYL-2'-DEOXYURIDINE AS NEW PYRIMIDINE NUCLEOSIDE ANALOGS.
 SI - ICDB/75/01651
 SO - J Org Chem; 40(16):2377-2379 1975
 LA - ENG
 AB - Syntheses of 5-vinyluridine and 5-vinyl-2'-deoxyuridine were carried out because of their possible antiviral activity. Condensation of 5-formyluracil was conducted smoothly with carbethoxymethylenetriphenylphosphorane to give trans- and cis-3-(5-uracilyl)acrylic acid ethyl ester. Using an analogous reaction with methylenetriphenylphosphorane failed to yield 5-vinyluracil. 5-Chloromethyluracil was converted by reaction with triphenylphosphine to the phosphonium salt, 5-uracilylmethyltriphenylphosphonium chloride, which readily condensed with paraformaldehyde in the presence of base to yield good amounts of 5-vinyluracil. The trimethylsilyl derivative of 5-vinyluracil was condensed with 1-O-acetyl-2,3,5-tri-O-benzoyl-beta-D-ribofuranose in the presence of stannic chloride to give, after deblocking, 5-vinyluridine. Condensation of the trimethylsilyl derivative, 2,4-bis(trimethylsilyloxy)-5-vinylpyrimidine, with 2-deoxy-3,5-di-O-p-toluoxy-0-erythro-pentofuranosyl chloride, followed by transesterification with sodium methoxide, gave 5-vinyl-2'-deoxyuridine and its alpha anomer, 1-(2-deoxy-alpha-D-erythro-pentofuranosyl)-5-vinyluracil.
- 59 AU - Eisch JJ ; Comfort DR
 AD - Dept. Chemistry, State Univ. New York, Binghamton, N.Y. 13901
 TI - HYDROGEN AND ALKYL TRANSFER IN THE REARRANGEMENTS OF 2-ALKENYL-1,2-DIHYDROQUINOLINES.
 SI - ICDB/75/01643
 SO - J Org Chem; 40(16):2289-2295 1975
 LA - ENG
 AB - Vinyl- or allylmagnesium chloride was added to quinoline. At 258 under hydrolysis conditions, the corresponding 2-alkenyl-1,2-dihydroquinoline was formed. Heating the Grignard adduct with quinoline directly, or heating the isolated dihydroquinoline, caused isomerization to the corresponding 2-n-allylquinoline or its magnesium salt, respectively. When 2-deuterioquinoline was used to prepare the respective adducts, the 2-n-alkylquinolines formed after isomerization were deuterated exclusively at the Beta position of the side chain. When 2-allyl-1,2-dihydroquinoline and 2-allyl-2,4-dideutero-1,2-dihydroquinoline were subjected to isomerization, much monodeuterated 2-n-propylquinoline was formed, indicating that such hydrogen transfer is largely intermolecular. 1,2-Dihydroquinolines and their N-metallic salts underwent easy 1,2 elimination of PH or PM. For example,

2-allyl-2-methyl-1,2-dihydroquinoline, as its N-magnesium chloride salt, easily reverted to quinaldine and allylmagnesium chloride. At higher temperatures these components recombined, yielding 4-allyl-2-methyl-1,4-dihydroquinoline as its N-magnesium salt. The results of these experiments suggest the existence of two distinct pathways for intermolecular hydrogen transfer. One pathway involves the Grignard isomerization, a sequence for $MgHCl$ elimination, allyl-propenyl group isomerization, and 1,4 readdition of $MgHCl$. The other pathway is composed of dihydro isomerization, elimination of RH in a free-radical initiation step, followed by concerted 6-center hydrogen transfers and base-promoted allyl-propenyl group isomerization.

- 60 AU - Anonymous
AD - No affiliation given.
TI - NEW IMPETUS FOR PROBE.
SI - ICDB/75/00164
SO - Chem Week; 114(9):14 1974
LA - ENG
AB - Two former employees of B. F. Goodrich's Louisville, Ky, polyvinyl chloride (PVC) plant were afflicted with angiosarcoma of the liver. This has added new urgency to the investigation into the possible carcinogenicity of vinyl chloride monomer (VCM). At the same time Union Carbide also found that a former employee at its South Charleston, W. Va, PVC plant, died in 1968 of angiosarcoma. Reacting to the Goodrich problem, the Kentucky Safety and Health Standards Board had added VCM to the list of 14 restricted industrial carcinogens issued by OSHA and lowered the employee VCM exposure level from the federal standard to 75 ppm, with a time-weighted average of 50. Because of the lack of solid scientific data on the chemical and the possible huge economic impact, OSHA has not yet issued temporary emergency standards. Investigations pertinent to this matter continue.
- 61 AU - Reed DJ ; May HE ; Boose RB ; Gregory KM ; Baisstein MA
AD - Dept. Biochem. Biophys., Oregon State Univ., Corvallis
TI - 2-CHLOROETHANOL FORMATION AS EVIDENCE FOR A 2-CHLOROETHYL ALKYLATING INTERMEDIATE DURING CHEMICAL DEGRADATION OF 1-(2-CHLOROETHYL)-3-CYCLOHEXYL-1-NITROSOUREA AND 1-(2-CHLOROETHYL)-3-TRANS-4-METHYLCYCLOHEXYL-1-NITROSOUREA.
SI - CATH/75/*1720
SO - Cancer Res; 35(3):568-576 1975
LA - ENG
AB - The chemical degradation of 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU) or 1-(2-chloroethyl)-3-(trans-4-methylcyclohexyl)-1-nitrosourea (methyl CCNU) under physiological conditions is described. Using gas chromatography, reverse isotope dilution, and high pressure liquid chromatography, the decomposition of CCNU and methyl CCNU dissolved in 0.1M phosphate buffer (0.6mM drug concn) pH 7.4 at 37° for 3 hr was investigated. Half-lives of decomposition were 1.75 and 2.75 hr, resp. During this time, 18-25% of the molecule appeared as 2-chloroethanol, 5-10% as acetaldehyde, 32% as

cyclohexylamine and 1-2% each as vinyl chloride and ethylene. Methyl CCMU and CCMU degradation may not involve the loss of the chloro group as chloride but the loss of the H-3 hydrogen as a proton with the formation of a 2-chloroethyl diazene and corresponding isocyanate. Further conversion of 2-chloroethyldiazene to its hydroxide may yield the final alkylating form, possibly as a carbonium ion. (19 refs)

- 62 AU - Jaeger RJ ; Reynolds ES ; Conolly RB ; Moslen MT ; Szabo S
AU - Murphy SD
AD - Kresge Cent. Environ. Health, Harvard Sch. Public Health, Boston, Mass.
TI - ACUTE HEPATIC INJURY BY VINYL CHLORIDE IN RATS PRETREATED WITH PHENOBARBITAL.
SI - CARC/74/02895
SO - Nature (Lond); 252(5485):724-726 1974
LA - ENG
AB - The potential of vinyl chloride monomer to enhance liver injury in male Holzman rats pretreated with phenobarbital, an inducer of certain enzymes of the liver mixed function oxidase system, was studied. Four experimental groups were defined: exposed to air and not pretreated; exposed to vinyl chloride monomer and not pretreated; exposed to air and pretreated with phenobarbital (0.1% in drinking water for 7 days); and exposed to vinyl chloride monomer and pretreated with phenobarbital. Nonpretreated and phenobarbital-pretreated rats exposed to air alone had no increase in serum alanine-alpha-ketoglutarate transaminase (AKT) and sorbitol dehydrogenase, enzymes that are highly specific for liver injury. In nonpretreated groups, exposure to 0.5% or 5% vinyl chloride monomer for a single six hour period did not cause a substantial rise in serum alanine-alpha-ketoglutarate transaminase or sorbitol dehydrogenase, but after exposure to 10% vinyl chloride monomer there was a slight increase in these enzymes. Histologically, centrilobular hepatocellular vacuolization was noted only in the 10% exposure group. Phenobarbital pretreatment for seven days caused a marked enhancement of injury at the 5% level of exposure, with vacuolization of centrilobular parenchymal cells, focal necrosis of mid-zonal parenchyma, dilation of the rough endoplasmic reticulum, and formation of tubular snarls by smooth endoplasmic reticulum. Phenobarbital-pretreated rats killed after the last exposure to 5% vinyl chloride monomer following 5 consecutive days of exposure did not have increased activities of serum alanine-alpha-ketoglutarate transaminase or sorbitol dehydrogenase, suggesting that previous exposure to vinyl chloride monomer blocked the biochemical response which followed reexposure at short intervals.

- 63 AU - Makk L ; Creech JL ; Whelan JG ; Johnson MN
AD - St. Anthony Hosp., Louisville, Ky.
TI - LIVER DAMAGE AND ANGIOSARCOMA IN VINYL CHLORIDE WORKERS: A
SYSTEMATIC DETECTION PROGRAM.
SI - CARC/74/04080
SO - JAMA; 230(1):64-68 1974
LA - ENG
AB - Recently, five cases of angiosarcoma of the liver were discovered in Louisville, Kentucky; all of the patients had worked in a plant producing polyvinyl chloride (PVC). Since none of the patients had any specific abnormal findings on physical examination or routine laboratory tests, a program was designed whereby large numbers of workers could be screened for liver disease with relative ease. Significant abnormalities were evaluated by a combined program of clinical, comprehensive laboratory, and roentgenographic study. If abnormalities suggestive of serious liver disease or possible angiosarcoma were found, the patient was hospitalized and hepatic panangiography performed. If the angiograms suggested the possibility of tumor, open-liver biopsy was advised with consideration of hepatic lobectomy, if so indicated at exploration. Screening profiles were obtained from 1183 employees of the plant; comprehensive evaluations were performed on 75 workers with liver-related abnormalities. Two new cases of hepatic angiosarcoma and three cases of portal fibrosis were found on further evaluation. Of the liver function tests, the gamma-glutamic transpeptidase determination seemed to be the most useful in detecting abnormalities and reflecting the extent of liver lesions; alkaline phosphatase, serum glutamic-oxalacetic transaminase, serum glutamic-pyruvic transaminase, lactic acid dehydrogenase, and bilirubin tests were also useful. No test was specific for angiosarcoma. Liver scans and angiographic studies correlated well with the results of laboratory tests and biopsy examinations in the detection of cirrhosis, and hepatic panangiography was helpful in differentiating neoplastic from nonneoplastic lesions.
- 64 AU - Block JB
AD - Med. Consulting Group, Kentucky Dept. Labor, Frankfort
TI - ANGIOSARCOMA OF THE LIVER FOLLOWING VINYL CHLORIDE EXPOSURE.
SI - CARC/74/03406
SO - JAMA; 229(1):53-54 1974
LA - ENG
AB - Recently, six workers exposed to vinyl chloride have died of angiosarcoma of the liver. The patients were all men, aged 38-58 yr. They had worked with vinyl chloride 12-28 yr (mean, 18 yr) prior to first hospital admission. Four of the patients had some nonalcoholic form of cirrhosis of the liver, and in three cases the liver neoplasms were first diagnosed as gastric ulcers. In vinyl chloride workers, the serum alkaline phosphatase determination appears to be more sensitive than other serological tests. SGOT levels are also frequently elevated, but this does not occur until late in the course of the disease. Carcinoma of

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the liver can be cured only by surgical excision of well-localized lesions; chemotherapeutic agents are of palliative value only and radiation therapy may alleviate symptoms but does not prolong survival. It should be determined whether the development of angiosarcoma of the liver is the result of low-level exposure of vinyl chloride over a period of years or whether the tumor results from high-level exposure many years previously.

- 65 AU - Tabershaw IR ; Gaffey WR
AD - Tabershaw-Cooper Assoc., Inc., Rockville, Md.
TI - MORTALITY STUDY OF WORKERS IN THE MANUFACTURE OF VINYL CHLORIDE AND ITS POLYMERS.
SI - CARC/74/02605
SO - J Occup Med; 16(8):509-518 1974
LA - ENG
AB - This study of 8384 men who had at least one yr of occupational exposure to vinyl chloride before December 31, 1972, demonstrates that cancers of the digestive system (primarily angiosarcoma), respiratory system, brain, and cancers of unknown site, as well as lymphomas, occurred more often than expected in those members of the study population with the greatest estimated exposure. The mortality from other cancers was lower than that of the general male population with the exception of cancer of the buccal cavity and pharynx. There was an excess of these cancers, which however was inversely related to estimated exposure. No explanation has been found for the latter finding. The other major findings of the study are: 1) the overall mortality of the study population was approximately 75% of what would be expected in a comparable population of U. S males; 2) no cause of death showed a statistically significant excess over what would be expected in a comparable U. S male population; and 3) no deaths identified as angiosarcoma of the liver were found other than those previously identified. This is the first epidemiological study suggesting that vinyl chloride may also be associated with human cancer of multiple sites.
- 66 AU - Monson RR ; Peters JM ; Johnson MN
AD - Harvard Sch. Public Hlth, Boston, Mass.
TI - PROPORTIONAL MORTALITY AMONG VINYL-CHLORIDE WORKERS.
SI - CARC/74/02598
SO - Lancet; 11(7877):397-398 1974
LA - ENG
AB - In a proportional-mortality analysis of 161 deceased workers in two plants using vinyl chloride, a 50% excess of deaths due to all cancer was seen. Specific sites of cancer with the greatest excess included liver and biliary tract, lung, and brain. The excess in fatal cancer was seen mainly in men who died before age 60. Also, there was a trend in time in the ratio of observed to expected deaths: since 1970 the expectancy of deaths from cancer has more than doubled.

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- 67 AU - Falk H ; Creech JL ; Heath W ; Johnson MN ; Key MM
AD - Ctr. Dis. Control, Atlanta, Ga.
TI - HEPATIC DISEASE AMONG WORKERS AT A VINYL CHLORIDE POLYMERIZATION PLANT.
SI - CARC/74/02585
SO - JAMA; 230(1):59-63 1974
LA - ENG
AB - Eleven cases of hepatic disease, including seven cases of hepatic angiosarcoma, have been identified to date among men employed at one vinyl chloride polymerization plant in Louisville. The earliest diagnosis was made in April 1964. The two most recent cases, both angiosarcoma, were diagnosed in February 1974 as a result of systematic medical screening for liver abnormalities among workers at the plant. Ages at diagnosis have ranged from 36 to 58 yr for the seven patients with angiosarcoma and from 28 to 56 yr for the four patients with nonmalignant disease; durations of employment before diagnosis have ranged from 12 to 28 yr (average 18.0) and from 5 to 29 yr (average 20.6). All 11 persons had worked in close and continuous contact with various phases of the vinyl chloride polymerization process. Review of pathologic material suggests the presence in both tumor and nontumor cases of portal fibrosis and atypical sinusoidal lining cells. A direct causal relationship between exposure to vinyl chloride monomer and pathologic findings is postulated.
- 68 AU - Lange CE ; Jushe S ; Veltman G
AD - Univ. Derm. Clin., Bonn-Venusberg, W. Germany
TI - LIVER ANGIOSARCOMA IN TWO WORKERS IN A PVC-PRODUCING FACTORY.
SI - CARC/74/02403
SO - Dtsch Med Wochenschr; 99(31):1598-1599 1974
LA - GER
AB - Two fatal cases of angiosarcoma of the liver following prolonged exposure to vinyl chloride in a PVC manufacturing plant are reported. Hemangioendothelial sarcoma of the liver was diagnosed in one 38-yr-old worker who worked in the PVC manufacturing plant for 12 yr. A blood sedimentation reaction of 22/67 mm, considerable anemia, reticulocytosis at the 6% level, serum iron level of 25 microg/100 ml, a gamma-globulin fraction of 25% rel at 7.2 g/100 ml protein content, an alkaline phosphatase activity of 12 Bodansky U and a glutamic-oxalacetic transaminase activity of 24 mU/ml serum were measured. Bilaterally localized, polytopically growing, malignant primary angiosarcoma of the liver was diagnosed in another 39-yr-old patient who had been working in PVC production for 11 yr. In view of similar reports from other countries, as well as of related animal tests, the present findings indicate a possible causal relationship between such malignant tumors and exposure to vinyl chloride.

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- 69 AU - Viola PL ; Bigotti A ; Caputo A
AD - Regina Elena Inst. Cancer Res., Rome, Italy
TI - ONCOGENIC RESPONSE OF RAT SKIN, LUNGS, AND BONES TO VINYL CHLORIDE.
SI - CARC/71/02200
SO - Cancer Res; 31(5):516-522 1971
LA - ENG
AB - Male rats were exposed to vinyl chloride vapors for 4 hr per day, 5 days per wk for 12 months; The vinyl chloride was diffused into the air of the containers which held the rats in amounts of 3% vinyl chloride v/v (30,000 ppm). Almost all the rats developed tumors of the skin and lungs. Among 17 rats surviving the 12 month course, all had skin tumors and 6 had lung tumors; 5 of the 17 had bone tumors. Most skin tumors were epidermoid carcinomas; there were 2 mucoepidermoid carcinomas and 2 epidermoid carcinomas of the keratinizing type. Among lung tumors, there were 3 adenocarcinomas, a squamous cell carcinoma and an adenocanthoma. Bone tumors were localized in the metacarpal and metatarsal bones of all 4 extremities; all were osteochondromas. Skin tumors were localized in the area of the submaxillary and parotid glands.
- 70 AU - Johnson KH ; Buoen LC ; Buoen I ; Brand I ; Brand KG
AD - U. Minnesota Coll. Vet. Med., Minneapolis
TI - POLYMER TUMORIGENESIS: CLONAL DETERMINATION OF HISTOPATHOLOGICAL CHARACTERISTICS DURING EARLY PRENEOPLASIA; RELATIONSHIPS TO KARYOTYPE, MOUSE STRAIN, AND SEX.
SI - CARC/70/02300
SO - JNCI; 44(4):785-793 1970
LA - ENG
AB - Histological examination of tumors induced in CBA/H and CBA/H-T6 mice by sc implantation of plastic films (unplasticized vinyl chloride acetate copolymer) demonstrated 4 classes of tumors: well-differentiated fibrosarcomas; spindle cell sarcomas; anaplastic round-cell sarcomas without giant cells; and anaplastic sarcomas with giant cells. Very similar morphologic characteristics were seen for homologous tumors arising from segments of the same implant transferred (6 or more mo after initial implantation) to recipient mice during the preneoplastic phase. The hypothesis that a preneoplastic cell clone is present on the film surface soon after implantation and that homologous tumors are derived from cells of the same clone is substantiated by these results. Tumors in classes with higher anaplasticity tended strongly to tetraploidy. CBA/H mice tended to produce more anaplastic tumors than did CBA/H-T6 mice. Tumors from female mice predominated in morphologic classes with lower anaplasticity, whereas the few tumors from male mice fell into classes with higher anaplasticity.

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- 71 AU - Colvin M ; Cowens JW ; Brundrett RB ; Kramer BS ; Ludlum DB
AD - Oncol. Cent., Johns Hopkins Univ. Sch. Med., Baltimore, Md.
TI - DECOMPOSITION OF BCNU (1,3-BIS(2-CHLOROETHYL)-1-NITROSOUREA) IN
AQUEOUS SOLUTION.
SI - CATH/74/04685
SO - Biochem Biophys Res Commun; 60(2):515-520 1974
LA - ENG
AB - The volatile products of the spontaneous aqueous decomposition of
BCNU labeled with ^{14}C in the chloroethyl groups were identified
by gas chromatography and mass spectrometry as vinyl chloride,
acetaldehyde, dichloroethane, and chloroethanol. This set of
products is consistent with the existence of chloroethylcarbonium
ions as reactive intermediates which would produce the previously
described substituted nucleotides. (4 refs)
- 72 AU - Block JB
TI - VINYL CHLORIDE AND ANGIOSARCOMA.
SI - CATH/74/02655
SO - J Ky Med Assoc; 72(9):483-485,505 1974
LA - ENG
AB - Primary carcinoma of the liver is uncommon and those of
mesodermal origin such as liver angiosarcoma (AS) are extremely
rare. Pre-existing cirrhosis of the liver plays an important role
in the genesis of AS. Clinically, the liver is enlarged in 89% of
the cases, nausea and vomiting and a sense of fullness and
pressure are present and gastric disturbances are found in 2/3 of
patient Liver function tests are of little value in screening
because extensive liver damage must occur before there is
significant functional impairment. Photoscanning and
arteriography may be helpful in identification of the tumor and
in planning for surgery. Photoscanning using iodine, rose bengal
and gold was diagnostic in 23/26 and 19/21 cases in 2 separate
instances. Biopsy is contraindicated when AS is suspected because
of the vascular nature of AS and the possibility of
exsanguinating hemorrhage. Surgical excision offers the only cure
for AS of the liver. Chemotherapeutic agents such as
5-fluorouracil, and thio-TEPA are only palliative, as is
radiotherapy. (31 refs)
- 73 AU - Anonymous
TI - BATTLE LINES DRAWN ON VINYL CHLORIDE ISSUE.
SI - CARC/74/91232
SO - Chem Eng News; 52(8):16 1974
LA - ENG
AB - Controls on the occupational exposure to vinyl chloride or other
chemicals used in making the monomer or in polymerizing it to
polyvinyl chloride have been requested by the labor unions.
These controls include no measurable exposure to the carcinogen,
safer work practices, closed systems, use permits, periodic
medical and lab tests, plus a cut of residual vinyl chloride in
PVC resins to less than 0.01% (100 ppm). The deaths of 4
polymerization section workers at the Louisville, Ky plant of B.

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F. Goodrich have been attributed to angiosarcoma of the liver. These workers had average exposures of some 19 years to vinyl chloride and 10 years to vinylidene chloride with variable exposure to vinyl acetate, methyl acrylate, ethyl acrylate, methanol and chlorinated solvents. Angiosarcoma of the liver is a rare occurrence, accounting for only 20 to 30 deaths per year in the entire U. S. and can be mis-diagnosed as cirrhosis of the liver. Liver angiosarcomas have been experimentally created in rats inhaling vinyl chloride down to the 250 ppm level. The rats also developed zymbal (sic) glands carcinomas and kidney nephroblastomas.

- 74 AU - Anonymous
 TI - VINYL CHLORIDE, PVC AND CANCER.
 SI - CARC/74/01204
 SO - Lancet; (7870):1323-1324 1974
 LA - ENG
 AB - To date, 19 workers throughout the world have reportedly developed angiosarcoma of the liver following a history of intermittently heavy exposure to vinyl chloride (VC) over periods of 12-27 years in polyvinyl chloride (PVC) manufacturing plants. Experimental work indicating a relationship between VC and cancer has heretofore gone unheeded because the experimental exposure levels were very high in comparison to those to which PVC workers are exposed and because experimentalists have often warned of hazards where no adequate evidence of real hazard exists. There is no indication that PVC is itself dangerous or that it depolymerizes to produce VC. Unreacted VC which is present in newly manufactured PVC may, however, be released during storage and when the material is heated during the manufacture of PVC products. There have been no cases of angiosarcoma of the liver among PVC processors. In Great Britain, the current upper limit for exposure to VC in PVC manufacturing plant is 50 ppm with a maximum time-weighted average exposure of 25 ppm. In light of evidence that rats develop angiosarcoma of the liver following exposure to 50 ppm VC, these limits may be lowered. More systematic evaluation of industrially used chemicals is needed to determine the carcinogenic risks to workers.
- 75 AU - Lee FI ; Harry DS
 AD - Dept. Med. Victoria Hosp., Blackpool, Great Britain
 TI - ANGIOSARCOMA OF THE LIVER IN A VINYL-CHLORIDE WORKER.
 SI - CARC/74/00667
 SO - Lancet; 1(3870):1316-1318 1974
 LA - ENG
 AB - A 71-year-old man was admitted to the hospital with massive edema, moderate ascites, and a palpable liver. The spleen was also enlarged, serum bilirubin raised, serum albumin decreased, and prothrombin activity 35%. The liver architecture was normal and there was no evidence of hepatoma. The patient died suddenly 2 weeks later. Postmortem examination revealed angiosarcoma of the liver and several small sessile polyps on the mucosa of the fundus of the stomach. The spleen was enlarged due to portal

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hypertension and the other organs were normal. The patient has been a process worker in the manufacture of polyvinyl chloride from vinyl-chloride monomer for 20 years. There is strong evidence that angiosarcoma of the liver is an occupational tumor and that vinyl chloride is the carcinogen; there is no evidence that the finished polymer carries any risk.

- 76 AU - Anonymous
 TI - NEW VINYL CHLORIDE-EXPOSURE REGS DRAW FIRE.
 SI - CARC/74/02003
 SO - Oil Gas J; 72(40):52 1974
 LA - ENG
 AB - Industry reaction to the Labor Department's new vinyl chloride exposure regulation, which sets levels of 1 ppm averaged over an 8-hr period, are summarized. It will become mandatory for workers exposed to more than the 1 or 5 ppm (for any 15-min period within the 8-hr time span) levels to wear respirators. Industry questions its ability to meet the level of 1 ppm in the time specified and is seeking remedies through the judicial process. The standard also calls for regular monitoring of plant air, regular medical examinations for workers, and the setting up of regulated areas where vinyl chloride exposure is high.
- 77 AU - Schanche DA
 AD - No affiliation
 TI - VINYL CHLORIDE: TIME BOMB ON THE PRODUCTION LINE.
 SI - CARC/74/01898
 SO - Today's Health; 52(9):16-1970- 1974
 LA - ENG
 AB - The dangers of vinyl chloride, which are beginning to be uncovered as a result of the deaths from angiosarcoma of the liver of at least 20 American and foreign vinyl chloride workers are reviewed together with measures being taken by various companies and government agencies to limit exposure to this carcinogenic gas. All of the occupationally related deaths occurred in men who had long-term exposure (from 12-20 yr) to extremely high concentrations of vinyl chloride. The deaths from angiosarcoma of three women in the Buffalo-Niagara Falls area have also been attributed to vinyl chloride in the air, apparently caused by pollution from a nearby Goodyear Rubber factory. An emergency exposure level of 50 ppm has been set by the government. The National Institute for Occupational Safety and Health has urged the labor department to reduce its vinyl chloride emergency standard permanently to 'no detectable level'.
- 78 AU - de Engelse L ; Emmelot P
 AD - Netherlands Cancer Inst., Amsterdam
 TI - THE CARCINOGENIC PROPERTIES OF VINYL CHLORIDE.
 SI - CARC/74/01808
 SO - Chem Weekbl; 70(28/29):5 1974
 LA - OUT
 AB - Recent studies on the carcinogenicity of vinyl chloride and related legislation are reviewed in the light of the

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significantly increased incidence of angiosarcoma of the liver in workers exposed to this compound in the air of polyvinylchloride (PVC) plants. A total of 19 cases of angiosarcoma of the liver have thus far been detected in workers exposed to vinyl chloride.

Angiosarcoma of the liver and other tumors developed in rats and mice exposed to 250 and 50 ppm concentrations of vinyl chloride for 4 hr/day, 5 days/wk, for several months. These findings have prompted a reduction of the maximum permissible concentration to 50 ppm, but a further reduction of this limit appears necessary. Extensive epidemiological surveys on the incidence of liver injury and liver tumors among active and retired workers in PVC manufacturing plants, and experiments on the carcinogenicity of vinyl chloride at concentrations lower than 50 ppm are being conducted.

- 79 AU - Gutsche W ; Jungstend W ; Wohlrabe K ; Fischer GW ; Lohs K
 AD - Cent. Inst. Microbiol. Exp. Ther., Jena, E. Germany
 TI - CYTOSTATIC EFFECT OF VINYL-SUBSTITUTED NITROGEN MUSTARD AMMONIUM SALTS AGAINST TRANSPLANTABLE TUMORS IN AN AUTOMATIC PRELIMINARY TEST AND A SEQUENTIAL TEST.
 SI - CATH/72/01490
 SO - Arch Geschwulstforsch; 39(2):121-127 1972
 LA - GER
 AB - Several 2-vinyl substituted derivatives of methyl-bis(2-chloroethyl)vinyl ammonium chloride were tested for their effectiveness against Ehrlich ascites carcinoma (EAC) in a partially automatic preliminary test in which an electronic particle counter is used; in a previously described sequential test, they were also tested against sarcoma 180 P (Sa 180 P), against a transplantable myeloid leukemia (LAJ I) in ABAF(1) mice, and against Walker 256 carcinosarcoma (Wa 256) in rats. Substituents were benzoyl, p-toluoyl, p-fluorobenzoyl, p-chlorobenzoyl, p-bromobenzoyl, and p-methoxybenzoyl. Acceptability criteria were a right shift of the frequency distribution of tumor cell volumes and reduction of number of cells per ascites vol in the EAC pretest, a >50% increase in survival period for LAJ I, a reduction in tumor wt by >35% with respect to controls for Sa 180 P, and a >90% reduction in tumor wt for Wa 256. All the compounds were highly effective against EAC. All except the p-bromobenzoyl derivative were effective against LAJ I. The benzoyl, p-toluoyl, and p-methoxybenzoyl derivatives exceeded acceptance criteria with Wa 256 as did the p-chlorobenzoyl derivative with Sa 180 P. The p-toluoyl derivative attained a therapeutic index for LAJ I that was comparable to that of cyclophosphamide, and the p-fluorobenzoyl derivative exceeded it; the 2-benzoyl derivative was as effective as cyclophosphamide against Wa 256. (15 refs)

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