

14

P3103651

```
*****
*
*   THIS IS AN OFF-LINE BIBLIOGRAPHIC CITATION LIST GENERATED BY
*
*               MEDLARS II
*
*   N.L.M.'S NATIONAL INTERACTIVE RETRIEVAL SERVICE
*
*****
```

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED
NUMBER OF CITATIONS PRINTED = 203
THIS SEARCH WAS PERFORMED ON THE TOXLINE
JANUARY 14, 1988
FILE.

SORT WAS NOT REQUESTED

REQUESTED BY
E. GRESCH

R E C E I V E D

JAN 20 1988

LEGAL DEPARTMENT

PLEASE SEND THIS LISTING TO

DIANE WROBLEWSKI
1803 BUILDING
MIDLAND, MICHIGAN 48640

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

- 1 AU - Chen CW ; Blancato JN
AD - Environmental Protection Agency, Washington, DC. Office of Health and Environmental Assessment.
TI - Incorporation of Biological Information in Cancer Risk Assessment: Example--Vinyl Chloride,
SO - Govt Reports Announcements & Index (GRA&I), Issue 18, 1987
AB - TD3: Vinyl chloride (VC) is used as an example to demonstrate how biological information can be incorporated into quantitative risk assessment. The information included is the pharmacokinetics of VC in animals and humans and the data-generated hypothesis that VC primarily affects the initiation stage of the multistage carcinogenesis. The emphasis in the paper is on the improvement of risk assessment methodology rather than the risk assessment of VC per se. Sufficient data are available to construct physiologically-based pharmacokinetic models for both animals and humans. These models are used to calculate the metabolized dose corresponding to exposure scenarios in animals and in humans. On the basis of the data on liver angiosarcomas and carcinomas in rats, the cancer risk per unit of metabolized dose is comparable, irrespective of routes (oral or inhalation) of exposure. The tumor response from an intermittent/partial lifetime exposure is shown to be consistent with that from a lifetime exposure when VC is assumed to affect the first (initiation) stage of the multistage carcinogenic process. Furthermore, the risk estimates calculated on the basis of animal data are shown to be consistent with the human experience.
- 2 AU - NIOSH
TI - NIOSH Testimony on Vinyl Chloride by M. M. Key, June 25, 1974
SO - NIOSH, 12 pages, 1974
AB - Testimony was presented to aid in the determination of an acceptable level of exposure for vinyl-chloride (75014). The testimony pertained to the areas of epidemiology and surveillance, sampling and analysis, respiratory protection, and exposure levels. Three deaths from angiosarcoma of the liver among polyvinyl-chloride (PVC) workers triggered the organization of a surveillance network to establish the number of deaths from this disease and its possible relationship to occupational exposure to VC and/or PVC. A total of 18 cases among PVC workers has been identified and one for a VC monomer production worker. Average age at death for the PVC workers was 48.5 years. The estimated latent period for this disease was about 20 years. Two additional cases were recently discovered among men employed at factories using PVC to fabricate other products. This tumor has been induced in two animal species exposed to VC down to and including 50 parts per million (ppm). Other health effects from VC exposure may include a disabling liver fibrosis. Results of NIOSH Walk Through Surveys were briefly presented. A compilation of data from air sampling in seven PVC fabrication facilities showed that breathing zone samples ranged from 0.3 to 12ppm with a mean of 3ppm. Estimated time weighted average exposures were about 2ppm. Peak levels of at least 300ppm were noted. Extended

R&S 102686

00003040

PAGE 2

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

exposures at these levels were not considered probable; however, maintenance and repair workers may experience such levels.

- 3 AU - Knight KR ; Gibbons R
TI - Increased Collagen Synthesis and Cross-Link Formation in the Skin of Rats Exposed to Vinyl Chloride Monomer
SO - Clinical Science, Vol. 72, No. 6, pages 673-678, 25 references, 1987
AB - The effects of vinyl-chloride monomer (75014) (VCM) on skin collagen synthesis and cross/link formation were studied in rats. Adult Wistar-rats were given daily oral doses of 0, 3, 30, or 300mg/kg VCM for 95 to 125 weeks. Most of these rats were part of another study investigating the metabolic fate of VCM. The rats were observed for clinical signs of toxicity. Dead rats were necropsied. Surviving rats were killed, and the skin from the backs was dissected and assayed for collagen content, reducible cross/links, and collagen glycosylation. Doses of 0 to 30mg/kg VCM produced no change in terminal body weight. The 300mg/kg dose was lethal to all rats within 60 days. Five of 15 rats given 30mg/kg and one out of 16 given 3mg/kg VCM died. All rats in the 300mg/kg group and 11 out of 15 in the 30mg/kg group developed liver tumors, primarily angiosarcomas. Only one rat in the 3mg/kg group developed a small liver tumor. Water content of VCM treated rat skin was 20 percent higher than the control value. Skin from VCM treated rats had 25.6 percent more collagen on a dry weight basis than the controls. There was a significant increase in the occurrence of major intermolecular cross/links in VCM treated skin, range 13.5 to 41.6 percent. Glycosylation of collagen molecules in treated skin was significantly enhanced. The authors conclude that fibrosis of the skin is one of the manifestations of VCM toxicity.
- 4 AU - Purchase IFH ; Stafford J ; Paddle GM
TI - Vinyl Chloride: An Assessment of the Risk of Occupational Exposure
SO - Food and Chemical Toxicology, Vol. 25, No. 2, pages 187-202, 67 references, 1987
AB - The toxic effects of exposure to vinyl-chloride (75014) (VC) were reviewed with emphasis on the risk presented by occupational exposure to high concentrations of the monomer. Animal studies have produced extensive evidence of the mutagenicity and carcinogenic activity of VC. The results of epidemiological studies encompassing 45,000 workers have demonstrated a relationship between occupational exposure to VC and an increase in the incidence of liver neoplasms, especially liver angiosarcoma. The latent period between the first occupational exposure and death from liver angiosarcoma is estimated at 21.9 years. Studies of populations living close to VC production facilities have shown a higher risk of acquiring angiosarcoma of the liver than that of the general population. In general, it has been established that exposures to very high levels of VC are necessary to induce the neoplasm, although accurate estimates are not available. An estimate of the dose for a 10(-6) lifetime risk in man yields a value of 100 parts per billion, which is

compatible with the highest estimates yielded by studies carried out in animals and also with the actual occupational experience.

- 5 AU - Cone JE
TI - Occupational Lung Cancer
SO - Occupational Medicine: State of the Art Reviews, Vol. 2, No. 2, pages 273-295, 121 references, 1987
AB - Aspects of addressing the question of whether or not a case of lung cancer is due to occupational factors are discussed. While the proportion of all lung cancers that is due to occupational exposure to hazardous materials is unknown, a recent Norwegian study indicated that 13 to 27 percent of cases occurring in males are the result of such occupational exposures. The importance of the clinician in determining the cause is noted. It is necessary to determine that there has indeed been a possibility of exposure to a known carcinogen. The quantitative measure of exposure must be determined as closely as possible. The period of latency between exposure and the development of the cancer must be measured and a determination made as to its adequacy for the development of the disease. The histological type of tumor must be identified, and the probability of association between this type of tumor and the type of occupation or exposure must be assessed. Possible risk modification factors must be examined, along with demographic information related to sex, age and ethnic background. A brief review of the literature is given citing specific hazards associated with definite increased risk for cancer development and listing the associated occupations. These substances include acrylonitrile (107131), arsenic (7440382), beryllium (7440417), bis(chloromethyl)ether (542881), chloromethyl-methyl-ether (107302), cadmium (7440439), chromium (14392020), mustard-gas (505602), nickel (7440020), radiation, and vinyl-chloride (75014). Occupations reportedly associated with increased risk include aluminum industry workers, butchers, foundry workers, coke plant workers, carbon-black process workers, man made mineral fibers workers, motor vehicle drivers, and rubber industry workers. Possible interventions for the prevention of occupational lung cancer are discussed.
- 6 AU - Morgan RW ; Larson SR
TI - Newer Occupational Lung Carcinogens
SO - Occupational Lung Disease, J. B. L. Gee, W. K. C. Morgan, and S. M. Brooks, Editors; New York, New York, Raven Press, pages 69-77, 84 references, 1984
AB - Newer occupational lung carcinogens are discussed. Newer agents are defined as those suspected, identified or confirmed as lung carcinogens in the past 10 years, although the agents themselves are not new. It is noted that the history of lung cancer has focussed primarily on two etiologic factors: cigarette smoking and asbestos. Each of these has been characterized as producing a greatly increased relative risk, along with an impressive attributable risk. Cigarette smoking is estimated to be responsible for 90 percent of all lung cancer cases. Newer agents probably cause less than 10 percent of all lung cancer

00003042

PAGE 4

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

cases. Their action is probably enhanced by smoking. Agents newly suspected or known to be lung carcinogens are discussed. These include arsenic (7440382), beryllium (7440417), chloromethyl ethers, chromates, nickel (7440020), vinyl-chloride (75014), and less specific exposures of air pollution and certain occupations for which exposures are mixed. It is noted that these newer agents are important to certain groups of workers, but carry very low risk for the general population. A small body of available data suggests that occupational lung cancer is decreasing as better engineering controls are put in place. However, with declining cigarette smoking, these carcinogens are expected to produce an increasing percentage of a decreasing incidence of lung cancer.

- 7 AU - Storetvedt Heldaas S ; Andersen AA ; Langard S
TI - Incidence of Cancer Among Vinyl Chloride and Polyvinyl Chloride Workers: Further Evidence for an Association with Malignant Melanoma
SO - British Journal of Industrial Medicine, Vol. 44, No. 4, pages 278-280, 15 references, 1987
AB - The relationship between malignant melanoma incidence and occupational exposure to vinyl-chloride (75014) (VCM) and polyvinyl-chloride (9002862) was investigated based on a follow up of a previously reported study. In the present report, increased incidences of cancer in the follow up period 1980 to 1984 were presented. Nine exposure categories were combined into three groups representing high, medium, and low exposure to VCM. The increased incidence of cancer of the colon, bronchial cancer, and malignant melanoma of the skin (MMS), reported previously, was confirmed for the high exposure group. No new cases of liver angiocarcinoma appeared during the period. Six MMS cases were observed in the whole study population versus 1.1 expected. Two new cases appeared in the extended follow up period versus 0.3 expected. Seven cases of lung cancer occurred versus 4.0 expected and two new cases appeared in the extended follow up period versus 1.4 expected. Five cases of colon cancer were observed versus 2.1 expected and two new cases occurred in the extended follow up period versus 0.7 expected. The highest incidence of malignant melanoma was observed for the shortest follow up period: 2 observed versus 0.1 expected. There was no apparent difference in the rate ratio for lung cancer between observation periods. The authors conclude that the two new cases of malignant melanoma during the extended observation period confirmed the results from the first investigation which suggested an association between exposure to VCM and malignant melanoma of the skin.

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

- 8 AU - Kessler E ; Brandt-Rauf PW
TI - Occupational Cancers of the Brain and Bone
SO - Occupational Medicine: State of the Art Reviews. Occupational Cancer and Carcinogenesis, Vol. 2, No. 1, P. W. Brandt-Rauf, Editor; Philadelphia, Pennsylvania, Hanley and Belfus, Inc., pages 155-163, 10 references, 1987
AB - Occupational cancers of the brain and bone were discussed. Mortality and incidence of malignant tumors of the brain and central nervous system have been increasing since the 1940's for individuals over the age of 55. Although the etiology of primary brain tumors is not well understood, epidemiologic studies have linked occupation in synthetic rubber manufacturing, polyvinyl-chloride (9002862) production, oil refining, petrochemical production, and the nuclear industry to this disease. Vinyl-chloride (75014) manufacture is the only case where a single carcinogenic agent has been identified: in other industries, multiple chemical exposures occur and no one chemical or chemical process has been linked to an excess of brain tumors. Some of the exposures, however, are similar for these industries and include organic solvents, formaldehyde (50000), polycyclic aromatic hydrocarbons, lubricating oils, phenols, vinyl-chloride, and petroleum. Reported brain tumor excesses have been reported in embalmers, professional artists, and pathologists in association with use of formaldehyde and solvents, and in farmers in association with organochlorine pesticides. Brain tumors have been induced in experimental animals. An increased incidence of brain tumors (gliomas and neuromas) occurred in the offspring of pregnant rats injected intravenously with ethylnitrosourea (759739) during the latter half of pregnancy. Although these observations have not been carried over directly to human studies, the possibility has been raised in epidemiologic studies that children of fathers who work in hydrocarbon related occupations may be at increased risk of cancer, a large proportion of which have been nervous system cancers. Although cancer of the bone has been induced in animals by different chemicals, ionizing radiation is the only known occupational agent to produce this disease in humans. Studies of radium dial painters working before 1925 demonstrated a dose response relationship between ingestion of bone seeking isotopes and osteosarcomas at calculated doses of over 1000 to 1200 rads. Chemically induced bone tumors have been produced by beryllium (7440417) and vinyl-chloride in rabbits and rats, respectively. These findings do not appear to carry over to human studies; however, the possibility that these agents could induce bone tumors in humans should merit serious consideration.

R&S 102690

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

- 9 AU - Neugut AI ; Wylie P ; Brandt-Rauf PW
TI - Occupational Cancers of the Gastrointestinal Tract. II.
Pancreas, Liver, and Biliary Tract
SO - Occupational Medicine: State of the Art Reviews. Occupational
Cancer and Carcinogenesis, Vol. 2, No. 1, P. W. Brandt-Rauf,
Editor; Philadelphia, Pennsylvania, Hanley and Belfus, Inc.,
pages 137-153, 20 references, 1987
AB - Occupational cancers of the pancreas, liver, and biliary tract
were discussed. Some associations have been shown to exist
between pancreatic cancer and exposure to metals, petrochemicals,
and industrial chemicals among rubber workers, wood workers, pulp
and paper workers, workers in petrochemical and oil refineries,
and metal workers and refiners. Asbestos workers do not seem to
be at increased risk for pancreatic cancer. Further studies are
needed to confirm and better define these causal relationships.
Primary liver cancer is relatively rare in the industrialized
world, and occupational cancers have not generally been noted
with the striking exception of the definite relationship between
exposure to vinyl-chloride (75014) and liver cancer, especially
hepatic angiosarcoma. Some associations between liver cancer and
inorganic arsenicals and solvents, such as carbon-tetrachloride
(56235), trichloroethylene (79016) and tetrachloroethylene
(127184), rubber chemicals, and furniture manufacturing chemicals
have been suggested. However, very little investigation of
possible confounding or nonoccupational factors has been
performed. There is very little available data on occupational
factors associated with biliary tract cancer. Possible
associations have been suggested for exposure to rubber,
chemical, automotive, textile, metal fabricating, petroleum,
paper and shoe industries in the case of gall bladder cancer,
exposure to asbestos (1332214), aircraft, automotive, chemical,
rubber and wood finishing industries for bile duct cancer, and
exposure to chemical and rubber industries for ampullary cancer.
More extensive investigations are necessary.
- 10 AU - Frank AL
TI - Occupational Cancers of the Respiratory Tract
SO - Occupational Medicine: State of the Art Reviews. Occupational
Cancer and Carcinogenesis, Vol. 2, No. 1, P. W. Brandt-Rauf,
Editor; Philadelphia, Pennsylvania, Hanley and Belfus, Inc.,
pages 71-83, 106 references, 1987
AB - Occupational cancers of the respiratory tract were reviewed, and
the historical development of lung cancer as an occupational
disease was summarized. At the beginning of the twentieth
century, lung cancer was rare; however, today more than 125000
deaths occur annually in the United States due to lung cancer,
and it is the leading cause of cancer deaths in many countries.
In 1985, lung cancer replaced breast cancer as the leading cause
of cancer deaths in females. Tobacco use among both males and
females accounts for most cases of lung cancer. Although this
relationship is now irrefutable, the exact mechanism and
components in cigarette smoke that give rise to lung cancer are

11

00003045

PAGE 7

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

still unclear. Hundreds of chemicals have been found in cigarette smoke and many have been identified as carcinogens or cancer promoters. A variety of etiologic agents in occupational lung cancer were discussed including arsenic (7440382), asbestos (1332214), beryllium (7440417), chloromethyl ethers, chromium compounds, polycyclic aromatic hydrocarbons, mustard gas, nickel (7440020), ionizing radiation, and a variety of suspected carcinogens including vinyl chloride (75014), fibrous mineral materials, chloroprene (126998), and vegetable dusts. Although prevention is regarded as the best approach for managing lung cancer, it does not always work. With no clear understanding of how lung cancer is produced, there is an ongoing need to identify and monitor possible cancer causing agents in occupational exposures.

- 11 AU - Rosenstock L ; Cullen MR
- TI - Neurologic Disease
- SO - Clinical Occupational Medicine; Philadelphia, Pennsylvania, W. B. Saunders Company, pages 118-134, 11 references, 1986
- AB - Occupational diseases of the nervous system are discussed, including central nervous system disorders such as toxic encephalopathy (either acute or chronic), tumors, and Parkinsonian movement disorders as well as peripheral nervous system disorders such as toxic polyneuropathy, neuromuscular junction blockade and traumatic disorders including interstitial (vascular related to vibration) and parenchymal (compressive or entrapment mononeuropathy) disorders. Agents which have been shown to produce brain tumors in experimental animals are listed. Occupations in which epidemiologic studies suggest an excess of brain tumors include aluminum (7429905) workers, chemists, lead smelter workers, machinists, medical personnel, oil refinery workers, petrochemical workers, pharmaceutical workers, rubber workers, veterinarians, and vinyl-chloride (75014) workers. Substances which cause peripheral neuropathies fall into the following categories: metals including lead (7439921), arsenic (7440382), mercury (7439976), and thallium (7440280); solvents including hexacarbons, trichloroethylene (79016), and carbon-disulfide (75150); gases such as methyl-bromide (74839) and carbon-monoxide (630080); pesticides and herbicides including chlordane (143500), some organophosphates, and chlorinated phenol derivatives; and plastics including acrylamide (79061), dimethylaminopropionitrile (1738256), and styrene (9003536). A number of such agents can also cause central neuropathies, including organic solvents, asphyxiant gases, pesticides and heavy metals.

11

00003046

PAGE 8

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

- 12 AU - Michot F ; Bruggisser D ; Fehr H ; Yurtsever H ; Anabitarte M
 TI - [Microangiopathic hemolytic anemia, erythrophagocytosis and consumption coagulopathy in vinyl chloride-induced hemangiosarcoma of the spleen and liver]
 SO - Schweiz Med Wochenschr; VOL 117, ISS 26, 1987, P990-5
 AB - A case of angiosarcoma of the liver and the spleen following vinyl chloride exposure is described. The main symptoms in clinical diagnosis were microangiopathic hemolysis, disseminated intravascular coagulation, hepatosplenomegaly and exposure to vinyl chloride thirty years ago. It is the first case in which liver and spleen are involved in angiosarcoma due to vinyl chloride exposure. The tumor cells showed angioformative and solid histiocytoid growth with erythrophagocytosis.
 LA - Ger
- 13 AU - Belli S ; Bertazzi PA ; Comba P ; Fo'a V ; Maltoni C ; Masina A
 AU - Pirastu R ; Reggiani A ; Vigotti MA
 TI - A cohort study on vinyl chloride manufacturers in Italy: study design and preliminary results.
 SO - Cancer Lett; VOL 35, ISS 3, 1987, P253-61
 AB - A cohort mortality study of 5000 vinyl chloride manufacturers is ongoing in 9 Italian plants. They represent the entire workforce of those ever employed in the production of the monomer and its polymerization. The objectives of the study are to investigate the mortality of the exposed population and to clear up the carcinogenic spectrum of vinyl chloride. This article gives the results for 3 out of 9 plants, Rosignano, Ferrara and Ravenna, which represent about 25% of the total cohort. The expected deaths have been calculated using the mortality rates of the Italian population. For the deceased persons information from the death certificates were used in the analysis of mortality; additional clinical and pathological data were collected (best pathological evidence, b.p.e.). In Ferrara a statistically significant excess for all malignant tumors and lung cancer was detected. In Rosignano and Ravenna the number of observed deaths were small and therefore no comments can be made on cancer mortality. The cohort study is ongoing in the 6 remaining cohorts and the future analysis will consider duration and level of exposure and latency.
 LA - Eng
- 14 AU - Burch JD ; Craib KJ ; Choi BC ; Miller AB ; Risch HA ; Howe GR
 TI - An exploratory case-control study of brain tumors in adults.
 SO - JNCI; VOL 78, ISS 4, 1987, P601-9
 AB - An exploratory study of brain tumors in adults was carried out using 215 cases diagnosed in Southern Ontario between 1979 and 1982, with an individually matched, hospital control series. Significantly elevated risks were observed for reported use of spring water, drinking of wine, and consumption of pickled fish, together with a significant protective effect for the regular consumption of any of several types of fruit. While these factors are consistent with a role for N-nitroso compounds in the

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

etiology of these tumors, for several other factors related to this hypothesis, no association was observed. Occupation in the rubber industry was associated with a significant relative risk of 9.0, though no other occupational associations were seen. Two previously unreported associations were with smoking nonfilter cigarettes with a significant trend and with the use of hair dyes or sprays. The data do not support an association between physical head trauma requiring medical attention and risk of brain tumors and indicate that exposure to ionizing radiation and vinyl chloride monomer does not contribute any appreciable fraction of attributable risk in the population studied. The findings warrant further detailed investigation in future epidemiologic studies.

LA - Eng

- 15 AU - Purchase IF ; Stafford J ; Paddle GM
TI - Vinyl chloride: an assessment of the risk of occupational exposure.
SO - Food Chem Toxicol; VOL 25, ISS 2, 1987, P187-202 (REF: 67)
AB - There is little doubt that exposure to high levels of VCM as a consequence of occupation can result in an increased incidence of ASL. A review of 20 epidemiological studies involving about 45,000 workers occupationally exposed to VCM showed that neoplasms of the liver showed an increase in incidence in the majority of studies. For brain cancer the association between exposure to VCM and an increased incidence was less clear because of the lower relative risk. Neoplasms of the respiratory tract, digestive system, lymphatic and haemopoietic system, buccal cavity, and pharynx, cardiovascular system and colon/stomach were reported to show an increased incidence in one or more studies, but to show no increase, or in some cases a decrease, in incidence in other studies. In view of the increased incidence of breast neoplasms in rodents exposed to VCM, the studies of Chaizze et al. (1980), who did not confirm these findings in humans, are of importance. The register of ASL cases now contains records of 99 persons with confirmed ASL and occupational exposure to VCM. The average latent period between first exposure to VCM and death from ASL is 21.9 years. The majority of cases occurred in autoclave workers, who are recognized as having been exposed to extremely high levels. Although precise estimates of exposure are not available for the periods of most interest, the pattern of cases roughly suggests that extremely high exposures were necessary for the induction of ASL. For example, ASL cases tended to occur in larger numbers in some plants than in others, a finding that can be explained most easily by differences in exposure patterns. There is an extensive series of animal studies on the carcinogenicity of VCM. Some of these precede the epidemiological studies confirming the association between VCM exposure and ASL in man. ASL and neoplasms of a number of other organs have been induced in laboratory rodents by VCM. Estimation of the exposure levels likely to cause a lifetime risk of ASL of $10(-6)$ on the basis of these data give extremely low levels (down to $3.9 \times 10(-7)$ ppb) which appear to be unrealistic estimates for

R&S 102694

00003048

PAGE 10

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

man. Part of the reason for this is that laboratory studies have shown that VCM is metabolized in the liver (and elsewhere in the body) to the reactive metabolites chloroethylene oxide and chloroacetaldehyde. The rate of conversion is limited at high levels of exposure giving inaccurate estimates of the slope of the dose-response relationship. (ABSTRACT TRUNCATED AT 400 WORDS)

LA - Eng

- 16 AU - Zwi LJ ; Evans DJ ; Wechsler AL ; Catovsky D
 TI - Splenic angiosarcoma following chemotherapy for follicular lymphoma.
 SO - Hum Pathol; VOL 17, ISS 5, 1986, P528-30
 AB - A case of splenic angiosarcoma in a patient who had been treated for a follicular lymphoma with chemotherapy over a period of about nine years is reported. The etiologic agents for angiosarcomas at various sites, and their associations with other tumors, are reviewed. The most important of these associations are radiotherapy and lymphedema with tumors of the skin and soft tissues; and vinyl chloride, arsenic, and thorium dioxide with hepatic tumors. For splenic angiosarcomas, only isolated associations with breast carcinoma and thorium dioxide exposure have been reported. In the present case long-term combination chemotherapy seems to be the most likely etiologic association.
 LA - Eng
- 17 AU - Sweeney MH ; Beaumont JJ ; Waxweiler RJ ; Halperin WE
 TI - An investigation of mortality from cancer and other causes of death among workers employed at an east Texas chemical plant.
 SO - Arch Environ Health; VOL 41, ISS 1, 1986, P23-8
 AB - The cause-specific mortality of 2,510 males employed at an east Texas chemical plant was examined in a historical prospective study to evaluate a suspected increase in deaths from multiple myeloma and brain cancer. Potential exposures from chemicals, either used in manufacturing processes or produced during the study period 1952-1977, included the fuel additive tetraethyl lead, ethylene dibromide and dichloride, inorganic lead, and vinyl chloride monomer. Overall mortality for all workers (156 observed vs. 211.14 expected) and for workers first employed between 1952 and 1959 (131 observed vs. 167.33 expected) when tetraethyl lead was the single major product was lower than expected when compared to the United States general population. There were no significant increases in mortality from malignancies or other causes of death. The deficits may be due to the small number of total deaths, and the low power for detecting excess risk of mortality from multiple myeloma (Z1-beta = 27, alpha = .05), brain cancer (Z1-beta = 31, alpha = .05), or other rare causes of death; lack of complete workplace exposure data for production workers; and the absence of historical measurements on the extent of environmental exposure to tetraethyl lead and other chemicals.
 LA - Eng

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

- 18 AU - Adkins B Jr ; Van Stee EW ; Simmons JE ; Eustis SL
TI - Oncogenic response of strain A/J mice to inhaled chemicals.
SD - J Toxicol Environ Health; VOL 17, ISS 2-3, 1986, P311-22
AB - Strain A/J mice were exposed by inhalation for 6 h/d, 5 d/wk, for 6 mo to carbon disulfide, 1,2-dibromoethane, ethylene oxide, naphthalene, nitrogen dioxide, or vinyl chloride. Significant increases in pulmonary adenoma formation were observed following exposure to 300 ppm carbon disulfide; 20 and 50 ppm 1,2-dibromoethane; 70 and 200 ppm ethylene oxide; 10 ppm nitrogen dioxide; and 50, 200, and 500 ppm vinyl chloride compared to control animals. Repeated studies with 1,2-dibromoethane, ethylene oxide, and vinyl chloride gave similarly significant results. Exposure of mice to 30 ppm naphthalene did not elicit a significant adenoma response. Histopathological examination of lungs from animals in these studies revealed multiple alveolar adenomas. Results from earlier studies with these chemicals, using strain A mice and Swiss mice, and bioassay information with rats and mice were compared with these data. These results provide further information for the validation of this in vivo model as a tool for predicting oncogenic potential following chemical exposure.
- LA - Eng
- 19 AU - Jones RD
TI - Epidemiology of brain tumours in man and their relationship with chemical agents.
SD - Food Chem Toxicol; VOL 24, ISS 2, 1986, P99-103
AB - The 2000 or so deaths that result each year in England and Wales from brain tumours, as defined by ICD 191, represent approximately 0.3-0.4% of all deaths, with a slightly greater incidence in men than in women. Because of the low incidence of mortality from other causes in childhood, brain cancer accounts for 3.5% of all deaths in the 1-14-year age group. Mortality from brain cancer increased considerably between 1931 and 1961 but this is probably explained by changes in disease classification and improvements in diagnostic techniques. Because of the relatively low incidence of brain cancer in man, cohort studies need to be large in order to accrue sufficient cases for meaningful interpretation. Large cohort studies may run the risk of diluting a high-risk group of workers with lesser or non-exposed individuals. These considerations have encouraged the investigation of brain cancer by case-control studies and the interpretation of these must take into account possible sources of bias. At present the evidence for any chemical causation of brain cancer in man is inconclusive.
- LA - Eng

R&S 102696

00003050

PAGE 12

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

- 20 AU - Fukumura A ; Mano H ; Higuchi T ; Hananouchi M ; Murase K
 AU - Kidokoro R ; Aoi T ; Hasegawa N
 TI - Case of hepatoangiosarcoma in a cleaner of vinyl chloride polymerisation reactors
 SO - Japanese Journal of Traumatology and Occupational Medicine Dec. 1986, Vol.34, No.12, p.976-982. Illus. 16 ref.
 AB - A 50-year-old Japanese male had been employed in a polyvinyl chloride (PVC) plant; his job involved cleaning of the tanks for the polymerisation of vinyl chloride monomer (VCM). The patient died of hepatoangiosarcoma in 1985. During the previous 10 years he had received periodic medical examination every 6 months. The tumour appeared 20 years after the initiation of exposure to VCM. The duration of exposure was about 4 years, but the amount of exposure was presumed to be considerably higher than that of other workers. Neither clinical manifestations nor abnormal data on laboratory examinations had been observed prior to onset of his illness, except persistent thrombocytopenia.
 LA - Jap
- 21 AU - Bond GG ; McLaren EA ; Baldwin CL ; Cook RR
 TI - An Update of Mortality Among Chemical Workers Exposed to Benzene
 SO - British Journal of Industrial Medicine, Vol. 43, No. 10, pages 685-691, 15 references, 1986
 AB - A study of leukemia incidence in 594 workers exposed to benzene (71432) was updated from 1973 to 1982; 362 exposed employees not studied originally were added. Analyses were carried out by production area, duration of exposure, and by cumulative dose index. Standardized mortality ratios (SMRs) were calculated. Analyses were made both including and excluding employees with past exposure to arsenic (7440382), asbestos (1332214), or high levels of vinyl-chloride (75014). A total of 225 deaths were identified, 25 of which were among the 68 employees who also had been exposed to asbestos, arsenic, or vinyl-chloride. The mean duration of exposure to benzene was 7.0 years. Nearly 25 percent (229 subjects) of the cohort members were exposed in jobs categorized as 30 parts per million (ppm) time weighted average (TWA) benzene exposure, and nearly a third (311) were exposed at 17ppm TWA. The all causes SMR was 84. A significant excess was observed for skin cancer, based on four deaths. A substantial and significant deficit was observed for accidental deaths. Four deaths were observed from leukemia, which was not significant. There was a nonsignificant excess of deaths in the category of other and unspecified cancers. The analysis of mortality in the total cohort was carried out allowing for a 15 year minimum latency. Specific cancer rates varied in different work areas. Cancer mortality was largely independent of duration of exposure. Dose response studies showed that all four skin cancers were in the lowest dose category. Two new and two previously reported cases of leukemia were from myelogenous leukemia; this was a significant excess. A death from myelofibrosis was of interest because of its similarity to myelogenous leukemia. The unexpected significant excess of skin cancer could not be linked

00003051

PAGE 13

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

to benzene exposure. Analysis by work area, duration of exposure, and cumulative dose index did not show patterns suggestive of a causal association between benzene exposure and any particular cause of death.

- 22 AU - Adkins B Jr ; Van Stee EW ; Simmons JE ; Eustis SL
TI - Oncogenic Response Of Strain A/J Mice To Inhaled Chemicals
SO - Journal of Toxicology and Environmental Health, Vol. 17, No. 2-3, pages 311-322, 32 references, 1986
AB - The oncogenic response of A/J-mice to various chemicals was evaluated. The purpose of the study was to test the carcinogenic response of the strain A-mouse model, using pulmonary adenoma formation as the endpoint, to a number of chemicals of occupational concern. The mice were exposed by inhalation to 300 parts per million (ppm) carbon-disulfide (75150), 20 or 50ppm 1,2-dibromoethane (106934), 70 or 200ppm ethylene-oxide (75218), 10 or 30ppm naphthalene (91203), 1, 5, or 10ppm nitrogen-dioxide (10102440), or 50, 200, or 500ppm vinyl-chloride (75014) 6 hours daily, 5 days per week for 6 months. The health status of all animals was observed twice weekly. The animals were killed at 6 months, and the lungs were removed and examined for pulmonary tumors. Treatment related mortality was observed in mice given 20 and 50ppm 1,2-dibromoethane and 500ppm vinyl-chloride. Significant increases in the tumor per mouse (expressed as adenomas per mouse) and tumor per tumor bearing mouse incidences were observed with animals exposed to carbon-disulfide, 1,2-dibromoethane, ethylene-oxide, nitrogen-dioxide, and vinyl-chloride. Exposure to 300ppm carbon-disulfide resulted in a small but significant increase in adenoma formation. Histopathologic examination of the lungs revealed multiple alveolar adenomas in treated animals and single alveolar adenomas in untreated animals. The authors claim that their results provide further data for validating in-vivo pulmonary adenoma formation in A/J-mice as a means for predicting the oncogenic potential of chemical agents.
- 23 AU - Thomas TL ; Waxweiler RJ
TI - Brain Tumors And Occupational Risk Factors. A Review
SO - Scandinavian Journal of Work, Environment, and Health, Vol. 12, No. 1, pages 1-15, 104 references, 1986
AB - The association between brain tumors and occupational risk factors are reviewed. Little is known about the etiology of brain tumors and other tumors of the central nervous system but some associations have been made with occupational and other environmental factors. Causal agents have not been identified but brain tumors seem to cluster in certain industries. The first such association recognized was reported among rubber workers. Elevated brain cancer risk has been suggested for some white collar groups. These workers may be somewhat more likely to have a brain tumor diagnosed. Brain cancer mortality ratios have been seen to be elevated among electricians and power servicemen. A significant increase in the occurrence of brain tumors has been observed for workers involved in

polyvinyl-chloride (9002862) production. Some reports have suggested elevated brain tumor risk among oil refinery workers. Inconsistent results have been found for other industries with chemical exposures. Some excess mortality from brain tumors has been reported for the nuclear industries, whether in fuels production or weapons production. No associations have been drawn from any particular radiation level. Most information about occupationally related brain tumors has been derived from studies with small numbers of observed and expected cases. Limitations of methodology and the lack of case/comparison studies have not allowed the definitive study of occupational brain tumors. The authors conclude that further studies must include as many cases as possible with diagnostic confirmation of tumor type and careful selection of comparison groups.

- 24 AU - GUENGERICH FP
AD - VANDERBILT UNIVERSITY, DEPARTMENT OF BIOCHEMISTRY, NASHVILLE, TENN 37232
TI - Bioactivation and covalent binding of toxic haloalkenes (human, rats)
SO - Crisp Data Base National Institutes Of Health
AB - RPROJ/CRISP The objectives of the proposed research concerning activation and detoxification of toxic and carcinogenic haloalkenes are enumerated below: 1) Determination of the alkylating agents involved in the covalent binding of vinyl chloride, vinylidene chloride, trichloroethylene, vinyl bromide and acrylonitrile to protein and nucleic acids, 2) elucidation of the role of epoxide hydratase in the metabolism of vinyl halides in vivo and in vitro, 3) immunohistochemical localization of epoxide hydratase in liver and lung, 4) examination of vinyl halide metabolism in the lung in vitro, 5) determination of the mechanism of cytochrome P-450 heme destruction that occurs during haloalkene metabolism, and 6) examination of DNA-chromatin protein crosslinking by metabolites of haloalkenes.
LA - ENG
- 25 AU - Thomas TL ; Waxweiler RJ
TI - Brain tumors and occupational risk factors
SO - Scandinavian Journal of Work, Environment and Health Feb. 1986, Vol.12, No.1, p.1-15. 104 ref.
AB - Some studies have shown that certain white-collar professional groups (artists, scientists, veterinarians, embalmers) and blue collar workers (rubber, oil refinery and chemical plant workers, machinists) appear to have an elevated risk of brain tumors. Most of the workers are potentially exposed to multiple chemicals; nevertheless they have some exposures in common: organic solvents, lubricating oils, acrylonitrile, vinyl chloride, formaldehyde, polycyclic aromatic hydrocarbons, and phenolic compounds.
LA - Eng

00003053

PAGE 15

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

- 26 AU - Moss AR
TI - Occupational exposure and brain tumors.
SO - J Toxicol Environ Health; VOL 16, ISS 5, 1985, P703-11
AB - Epidemiological evidence of an occupational risk of brain cancer has been reported in four industries where chemical exposures are likely, most recently in a series of prospective studies in the petrochemical industry. However, only in the case of vinyl chloride exposure has an occupational central nervous system carcinogen been identified. This report reviews the convergence of epidemiological and laboratory evidence that established the occupational carcinogenicity of vinyl chloride, and discusses in detail the current evidence for an occupational risk of brain tumors in the petrochemical industry.
LA - Eng
- 27 AU - Halama J ; Becker-Stone S ; Halama JM
TI - [Hemangiosarcoma of the liver in workers of the PVC industry and other VC-induced diseases with angiologic-dermatologic, hepatologic, radiologic and neurologic symptoms]
SO - Radiologe; VOL 25, ISS 1, 1985, P22-9
AB - Occupational diseases resulting from exposure to vinyl chloride (VC) include angiosarcoma of the liver and other neoplasms. Among workers exposed to VC we have found capillary abnormalities in the extremities, with scleroderma and Raynaud syndrome, acro-osteolysis, neurological and psychiatric diseases and chromosome abnormalities, as well as abnormal liver metabolism and haematological findings.
LA - Ger
- 28 AU - Dietz A ; Langbein G ; Permanetter W
TI - [Vinyl chloride induced hepatocellular carcinoma]
SO - Klin Wochenschr; VOL 63, ISS 7, 1985, P325-31
AB - On the occasion of a hitherto unique observation of three hepatocellular carcinomas in workers of the same industrial plant within 7 years following long-term exposure to vinylchloride, the characteristics are discussed of a chemical carcinogenesis leading to two different malignant tumours: haemangiosarcoma and hepatocellular carcinoma. This carcinogenic sequence has been predicted by animal studies. It is not known why the transformation of hepatocytes into carcinoma is far rarer than of sinusoidal cells into sarcoma. Whereas the hepatocellular carcinoma predominantly develops in association with cirrhosis, vinyl chloride is able to cause cancer directly without other known co-carcinogenic agents. This hepatic carcinogenicity is dose-dependent. After the introduction of industrial prevention measures, a new initiation of the tumour is improbable. Nevertheless, because of its long latency period, estimated between 5 and 20 years, clinical manifestations are still possible. An early diagnosis by sonography and computertomography, possibly combined with puncture, in exposed persons or those formerly at high risk is conceivable, while laboratory data, even tumour markers are unreliable. Its

00003054

PAGE 16

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

fulminant course does not differ from that of other hepatocellular carcinomas and has until now hindered successful treatment.

LA - Ger

- 29 AU - Jarvisalo JO ; Stenman UH
 TI - Body fluid proteins and peptides as tumour markers in clinical cancer research and in monitoring exposure to carcinogens.
 SO - IARC Sci Publ, ISS 59, 1984, P403-11
 AB - A brief review is given of the various groups of peptides and proteins that have been applied as tumour markers in human studies. Special attention is given to markers used for detection of bronchogenic lung tumours. In addition, a review is made of the few published studies on the levels of certain tumour markers in working populations that have been exposed to carcinogens. There is a considerable lack of present knowledge on the applicability of tumour marker assays to monitoring of human exposure to carcinogens. When such studies are planned, it is valuable to combine these analyses with other types of indicators of carcinogen exposure and effects.
 LA - Eng
- 30 AU - Purchase IFH
 TI - Carcinogenic Risk Assessment: A Toxicologist's View
 SO - Risk Quantitation and Regulatory Policy. 19 Banbury Report. Hoel, D. G., R. A. Merrill, and F. P. Perera, Editors; Cold Spring Harbor, New York, Cold Spring Harbor Laboratory, pages 175-186, 23 references, 1985
 AB - A scheme for risk management is presented and discussed. Major components of risk management are: Hazard identification, hazard assessment, risk assessment, risk evaluation, and control measures. Carcinogenic risk assessment begins with an assessment of the hazard and relates it to actual circumstances of exposure. This requires an estimate of the hazard at doses well below those which are of practical use in laboratory experiments, judgement of the relevance of the hazard to man, and a projection of its magnitude. Low dose extrapolation by mathematical models fails to take into account complexities of biological processes and frequently relies on inadequate experimental data. Epidemiological studies on about 50,000 exposed people have confirmed that vinyl-chloride (75014) (VC) produces angiosarcoma of the liver and brain tumors, but have not provided adequate information on dose response due to lack of accurate exposure data. Present evidence suggests that the VC dose in man to produce a risk of 10^{-6} is likely to be in excess of 100 parts per billion. Observations on the metabolism and carcinogenic effect of trichloroethylene (79016) indicate that the compound is carcinogenic by a nongenetic mechanism, which involves stimulation of hepatic peroxisomes. Recent evidence indicates that clear thresholds may be present for genotoxic carcinogens. For nongenotoxic carcinogens, the threshold may be determined by establishing a limit for the primary toxic event. Data derived from human observations provide the most relevant risk

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

estimation. Overall risk assessment is obtained by integration of data from experimental work, epidemiology, and extent of exposure.

- 31 AU - Moss AR
TI - Occupational Exposure And Brain Tumors
SO - Journal of Toxicology and Environmental Health, Vol. 16, No. 5, pages 703-711, 31 references, 1985
AB - Epidemiological and laboratory evidence of brain tumors caused by occupational exposure to carcinogens is reviewed. Brain tumors, and the glioma series tumors in particular, are considered likely suspects in the search for occupationally related tumors. Some evidence of an excess of brain tumors has been reported for rubber workers, chemists, workers exposed to vinyl-chloride (75014), and petrochemical workers. A NIOSH study published in 1976 observed a significantly increased relative risk for brain tumors among vinyl-chloride workers exposed more than 15 years. To date, vinyl-chloride is the only occupational chemical carcinogen identified as a central nervous system carcinogen. The excess risk of brain tumors might not have been recognized had they not been discovered in the study of the rarer angiosarcoma of the liver associated with vinyl-chloride exposure. Several studies have given reasonably clear indications of an association between petrochemical exposure and brain cancer. No specific causative factor has been identified. No occupational nervous system carcinogen has been identified for the rubber industry or for chemists. Recent studies show that nuclear fabrication workers also appear at increased risk of brain tumors as well as increased risk of melanoma. The author concludes that a coherent program of research is required for the petrochemical and nuclear fabrication industries where increased risk of brain tumors appears associated with occupation.
- 32 AU - Goldsmith JR
TI - Occupational Health In Chinese Metallurgical Industries: Report Based On A Visit
SO - American Journal of Industrial Medicine, Vol. 7, No. 4, pages 353-357, 1985
AB - Principal occupational health problems in the People's Republic of China were reviewed. A group of international occupational health specialists visited China to discuss common problems and plan for collaborative work. General health statistics were reviewed, such as overall life expectancy; infant mortality; and rise in cancer and cerebrovascular diseases. Demographic statistics on the general population and the working population were reviewed. There were two outstanding features of the organization of occupational health and safety services: institutes of occupational safety and health operated a full range of health care facilities; and industrial hygiene covered both medical and engineering services. There was a high incidence of occupationally related and concern over high cancer rates among workers with silicosis. In one tin mine, 19 percent of the silicotics died of lung cancer. Cigarette smoking with

R&S 102702

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

occupational exposures was recognized as important in the epidemiology of lung cancer. Benzene (71432) poisoning and its management were of concern. In an occupational cancer survey of 20,000 workers, a relative risk of 5 to 7 was found for leukemia among workers exposed to benzene. Carbon-disulfide (75150) and vinyl-chloride (75014) were reported to cause spontaneous abortions and toxemia, respectively. To treat occupational health diseases, access to traditional herbal medicine, acupuncture, and western medicine was offered.

- 33 AU - Salmon AG
TI - Vinyl Chloride: The Evidence For Human Carcinogenicity In Different Target Organs
SO - British Journal of Industrial Medicine, Vol. 42, No. 2, pages 73-74, 9 references, 1985
AB - Evidence for human carcinogenicity of vinyl-chloride (75014) is discussed. Vinyl-chloride, because of the observation of angiosarcoma of the liver among those occupationally exposed to it, is one of the relatively few compounds whose carcinogenicity has not been deduced on the basis of animal studies but has been demonstrated in the human population. It is noted that the workers among whom these cases occurred were probably very heavily exposed, even by the less stringent standards of a few years ago. The number of observed cases remains relatively small in relation to the large number of workers that must have received some exposure. The success of epidemiological methods in demonstrating the human carcinogenicity of vinyl-chloride is due to the fact that angiosarcoma is very rare in the general population. It is considered important to determine if other less specific tumors can also be caused by exposure to vinyl-chloride. The incidence rate of other tumors could be much higher than the rate of angiosarcoma occurrence, while remaining difficult to demonstrate by epidemiological methods. It is noted that various studies have suggested an increase in lung cancer in populations exposed to vinyl-chloride. This is very difficult to demonstrate because of the high incidence of lung cancer in the general population and its relation to smoking habits. Epidemiological studies have also suggested associations between vinyl-chloride exposure and melanoma, and cancer of the colon and thyroid. The interpretation of these findings must be tentative due to the small number of observed cases. The findings are, however, significant, since an increase in the incidence of relatively common tumors such as those of the lung or colon could far outnumber the small number of angiosarcomas.
- 34 AU - Forman D ; Bennett B ; Stafford J ; Doll R
TI - Exposure to vinyl chloride and angiosarcoma of the liver: a report of the register of cases
SO - British Journal of Industrial Medicine Nov. 1985, Vol.42, No.11, p.750-753. 8 ref.
AB - Analysis of the information in the register of all cases (118 to 1984) of angiosarcoma of the liver (ASL) resulting from exposure to vinyl chloride monomer (VCM). The register is maintained by

R&S 102703

00003057

PAGE 19

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

the Association of Plastic Manufacturers in Europe, and its coverage is worldwide. Conclusions of the analysis: very high exposures to VCM are needed to induce ASL; a very low proportion of liver cancers is attributable to exposure to VCM (0.6% in the USA, 1.3% in the United Kingdom); the mean induction period (time from first exposure to initial diagnosis) is 22.6 years; another 200-250 deaths from VCM-related ASL are to be expected over the next 30 years.

LA - Eng

- 35 AU - Hardell L ; Bengtsson NO ; Jonsson U ; Eriksson S ; Larsson LG
 TI - Aetiological aspects on primary liver cancer with special regard to alcohol, organic solvents and acute intermittent porphyria--an epidemiological investigation.
 SO - Br J Cancer; VOL 50, ISS 3, 1984, P389-97
 AB - Some environmental factors of possible aetiological importance for primary liver carcinoma (PLC) in males were analysed in a case-control study including 83 cases of hepatocellular carcinoma (HCC), 15 cases of intrahepatic cholangiocellular carcinoma (CC), 3 cases of haemangiosarcoma and 1 case of unspecified sarcoma in the liver--102 cases in total. Two matched controls were used in each case. One case with haemangiosarcoma was exposed to polyvinyl chloride. The case with unspecified soft-tissue sarcoma was exposed to phenoxy acids. A 4-fold increase in the risk of HCC was seen in alcoholics, and regular drinking gave a 3-fold increase in the risk. Exposure to organic solvents gave a 2-fold increase in the risk of HCC. No increased risk was observed for cases exposed to various other chemicals. Three cases of HCC had a previous diagnosis of porphyria acuta intermittens (PAI), versus no control. Six cases of HCC had a previous diagnosis of porphyria acuta intermittens (PAI), versus no control. Six cases with PLC had polyphryia cutanea tarda (PCT) which in 4 cases was related to alcoholism and in one case to haemochromatosis.

LA - Eng

- 36 AU - Nicholson WJ ; Henneberger PK ; Seidman H
 TI - Occupational hazards in the VC-PVC industry.
 SO - Prog Clin Biol Res; VOL 141, 1984, P155-75
 AB - Overall, the results of the analysis of 12 studies of VC production and polymerization workers demonstrate an enormously elevated risk of liver malignancies, the possibility of a twofold increased risk of brain and central nervous system tumors and perhaps, also, of malignancies of the lymphatic and hematopoietic system. However, the role of other agents cannot be excluded in the etiology of nonhepatic malignancies. Bronchogenic carcinoma does not appear to be increased from exposures to VC monomer, although a relationship to PVC dust was suggested in one study. These conclusions must be considered in light of limited data on workers followed more than 25 years from onset of exposure. Considering the numbers of observed and expected deaths in all studies, it would appear that the excess of malignancies at nonhepatic sites is less than the excess of liver tumors. Data presented elsewhere in this volume (Nicholson and Henneberger,

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

R&S 102705

1983) suggest that exposure reductions in 1974 may have virtually eliminated the VC-associated risk of liver cancer if the current U.S. standard is met. To the extent that VC exposure is associated with other cancers, a similar risk reduction would be expected. Raynaud's phenomenon, acroosteolysis, scleroderma-like skin lesions, hepato- and splenomegaly with noncirrhotic hepatic fibrosis, and severe portal hypertension have been associated with past heavy exposures to VC. Evidence exists that the liver disease and portal hypertension may progress following cessation of exposure. However, all of the above syndromes were found largely in heavily exposed individuals. Their occurrence would be much less likely in workers exposed only to concentrations currently allowed. Pulmonary deficits, X-ray abnormalities, and, perhaps, lung cancer have been associated with VC/PVC exposure. Because of the possible contribution of PVC dust to these findings, engineering controls during polymer drying, bagging and usage are warranted.

LA - Eng

- 37 AU - Pastorino U ; Berrino F ; Gervasio A ; Pesenti V ; Riboli E
AU - Crosignani P
TI - Proportion of lung cancers due to occupational exposure.
SO - Int J Cancer; VOL 33, ISS 2, 1984, P231-7
AB - The proportions of male lung cancers due to occupational exposure and, respectively, to cigarette smoking in a highly industrialized area of Northern Italy were estimated in a population-based case-control study in 1976-9. Two hundred and four out of the 211 lung cancer cases and 351 controls sampled from the source population were questioned about their occupational and smoking histories. On the basis of the occupational history each subject was classified as probably exposed (+), possibly exposed (?), or unexposed (-) to one or more of the chemicals known to be carcinogenic for the human lung, namely asbestos, polycyclic aromatic hydrocarbons, arsenic, nickel and chromium compounds, BCME, CMME and vinyl chloride. Upon stratification by cigarette smoking, contrasting the occupationally exposed subjects, whether certainly or uncertainly defined, with the unexposed ones, the RR for lung cancer was 2.1 and the occupational etiologic fraction was 0.33 (95% confidence interval 0.19-0.47). The tobacco etiologic fraction was 0.81, while the two exposures together accounted for 89% of the total burden of incident cases. If 33% of all male lung cancers were of occupational aetiology, then this alone would represent 5% of all cancer deaths.

LA - Eng

31

00003059

PAGE 21

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

-
- 38 AU - Heldaas SS ; Langard SL ; Andersen A
 TI - Incidence of cancer among vinyl chloride and polyvinyl chloride workers.
 SO - Br J Ind Med; VOL 41, ISS 1, 1984, P25-30
 AB - The results of a follow up study of the incidence of cancer and the mortality in a cohort of 454 male workers producing vinyl chloride and polyvinyl chloride are presented. The study population was restricted to employees with more than one year's work experience in the study plant between 1950 and 1969 and the cohort was followed up from 1953 to the end of 1979. Twenty three new cases of cancer were observed compared with 20.2 expected; one case of liver angiosarcoma was found. Five cases of lung cancer were found (2.8 expected) and four cases of malignant melanoma of the skin were observed (0.8 expected). The possibility of a causal relationship between exposure to vinyl chloride and the development of malignant melanomas is discussed.
 LA - Eng
- 39 AU - Wagoner JK
 TI - Toxicity of vinyl chloride and poly(vinyl chloride): a critical review.
 SO - Environ Health Perspect; VOL 52, 1983, P61-6 (REF: 41)
 AB - In 1974, vinyl chloride (VC) was first reported in the open scientific literature to induce angiosarcoma of the liver both in humans and in animals. Additional research has now demonstrated the carcinogenicity of VC to other organs and at lower concentrations. The target organs for VC now clearly include the liver, brain and the lung, and probably the lymphohematopoietic system. The evidence for a carcinogenic risk has been extended to jobs associated with poly(vinyl chloride) exposure. Cases of liver angiosarcoma have been reported among individuals employed in PVC fabrication facilities and an epidemiological study has demonstrated a significant association between exposure to PVC dust and the risk of lung cancer mortality. Cases of angiosarcoma of the liver also have been reported among individuals living in near proximity to vinyl chloride-poly(vinyl chloride) plants. An association between PVC dust and pneumoconiosis also has been demonstrated. On the basis of findings, prudent control of PVC dust in the industrial setting is indicated.
 LA - Eng
- 40 AU - Evans DM ; Williams WJ ; Kung IT
 TI - Angiosarcoma and hepatocellular carcinoma in vinyl chloride workers.
 SO - Histopathology; VOL 7, ISS 3, 1983, P377-88
 AB - The livers from five vinyl chloride workers are described. They show angioformative and hepatocellular growth disturbance in varying proportions: angiosarcoma in four cases, liver cell hyperplasia in all, hyperplastic nodules in three cases and hepatocellular carcinoma in two cases. In one case the transition between hyperplastic nodule and hepatocellular carcinoma is demonstrated. The relationship between these changes and vinyl

11

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

chloride exposure is discussed, with evidence that they are causally related.

LA - Eng

- 41 AU - Drew RT ; Boorman GA ; Haseman JK ; McConnell EE ; Busey WM
AU - Moore JA
TI - The effect of age and exposure duration on cancer induction by a known carcinogen in rats, mice, and hamsters.
SO - Toxicol Appl Pharmacol; VOL 68, ISS 1, 1983, P120-30
AB - Female Golden Syrian hamsters, F-344 rats, Swiss CD-1 mice, and B6C3F1 hybrid mice were exposed 6 hr/day, 5 days/week to carcinogenic levels of vinyl chloride (VC) for 6, 12, 18, or 24 months (rats and hamsters only). Other groups of rodents were held for 6 or 12 months and then exposed for 6 or 12 months. At the end of the study the incidence of VC-induced neoplasms was compared in each of the groups to assess the effects of duration of exposure and age at the start of exposure on carcinogenicity of VC. In rats, with early initial exposure, hemangiosarcomas, hepatocellular carcinomas, and mammary gland carcinomas occurred with increasing incidence with longer exposure duration. Rats held for 6 months before exposure developed VC-related neoplasms, while rats held 12 months before the start of exposure failed to show a significantly increased incidence of these neoplasms. In hamsters, hemangiosarcomas, mammary gland carcinomas, gastric adenocarcinomas, and skin carcinomas resulted from VC exposure. The highest incidence of malignant neoplasms occurred in hamsters exposed for the first 12 months, whereas exposure begun after 12 months of age did not cause neoplasms. In both strains of mice, VC exposure during the first 6 months of the experiment induced a high incidence of hemangiosarcomas and mammary gland carcinomas. Swiss mice also developed lung carcinomas after only 6 months of exposure. In all three rodent species an initial 12 month exposure to VC was adequate to detect its carcinogenic potential, but the shortened survival of VC exposed mice and hamsters precluded a meaningful comparison with longer periods of exposure. Exposures were most effective when started early in life.
- LA - Eng
- 42 AU - Ives JC ; Buffler PA ; Greenberg SD
TI - Environmental associations and histopathologic patterns of carcinoma of the lung: the challenge and dilemma in epidemiologic studies.
SO - Ann Rev Respir Dis; VOL 128, ISS 1, 1983, P195-209 (REF: 123)
AB - An update of histopathologic classification schemes is provided for carcinoma of the lung and factors that influence proportional distributions of cell types, i.e., sources and preparations of tissue specimens, observer variability, and use of secondary sources of information. Consideration is given to the natural history and to current knowledge of the demographic characteristics of cell types of carcinoma of the lung. A review of studies reporting histopathologic associations with environmental exposures suggests that no single type of carcinoma

R&S 102707

00003061

PAGE 23

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

of the lung is specifically associated with exposure to tobacco smoke, arsenic, or beryllium. Furthermore, studies concerned with exposure to asbestos, chloroethers, chromates, nickel, vinyl chloride, and radioactivity lack sufficient information to conclude definitively that only one specific lung cancer cell type is associated with these exposures. In conclusion, an exclusive association of a single cell type of carcinoma of the lung with exposure to the physical or chemical agents reviewed has not been demonstrated.

LA - Eng

- 43 AU - Austin SG ; Schnatter AR
TI - A case-control study of chemical exposures and brain tumors in petrochemical workers.
SO - J Occup Med; VOL 25, ISS 4, 1983, P313-20
AB - The relationship between chemical exposures and deaths attributable to primary brain tumors among employees of a Texas petrochemical plant was investigated. Cases consisted of 21 deaths in which the underlying cause was confirmed as a primary brain tumor. Two control groups of 80 employees each were randomly selected from 450 decedents known to the company in June, 1979. Potential exposures while employed were compared between cases and controls for five known or suspect carcinogens. Exposure potentials were also compared for an additional 37 chemicals to which at least four cases were potentially exposed. Overall and 15-year latency analyses were performed. The proportion of cases exposed to the five potentially carcinogenic chemicals (including vinyl chloride) were lower than or consistent with the proportion of exposed controls. No statistically significant differences between the proportions of cases and controls exposed to the 37 other chemicals were found.

LA - Eng

- 44 AU - Langbein G ; Permanetter W ; Dietz A
TI - [Hepatocellular carcinoma after exposure to vinyl chloride]
SO - Dtsch Med Wochenschr; VOL 108, ISS 19, 1983, P741-5
AB - Hepatocellular carcinoma was diagnosed already during life in a 54-year-old workman who had been exposed to high concentration of vinyl chloride due to his occupation for more than twenty years. In addition, typical early changes as seen in experimental vinyl chloride induced angiosarcoma were observed. In recent years permissible room air concentration of vinyl chloride at work have been lowered drastically. However, due to the long latency occurrence of malignant liver tumours may still be expected in persons exposed formerly. Within the search programme for such patients at risk ultrasonography and computed tomography as non-invasive methods with high accuracy are advisable.

LA - Ger

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

- 45 AU - Frenzel-Beyne R
TI - Lung cancer mortality of workers employed in chromate pigment factories. A multicentric European epidemiological study.
SD - J Cancer Res Clin Oncol; VOL 105, ISS 2, 1983, P183-8
AB - This study was designed in an attempt to quantify the mortality from cancer and other diseases among workers of European factories producing chromate pigments. The prevailing mixed exposures to zinc as well as lead chromate pigment--although the latter was produced predominantly over the whole period of time made it impossible to distinguish those persons exposed to lead chromate pigment. This report deals with cancer of the respiratory tract and lung cancer in particular. The total workforce of each factory included in the study was followed up, more successfully when they were employed before 1960 than after that time owing to the rising number of foreign nationals. Observed deaths from five factories were compared with expected deaths calculated on the basis of mortality figures for the region in which a given factory was located. Further analysis concerned data of relevant cohorts, which comprised only persons observed for a minimum of 10 years (i.e., exposure beginning before 1965), certainty of complete records for the entire staff to assure a complete cohort instead of prevailing healthy survivors, and exclusion of all foreign nationals. As a result, the overall mortality did not deviate from the expected rates. Lung-cancer rates were always in excess of expected numbers, although only in one cohort to a statistically significant extent. The pattern of duration of exposure indicates that the lung-cancer risk does not show a clear dose-response effect with time of employment. Due to the mixed nature of exposure, conclusions must be limited with the effect that the results obtained are consistent with the hypothesis that working in a chrome-processing plant environment is associated with an increased incidence of lung cancer and with a higher probability of dying from lung cancer compared with the general population.
LA - Eng
- 46 AU - Holmberg B
TI - The Toxicology Of Monomers Of The Polyvinyl Plastic Series
SD - Progress in Clinical and Biological Research, Industrial Hazards of Plastics and Synthetic Elastomers, Vol. 141, Jarvisalo, J., P. Pfaffli, and H. Vainio, Editors; pages 99-112, 71 references, 1984
AB - The toxicology of monomers of the polyvinyl plastic series is reviewed. The polyvinyl series of thermoplastics is of great commercial and technical importance. Vinyl-chloride (75014) is widely produced for plastic production. Its acute toxicity is low in terms of lethality. The primary acute effect is central nervous system depression. Vinyl-chloride is rapidly absorbed by the lungs and is readily metabolized. It is mutagenic and is certainly a multipotential carcinogenic. Animal studies indicate that blood vessels are target tissues, a finding corroborated by human data showing skin capillary changes, Raynaud's phenomenon and acroosteolysis among workers exposed to polyvinyl-chloride

R&S 102709

00003063

PAGE 25

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

(9002862). Liver involvement in chronic vinyl-chloride exposure was recognized later than the immediate effects of central nervous system depression and acroosteolysis. Occupational standards in many countries for vinyl-chloride exposure have been lowered in view of the tumors, particularly of the liver, associated with long term exposure. Vinylidene-chloride (75354), a vinyl-chloride copolymer, has considerable commercial importance as well. As a liquid it is irritating to the skin. The vapor can cause nasal irritation. Although not teratogenic in rats and rabbits, vinylidene-chloride is mutagenic to *Salmonella* after microsomal activation and is mutagenic in some other cell types. In mice, rats and hamsters it is carcinogenic.

Data on human populations is limited and no conclusions can yet be drawn about long term hazards. Vinyl-acetate (108054) is used in production of homopolymers and copolymers, and in synthesis of other chemicals. The acute toxicity is more moderate, and mutagenicity and carcinogenicity have not been demonstrated in animals. Vinylcyclohexene-dioxide is, however, a suspected carcinogen.

- 47 AU - Nicholson WJ ; Henneberger PK ; Tarr D
 TI - Trend In Cancer Mortality Among Workers In The Synthetic Polymers Industry
 SO - Progress in Clinical and Biological Research, Industrial Hazards of Plastics and Synthetic Elastomers, Vol. 141, Jarvisalo, J., P. Pfaffli, and H. Vainio, Editors; pages 65-78, 30 references, 1984
 AB - Data on both experimental and human carcinogens from exposure to vinyl-chloride (75014) (VC) and on its metabolism is reviewed. Particular emphasis is given to information concerning dose/response relationships, and trends for future disease potential are suggested, based on the information. A high risk of death from liver hemangiosarcoma (HSA) has been documented from past exposures to VC. Similar to other carcinogens, the risk of VC induced liver HSA appears to increase as the second or third power of time from onset of exposure. It is possible to project future mortality using this power relationship, estimates of VC exposure, and observed mortality up to 1980. These projections suggest that 200 to 600 deaths may occur in the United States, and 550 to 2,800 deaths may occur in Western Europe, from liver HSA. These projections also suggest that a 1 part per million standard will go far in protecting workers exposed to VC from future malignant disease.
- 48 AU - Jarvisalo JO ; Stenman UH
 TI - Body Fluid Proteins And Peptides As Tumour Markers In Clinical Cancer Research And In Monitoring Exposure To Carcinogens
 SO - Monitoring Human Exposure to Carcinogenic and Mutagenic Agents, Proceedings of a Joint Symposium Held in Espoo, Finland, 12-15 December, 1983, IARC Scientific Publication No. 59, pages 403-411, 26 references, 1984
 AB - Peptides and proteins applied as tumor markers in human studies are reviewed. Most markers studied have been proteins or peptides which have been either normal, ectopic to the tissue

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

where the cancer has developed, or the products of tumor development, ectopic markers. This classification does not include products like immune complexes or acute phase reactants. Protein markers may also be classified on the basis of their antigens. Tumor markers detected in bronchogenic lung cancers are described. The carcinoembryonic antigen (CEA) is the most commonly used marker, although nonspecific elevation of CEA is fairly common. Thirty six peptide and protein markers studied in patients with lung cancer are listed; however, few of these markers have proved to be predictors of lung tumors even at the clinical stage of the disease. Factors to be considered when applying tumor markers assays to diagnosis and monitoring include the clinical sensitivity of a test; its specificity or negativity in health; the predictive value of a positive result; and the efficiency of a method. The importance of careful definition of the population under study and characterization of methods used is emphasized. Studies on chemical markers in tobacco smokers, vinyl-chloride (75014) and styrene (100425) exposed workers, and asbestosis patients are examined. Results show significant differences in the distribution of CEA concentrations in vinyl-chloride polymerization workers, a correlation of CEA with alkaline-phosphatase, and slightly higher mean CEA concentrations in styrene workers and asbestosis patients. The authors conclude that cross sectional and longitudinal studies are needed to correlate cancer occurrence with marker concentrations and disease programs. The nonspecificity of many markers may be useful in detecting people at higher cancer risk due to toxic exposures; however, ethical and economic aspects of considerable numbers of false positives should be considered.

- 49 AU - Tamburro CH ; Creech JL
TI - The Identification Of Hepatic Injury And Hepatic Angiosarcoma Among Vinyl Chloride Workers The Epidemiological Approach
SO - Sangyo Ika Daigaku Zasshi, Supplement 5, pages 37-48, 22 references, 1983
AB - An industrial epidemiological occupational health program for identification of hepatic injury and angiosarcoma among vinyl-chloride (75014) workers is reviewed. The program is best instituted prospectively, although it can be applied retrospectively. It consists of three programs: the epidemiological surveillance program, the medical surveillance program, and the medical disease detection and treatment program, each of which is described. Components of the epidemiological surveillance program include a job classification code, employee work history record, a rank ordered exposure rating system, and a medical illness and disease data base. In addition, a periodic medical examination and limited but specific laboratory screening studies make up the medical surveillance program. Addition of a multiple system testing program, a diagnostic triage program, and a therapeutic management protocol for early treatment comprise the medical disease detection and treatment program. The systematic diagnostic triage system used for vinyl-chloride is described as a model for other types of organ injury. Results of

R&S 102711

13

00003065

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

PAGE 27

8 years application of this surveillance system to an industrial cohort of approximately 1,200 vinyl-chloride workers provide verification of the role of vinyl monomers in induction of hepatic cancer. Results also demonstrate an inverse relationship between exposure and latency of vinyl-chloride cancer induction and demonstrate the effectiveness of clinical screening tests in the detection of chemically induced liver injury. Additional findings include assessment of screening tests in asymptomatic populations, assessments of possible vinyl-chloride injury to the pulmonary system, and a lack of correlation between cardiac irregularities and vinyl-chloride exposure. Initial program costs are estimated at 40 to 50 dollars/worker with maintenance costs of 5 to 7 dollars/year. The authors conclude that systematic epidemiological studies are feasible, economical, and provide the best means to identify and characterize agents which may produce occupationally related disease.

- 50 AU - Austin SG ; Schnatter AR
 TI - A Case-Control Study Of Chemical Exposures And Brain Tumors In Petrochemical Workers
 SO - Journal of Occupational Medicine, Vol. 25, No. 4, pages 313-320, 10 references, 1983
 AB - The relationship between occupational chemical exposure and death due to brain tumors was investigated among petrochemical workers. Cases of 21 workers who died of primary brain tumors were compared to a group of workers who died of other neoplasms and a group whose deaths were unrelated to cancer. Exposure to benzene (71432), ethylene-dichloride (107062), ethylene-oxide (75218), diethyl-sulfate (64675), and vinyl-chloride (75014) was determined based on job. A group of 37 other chemicals to which four brain tumor cases had been exposed was studied. The proportion of cases exposed to a chemical was compared to the proportion of comparisons exposed to the same chemical. The proportion of glioma cases was calculated. A slightly higher proportion of brain tumor cases than comparisons were employed fewer than 10 years. Cases and comparisons were similar in year of hire, payroll status, and race. Fewer cases survived to 70 years of age. Exposure determinations could not be made for about 55 percent of the cases and about 59 percent of comparisons. Analyses using hourly workers, who are more likely to be exposed than salaried workers, indicated little difference between cases and comparisons. There appeared to be less frequent exposure to the 37 other chemicals among cases than comparisons. The authors conclude that there is no evidence that exposures to the chemicals studied are related to brain tumor deaths.

14

00003066

PAGE 28

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

- 51 AU - Heldaas SS ; Langard SL ; Andersen A
 TI - Incidence Of Cancer Among Vinyl Chloride And Polyvinyl Chloride Workers
 SO - British Journal of Industrial Medicine, Vol. 41, No. 1, pages 25-30, 21 references, 1984
 AB - Cancer incidence and mortality from occupational exposure to vinyl-chloride (75014) and polyvinyl-chloride (9002862) were investigated in Norwegian workers. Company health records and job classifications were examined. Individual exposures were estimated based on prior measurements and job classifications. Individual records were then sought from the Cancer Registry of Norway. Results were compared with those from a constructed Norwegian population whose age distribution was identical with that of the study group. Deaths from all causes were elevated among workers involved in polyvinyl-chloride production, with a standardized mortality ratio of 1.16, and autoclave cleaning, with a standardized mortality ratio of 1.64. Deaths from all cancers were also elevated in these two groups: for polyvinyl-chloride production, ratio of observed to expected cases was 1.76; and for autoclave cleaning, this ratio was 1.94. The number of observed cancers was also elevated among packing and drying workers, a ratio of 1.69. When workers were divided into three groups reflecting high, medium, and low exposure, the increased incidence of cancer was accounted for almost entirely by the high exposure group. Five cases of lung cancer were observed in the study population compared with 2.8 expected; the latent period in these cases was 17.2 years. Four of the cases were in the high exposure group. Three cases of colonic cancer were observed in the high exposure group, versus 0.9 expected. Two cases of cancer of the thyroid gland were observed; both were medullary carcinomas. Four malignant melanomas of the skin were identified in the study population, whereas only 0.8 were expected. When the expected chance of developing cancer was related to the estimated weighted exposure value, the highest risk ratios were found among workers characterized by high exposure. The authors conclude that vinyl-chloride-monomer exposure is related to development of these cancers, particularly the malignant melanomas.
- 52 AU - Nicholson WJ ; Henneberger PK ; Seidman H
 TI - Occupational Hazards In The VC-PVC Industry
 SO - Industrial Hazards of Plastics and Synthetic Elastomers, Jarvisalo, J., P. Pfaffli, and H. Vainio, Editors; Alan R. Liss, Inc., New York, pages 155-175, 53 references, 1984
 AB - Occupational hazards in the vinyl-chloride (75014) (VC) polyvinyl-chloride (9002862) (PVC) industry are reviewed. Mortality studies of VC workers, examining 12 independent cohorts, show standardized mortality ratios (SMRs) for cancer of all sites ranging from 81 to 230 and SMRs for liver cancer ranging from 167 to 2,500. Hemangiosarcomas are reported in 8 of the 12 studies. Evidence for lung cancer is less clear, with SMRs for respiratory cancers in these studies ranging from 35 to

00003067

PAGE 29

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

289. Cancers of the brain and central nervous system are significantly elevated in a number of the studies, although results differ considerably across studies. For lung, brain and central nervous system cancers, data from animals is equivocal. Follow up studies to determine whether a high risk of liver cancer continues, following significant exposure reductions made in 1974 when the link with VC was first recognized, show that the risk of neoplastic VC disease continues undiminished. Morbidity and clinical findings among VC exposed workers are described. Raynauds phenomenon, acroosteolysis, scleroderma like skin lesions, hepatomegaly and splenomegaly with non cirrhotic hepatic fibrosis, and severe portal hypertension are reported in association with past heavy VC exposures. Increased frequency of chromosome abnormalities in the lymphocyte cultures of VC workers are reported, but later sampling suggests decreased chromosomal abnormalities attributable to decreased exposures. In the PVC processing industry, documentation of only two hemangiosarcomas is reported. A proportionate mortality study of 4,341 deaths of former employees of 17 PVC facilities shows an excess in total cancer mortality in white males and females and an excess of breast cancer in females. Pulmonary deficits, X-ray abnormalities and perhaps lung cancer are associated with VC/PVC exposures. The authors conclude that studies of VC production workers suggest an enormously elevated risk of liver malignancies and the possibility of an increased risk of brain and central nervous system tumors. Engineering controls during polymer drying, bagging, and usage are warranted.

- 53 AU - Holmberg B
 TI - The Toxicology Of Monomers Of The Polyvinyl Plastic Series
 SO - Industrial Hazards of Plastics and Synthetic Elastomers, Jarvisalo, J., P. Pfaffli, and H. Vainio, Editors; Alan R. Liss, Inc., New York, pages 99-112, 72 references, 1984
 AB - Studies on the toxicity of monomers of the polyvinyl plastic series are reviewed. Substances within the polyvinyl series include: polyvinyl-chloride (9002862); vinyl-chloride (75014) copolymers; polyvinylidene-chloride (9002851); polyvinyl-acetate (9003207); polyvinyl-alcohol (9002895); polyvinyl acetals; and polyvinyl ethers. The acute toxicity of vinyl-chloride is low in terms of lethality, but the agent is rapidly absorbed by the lung. Vinyl-chloride is both mutagenic and poses a carcinogenic risk to those exposed to the substance. Vinylidene-chloride has been found to irritate the skin and nasal passages of animals and is also considered carcinogenic in animals. Data on human populations is limited. Vinyl-acetate has affected livers, blood, and central nervous systems of test animals. Vinyl-acetate has also been a nasal and eye irritant to humans. Vinylcyclohexene-dioxide (106876) is of low acute toxicity for test animals. Irritations of the skin, respiratory system, and the eyes have been observed. Although limited studies are available, the toxicological information on this agent suggests low exposure limits. Vinylcyclohexene-dioxide is a suspected carcinogen.

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

R&S 102715

- 54 AU - Nicholson WJ ; Henneberger PK ; Tarr D
TI - Trends In Cancer Mortality Among Workers In The Synthetic Polymers Industry
SO - Industrial Hazards of Plastics and Synthetic Elastomers, Jarvisalo, J., P. Pfaffli, and H. Vainio, Editors; Alan R. Liss, Inc., New York, pages 65-78, 30 references, 1984
AB - Studies relating to both experimental and human carcinogenesis resulting from exposure to vinyl-chloride (75014) are reviewed. The metabolism of vinyl-chloride in humans and animals is considered, and estimates are given of trends in future disease potential from past exposures. Information is also presented on the efficacy of current occupational standards, with particular attention given to workers in the synthetic polymers industry (SIC-2821). A high risk of death from liver hemangiosarcoma has been documented from past exposures to vinyl-chloride. Similar to other carcinogens, the risk of vinyl-chloride induced liver hemangiosarcoma appears to increase as the second or third power of time from onset of exposure. It is possible to project future mortality using this power relationship, estimates of exposure to vinyl-chloride, and observed mortality. The authors conclude that these projections suggest that 200 to 600 deaths may occur in the United States and 550 to 2,800 deaths may occur in Western Europe from liver hemangiosarcomas. These projections also suggest that a 1 part per million standard in the vinyl-chloride industry will go far in protecting workers from future malignant disease.
- 55 AU - Kalmaz EE ; Kalmaz GD
TI - Carcinogenicity And Epidemiological Profile Analysis Of Vinyl Chloride And Polyvinyl Chloride
SO - Regulatory Toxicology and Pharmacology, Vol. 4, No. 1, pages 13-27, 81 references, 1984
AB - Carcinogenicity caused by vinyl-chloride (75014) and polyvinyl-chloride (9002862) exposure is reviewed. Vinyl-chloride and polyvinyl-chloride are among the most widely used synthetic organic chemicals. In the workplace, the production processes, the final product, and other materials used for production must be considered before valid toxicological and health effects can be assessed. Exposure in work environments is generally at higher concentrations than that which occurs in the general environment. A historical perspective of the carcinogenicity of vinyl-chloride and polyvinyl-chloride is given. Studies have indicated that workers in synthetic chemicals industries are susceptible to the toxicity and carcinogenicity of these chemicals. Bioassays demonstrate that vinyl-chloride and polyvinyl-chloride induced cancer is seen in the lung, liver, brain, and lymphatic system. Mutagenicity studies in humans and microorganisms demonstrate clearly that vinyl-chloride is a potent mutagen. Recent studies of liver cancer patients who were occupationally exposed to vinyl-chloride are summarized. The incidences of lung cancer and other complications in humans are described; mortality from lung and

11

00003069

PAGE 31

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

breast cancer of workers exposed to vinyl-chloride and polyvinyl-chloride is examined. The synthetic chemicals industry employs thousands of workers and these workers are exposed on an average to 0.1 milligram vinyl-chloride or polyvinyl-chloride per cubic meter of air.

- 56 AU - Gori GB
 TI - Cancer Hazards, Risks And Thresholds: An Assessment
 SO - Cancer and the Environment, pages 219-234, 1983
 AB - Hazards due to cancer are discussed. The history of the experimental approach to understanding the process of cancer in animals and humans is presented. The complexity of factors that interplay in causing cancer is described. The well documented case of smoking tobacco and the ensuing lung cancer is outlined. The effects of natural and medical radiation, dietary habits, and excessive alcohol consumption are described. The limitations of an in-vitro testing for cancer is presented in light of the complexity of the disease. Facts on risk as the sum of baseline or background risk plus excess risk are outlined and discussed. Epidemiological studies have provided several notable examples of no observable effect thresholds and practical thresholds. Examples of these are described with arsene (7440382) and aflatoxin (55598806), cigarette smoking, and the presence of compounds in a work environment such as vinyl-chloride (75014) and beta-naphthylamine (91598). The anomalies of the so called generally recognized as safe list for providing sanctuary from government regulations are also described. Under no observable effect thresholds, the responsibilities and attitudes of humans living in the hazardous environment are outlined. The aspect of minimal risk and government regulation are discussed. The reality of life expectancy and its loss due to various causes is tabulated. The author concludes that safety and longevity are not precise limits in terms of carcinogenesis, but that thresholds are.
- 57 AU - Falk H
 TI - Vinyl Chloride And Polyvinyl Chloride
 SO - Environmental and Occupational Medicine, pages 579-588, 79 references, 1983
 AB - Medical and epidemiological findings involving vinyl-chloride (75014) (VC) and polyvinyl-chloride (9002862) (PVC) are reviewed. PVC is used in building and construction, home furnishings, recreational products, packaging, apparel, and transportation materials. Two very uncommon diseases, acroosteolysis and hepatic angiosarcoma, are linked to workers involved with PVC polymerization. In acroosteolysis, the main symptoms include Raynaud's phenomenon, osteolysis in the terminal phalanges, and thickening of the skin or raised nodules on the hands and forearm. Acroosteolysis occurs primarily in workers involved in the manual cleaning of reactors. Recent reports have identified some systemic changes in skin, bones, and the sacroiliac joint. Vascular changes in the digital arteries of the hand are also associated with acroosteolysis, including narrowing of the lumen

11

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

and partial or total occlusion. Hepatomegaly in VC workers is associated with abnormalities of liver function tests. The earliest findings in the precursor stage are areas of combined hyperplasia of hepatocytes and sinusoidal cells associated with an excess of reticulin and sinusoidal dilation. Exposure to PVC dust has resulted in deterioration of lung function, slight abnormalities of the chest radiograph, and complaints of slight dyspnea. Cytogenetic studies indicate increased frequencies of chromosomal aberrations of peripheral lymphocytes from VC exposed workers. High rates of congenital anomalies of the central nervous system have been reported in communities with PVC polymerization facilities. Other effects reported include hypertension changes and symptoms such as headaches and fatigue. Cases of hepatic angiosarcoma have been reported in individuals exposed to lesser concentrations of VC than PVC polymerization workers. Studies on animals have identified a multiplicity of tumors, in addition to hepatic angiosarcoma, following exposure to VC. OSHA requires that worker exposure to VC not exceed 1 part per million during an 8 hour time weighted average.

- 58 AU - Corn JK
TI - Vinyl Chloride, Setting A Workplace Standard: An Historical Perspective On Assessing Risk
SO - Journal of Public Health Policy, Vol. 5, pages 497-512, 38 references, 1984
AB - A historical perspective on assessing risk for vinyl-chloride (75014) (VC) and on setting its workplace standard is presented. Focus is placed on the intricate relationship between science and policy and the opposing interests that complicate regulatory decision making. Background material includes the production and principal uses of VC. The greatest potential for exposure occurs when VC is polymerized to form polyvinyl-chloride (9002862). The progress of OSHA in preventing diseases in the workplace and protecting workers is reviewed. In 1971, OSHA adopted national consensus standards and previously existing federal standards. The estimated concentrations for chemical substances included VC at 500 parts per million (ppm) part of air. Organized labor objected to the inability of the standards to protect workers. In 1974, a company manufacturing polyvinyl-chloride announced that three workers had died of angiosarcoma of the liver, a rare and incurable cancer. Subsequent policy decisions for the control of VC that were influenced by labor, industry, government, the press, public interest groups, and the scientific community are presented. On April 5, 1974, OSHA reduced the permissible exposure concentration from 500 to 50ppm as a temporary standard. On May 18, 1974, OSHA proposed a permanent standard of no detectable concentration. Hearing dates allowed 30 days for public comment. Employers, employees, labor unions, public affairs groups, physicians, and scientists testified and submitted information at the hearing. On October 4, 1974, OSHA promulgated the permanent standard for VC as 1ppm maximum exposure. The difficulties setting a VC standard as well as some related unanswered issues are discussed.

R&S 102717

00003071

PAGE 33

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

- 59 AU - Viola PL
TI - Vinyl And Polyvinyl Chloride
SO - Encyclopaedia of Occupational Health and Safety, Vol. 2, pages 2256-2260, 8 references, 1983
AB - Occupational health consequences from the production and use of vinyl-chloride (75014) and polyvinyl-chloride (9002862) are reviewed. Safety measures required in handling these compounds are discussed. Vinyl-chloride may be synthesized by hydrochlorination of acetylene (74862) or halogenation of ethylene (74851). Almost all of the vinyl-chloride-monomer (75014) produced is used in the synthesis of polyvinyl-chloride. Vinyl-chloride is flammable and explosive in air. It is easily absorbed through the respiratory system, the most common route for industrial poisoning. The center of the metabolic process is the liver through microsomal pathways. Acute exposure results in vertigo, impairment of hearing and vision, loss of consciousness at 70,000 parts per million, and death at higher concentrations. Long term exposure gives rise to vinyl-chloride disease, characterized by neurotoxic symptoms, Raynaud's syndrome, and skin, skeletal, and liver changes. After metabolic activation, vinyl-chloride has mutagenic effects in-vitro on bacteria, yeasts, and cultured mammalian cells. The most important feature of its pathogenic action is carcinogenicity exerted mainly in the liver. Vinyl-chloride may induce extremely rare tumors known as angiosarcomas. The mean period of incubation is about 20 years. Workers most often exposed to vinyl-chloride are those employed in polyvinyl-chloride production, particularly in maintenance. Operations must be designed to minimize exposure and to adhere strictly to threshold limit values. Personal protective equipment must be worn as prescribed. Transport and storage must be controlled. Polyvinyl-chloride is mainly used in producing resins. Polyvinyl-chloride dust is considered chemically inert but its combustion causes formation of very harmful substances such as hydrochloric-acid (7647010), phosgene (75445), and carbon-monoxide (630080). The author concludes that workers exposed to either vinyl-chloride or polyvinyl-chloride must receive adequate medical surveillance.
- 60 AU - Selikoff IJ
TI - Lessons For Living In A Chemical World
SO - Bulletin of Environmental Contamination and Toxicology, Vol. 33, No. 6, pages 682-695, 1 reference, 1984
AB - The experience of living in a chemically contaminated world is presented. The statistical picture of cancer incidence is traced over 28 years from 1950 to 1978, and the rates of specific cancers in different countries are described. The changes in the statistical rates of specific types of cancers in different geographic populations at different time periods are presented. Lung cancer produced by occupational exposure to such chemicals as nickel (7440020), acrylonitrile (107131), arsenic (7440392), asbestos (1332214), talc (14807966), radium (7440144), and hematite mining, and bladder cancer produced by mining, and

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

exposure to benzidine (92875), naphthylamine (134327), and aniline (62533) dye are described. The procedures used to establish these associations are reviewed. The importance of the latency period between exposure and appearance of cancers is illustrated by results from studies on large populations of smokers, and on asbestos and vinyl-chloride (75014) workers and their families. The problems associated with extrapolating from higher to lower dose and from animals to humans are presented and the disagreement on scientific interpretation, the significance of benign tumors, the importance of mutagenicity in in-vitro studies, and the significance of initiation, promotion, and enzyme induction during carcinogenesis are discussed.

R&S 102719

- 61 AU - Walles SAS ; Holmberg B
TI - Induction Of Single-Strand Breaks In DNA Of Mice After Inhalation Of Vinyl Chloride
SO - Cancer Letters, Vol. 25, No. 1, pages 13-18, 24 references, 1984
AB - Vinyl-chloride (75014) induced single strand breaks in DNA were investigated in mice. Female NMRI-mice were exposed 6 hours a day, 5 days a week, to 500 parts per million vinyl-chloride. Animals were killed 2 or 18 hours after exposure and cells from liver, kidney, lung, spleen, and brain were examined for single strand breaks. Mice killed 2 hours after an exposure of 117 hours showed increased single strand breaks in the lungs, liver, and kidney, but not in the brain. A plateau was reached for the kidney and lungs after 80 and 120 hours of exposure, respectively. The livers showed a slight increase of single strand breaks throughout the exposure period. The spleen showed a statistically significant increase in single strand breaks only at 234 hours. The number of single strand breaks after 234 hours of exposure was similar for kidney, lungs, and liver. Mice killed 18 hours after vinyl-chloride exposure showed normal single strand break values for kidneys, lung, and liver at 36 hours. After 114 and 231 hours of exposure the single strand break value for kidney, lung, and liver remained elevated, even 18 hours after exposure had ended. Brain single strand break values were increased for 18 hours after 114 hours of vinyl-chloride exposure. The single strand break values in brain at other exposure periods were inconsistent. The authors conclude that the lung is the most sensitive organ for vinyl-chloride carcinogenicity in mice.
- 62 AU - Suzuki Y
TI - Neoplastic Effect Of Vinyl Chloride In Mouse Lung Lower Doses And Short-Term Exposure
SO - Environmental Research, Vol. 32, No. 1, pages 91-103, 22 references, 1983
AB - The effect of vinyl-chloride (75014) on the lung was investigated in mice. A total of 220 CD1-mice were divided into groups and exposed to 600, 300, 100, 10, and 1 parts per million (ppm) vinyl-chloride vapor. They were then sacrificed either immediately, 12 weeks after exposure, or 40 weeks after exposure. The organs were subjected to histopathological or electron

microscopy procedures. In the 600 and 300ppm groups, alveologenic tumors developed after 12 weeks in 88.8 and 66.6 percent of the animals, respectively. Tumors did not appear at lower exposure concentrations. Multiple tumors occurred at 600ppm. After 41 weeks, pulmonary tumors were induced at all exposure concentrations. There was a clear dose response relationship for instances of alveologenic tumors and a latency period inversely related to dose. Tumors were not encapsulated by connective tissue, and the neoplastic cells were arranged in tubular, papillary, and adenomatous fashion. In rare cases, the tumors occupied the entire lobe of a lung. The neoplastic cells exhibited the ultrastructural characteristics of hyperplastic type 2 cells. The author concludes that alveologenic tumors are induced by vinyl-chloride and that type 2 alveolar cells are the progenitor cells of the tumors.

- 63 AU - Dolan BP ; Levine AM ; Dolan DC
 TI - Small Cleaved Follicular Center Cell Lymphoma: Seven Cases In California Plumbers
 SO - Journal of Occupational Medicine, Vol. 25, No. 8, pages 613-615, 12 references, 1983
 AB - Seven cases of small cleaved follicular center cell lymphoma among California plumbers (SIC-1711) were investigated. Cases were identified from a self administered questionnaire mailed directly to all California members on the rolls of the international plumbers and pipefitters union. Of these responses, only 10,200 or about 33 percent were complete enough to be analyzed. Of these, 66 stated they had had lymphatic cancer. A follow up identified eight cases of lymphoma, seven of which were small cleaved follicular center cell lymphoma. These cases were examined for similarities in history. Cases were aged from 37 to 68. Of the seven, six were union plumbers and one a non union plumber. Plumbers had worked at their trade from 12 years (the 37 year old) to 36 years. All of the men had fabricated plastic pipe for several years and four of the seven had had no other known toxic exposures. These plumbers had fabricated both acrylonitrile-butadiene-styrene (9003547) and polyvinyl-chloride (9002862) pipe. No common pattern of smoking, of drinking, or of asbestos or welding exposure was apparent. The authors conclude that the appearance of such a high incidence of histologically identical lymphomas in a cluster of workers with similar occupational exposure creates suspicion that a causal connection may exist. It is noted that the expected incidence of such lymphomas among 30,000 union plumbers would be approximately 1 case per year, yet 7 cases were found among 10,000 respondents. Further investigation of this connection is recommended.

11

00003074

PAGE 36

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

- 64 AU - Pepelko WE
 TI - Experimental Respiratory Carcinogenesis In Small Laboratory Animals
 SO - Environmental Research, Vol. 33, No. 1, pages 144-188, 167 references, 1984
 AB - Procedures for conducting experimental studies of respiratory carcinogenesis are reviewed. Advantages and disadvantages of mice, rats, or hamsters in studies of respiratory carcinogenesis are assessed. Mice have the advantage of small size and short life span; hamsters are resistant to pulmonary infection, have a low spontaneous lung tumor incidence, and develop tumors similar to those of humans; and rats are sensitive to induction of nasal cancer by organic chemicals. Oncogenic responses from inhalation of organic chemicals are tabulated. Chemicals studied include: acetaldehyde (75070), acrylonitrile (107131), acrolein (107028), benzo(a)pyrene (50328), benzene (71432), bis(chloromethyl)ether (542881), chloromethylmethylether (107302), diazomethane (334883), 1,2-dibromo-3-chloropropane (96128), dichloroethylene (25323302), dimethylcarbamoylchloride (79447), epichlorohydrin (106898), ethylene-dibromide (106934), furfural (98011), ethylene-oxide (75218), formaldehyde (50000), hexamethyl-phosphoramide (680319), methylcholanthrene (56495), urethane (51796), polyurethane (9009545), tetrachloroethylene (127184), trichloroethylene (79016), vinyl-bromide (593602), and vinyl-chloride (75014). Oncogenic responses from inhalation of metallic and nonmetallic compounds are presented. Induction of respiratory tract tumors by cigarette smoke inhalation, ambient air and smog, engine emissions, fossil fuel derived smoke and fumes, dusts and solid aerosols, and liquid aerosols is discussed. The author concludes that despite the limitations in the use of animal inhalation experiments to predict the likelihood of cancer induction in humans, there are no clear cut better alternatives at present. Long term inhalation studies are likely to continue with the aid of new strains that more closely resemble human tumor types, pharmacokinetic factors, and metabolic processes.
- 65 AU - Gwinner LM ; Laib RJ ; Filser JG ; Bolt HM
 TI - Evidence Of Chloroethylene Oxide Being The Reactive Metabolite Of Vinyl Chloride Towards DNA: Comparative Studies With 2,2'-Dichlorodiethylether
 SO - Carcinogenesis, Vol. 4, No. 11, pages 1483-1486, 28 references, 1983
 AB - The roles of chloroethylene-oxide (7763771) (CEO) and chloroacetaldehyde (107200) (CAA) in the carcinogenicity of vinyl-chloride (75014) (VC) were studied in rats. Wistar-rats were exposed by inhalation for 24 hours to carbon-14 labeled VC or 2,2'-dichlorodiethylether (111444) (DDE) for an uptake per animal of 0.18 to 0.25 milliCuries. Binding of metabolites to tissue proteins and RNA and DNA alkylation were determined. Other groups of newborn rats were exposed to doses of VC, DDE, or chloroethanol (107073) (CE) that generated comparable quantities

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

of CAA for 3 weeks and liver sections were analyzed for adenosine-triphosphatase (ATPase) deficient foci. Exposure to both DDE and VC caused binding of considerable portions of the derived radioactivity to liver proteins and small amounts of irreversibly bound metabolites in kidney, small intestine, lung, and spleen. High pressure liquid chromatography analysis of hydrolysates of rat liver DNA and RNA isolated after exposure to VC revealed a radioactive peak representing 7-N-(2-oxoethyl)guanine. DNA and RNA examined after exposure to DDE did not indicate the formation of 7-N-(2-oxoethyl)guanine or any of the other known alkylation products of VC. VC caused a large number of preneoplastic ATPase deficient foci in young rats, but DDE and CE did not. The authors conclude that the carcinogenicity of VC is due to CED and not CAA.

- 66 AU - Fawcett FJ ; Easterbrook P ; Smerdon GR
 TI - Angiosarcoma Of Liver And Spleen In A Scrap Metal Merchant
 SO - British Journal of Industrial Medicine, Vol. 40, No. 1, pages 113-114, 5 references, 1983
 AB - The case of a scrap metal merchant who died of an angiosarcoma was investigated. A 56 year old self employed scrap metal merchant collapsed and died 9 days after presenting with a 2 week history of lethargy, weight loss, indigestion, and abdominal pain. He had a history of indigestion and abdominal pain. Postmortem examination showed that death was due to a massive intraperitoneal hemorrhage from a multinodular hemorrhagic tumor of the liver. The spleen was greatly enlarged and had a firm, white, and fleshy cut surface. Histological examination of the tumor in the liver and spleen showed the appearances of an angiosarcoma. The subject had been a scrap metal merchant all of his working life and had been recovering copper (7440508) from plastic coated cable and a small amount of rubber coated cable for 15 years. This entailed burning about 500 kilograms of the cable at weekly to monthly intervals. To separate the copper from the plastic it was necessary to rake the burning cable constantly for 2 to 3 hours. The authors conclude that there was probably exposure to several carcinogens including vinyl-chloride (75014), copper, and arsenic (7440382), with alcohol acting as a possible cocarcinogen. It seems advisable for workers burning off scrap to use suitable protective measures until the carcinogenic effect of this practice is better established.
- 67 AU - Drew RT ; Boorman GA ; Haseman JK ; McConnell EE ; Busey WM
 AU - Moore JA
 TI - The Effect Of Age And Exposure Duration On Cancer Induction By A Known Carcinogen In Rats, Mice, And Hamsters
 SO - Toxicology and Applied Pharmacology, Vol. 68, No. 1, pages 120-130, 14 references, 1983
 AB - The effects of age and exposure duration on cancer induction by vinyl-chloride (75014) (VC) were compared in female golden-Syrian-hamsters, F-344-rats, Swiss-CD-1-mice, and B6C3F1-mice. Some animals were exposed to 50 parts per million (ppm) (mice), 100ppm (rats), or 200ppm (hamsters) VC, 6

R&S 102722

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

hours/day, 5 days/week for 6, 12, 18, or 24 months. Other animals were maintained for 6 or 12 months and then exposed for 6 or 12 months. Neoplasm incidence was compared among groups. In rats, 6 month exposures induced hemangiosarcomas only when begun early in life. Mammary gland adenocarcinomas were seen after 12 months of VC exposure if exposures began before 8 months of age. The incidence of fibroadenomas was higher when young rats were exposed. Hepatocellular carcinomas were induced in rats in a dose related manner when exposure began early in life. VC exposed hamsters developed hemangiosarcomas, mammary gland carcinomas, stomach adenomas, and skin carcinomas. The highest incidence of hemangiosarcomas and stomach adenomas was seen in animals exposed early in life for only 6 months; further exposures did not increase the incidence of these tumors. VC exposure induced hemangiosarcomas and mammary gland carcinomas in both strains of mice and lung carcinomas in Swiss-mice only. In B6C3F1-mice, exposures of 6 months or more induced 60 to 70 percent hemangiosarcomas, regardless of the animals age. Exposures beginning after 1 year of age produced mammary gland carcinomas in these mice, but at lower incidences than when started early in life. In Swiss-mice, exposure beyond 6 months did not increase neoplasm incidence. Delaying exposure for 6 or 12 months decreased incidence of all tumor types. The authors conclude that animals exposed early in life are more susceptible to the carcinogenic effects of VC. Mice and hamsters develop VC induced neoplasms after 6 months of exposure; in rats, 1 year of exposure is sufficient.

- 68 AU - Wagoner JK
TI - Toxicity Of Vinyl Chloride And Poly(Vinyl Chloride): A Critical Review
SO - Environmental Health Perspectives, Vol. 52, pages 61-66, 41 references, 1983
AB - The toxicity of vinyl-chloride (75014) (VC) and polyvinylchloride (9002862) (PVC) is reviewed. Adenomas and adenocarcinomas of the lung, angiosarcomas of the liver and other sites, lymphomas, mammary carcinomas, neuroblastomas of the brain, and other tumors have been induced in mice, rats, and hamsters exposed by inhalation to VC. Studies have shown an increased risk of liver angiosarcoma and cancers of other sites among employees of VC polymerization facilities. Indirect modes of exposure to VC have been shown to be associated with an excess risk of cancer. Liver angiosarcoma has been reported in individuals living less than 2 miles from facilities polymerizing VC or fabricating PVC. Experimental bioassay and epidemiological studies have shown high agreement for carcinogenicity of VC, specifically for liver angiosarcoma. The excess of liver angiosarcoma has been shown to persist from polymerization of VC to residences near such facilities. Experimental and epidemiological data indicate that PVC dust is probably associated with both neoplastic and non neoplastic respiratory effects.

R&S 102723

00003077

PAGE 39

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

- 69 AU - Fedotova IV
 TI - The Incidence Of Malignant Tumors Among Workers Engaged In The Manufacture Of Vinyl Chloride And Polyvinyl Chloride
 SO - Gigiena Truda i Professional'nye Zabolevaniya, No. 4, pages 30-32, 10 references, 1983
 AB - An epidemiological survey of the incidence of cancer among Soviet vinyl-chloride (75014) (VC) and polyvinyl-chloride (9002862) (PVC) workers was conducted. The cohort consisted of 3232 workers. The cohort was divided into three groups: individuals working in older factories in which VC exposures of several thousand milligrams per cubic meter (mg/m³) were estimated to have occurred, workers employed in a modern PVC facility in which the VC concentrations ranged from 30 to 300mg/m³, and workers engaged in production of VC monomer in which the average VC concentration was 6 to 8mg/m³. Personnel, municipal oncological dispensary, and medical records, and civil registry archives were reviewed. Incidence rates were calculated and compared with those of the city or region in which the factory was located. There was an increased incidence of lung cancer among males and gastric carcinomas among females compared with the population at large. Both males and females had increased incidences of malignant tumors of the lymphatic and hemopoietic tissues. The highest incidence of cancers occurred among the workers in the older factories who were exposed to very high VC concentrations. The author concludes that VC has a definite effect on the incidence of malignant tumors. (Russian)
- 70 AU - Suzuki Y
 TI - Neoplastic Effect Of Vinyl Chloride In Mouse Lung Lower Doses And Short-Term Exposure
 SO - Environmental Research, Vol. 32, No. 1, pages 91-103, 22 references, 1983
 AB - The neoplastic effects of low doses of vinyl-chloride (75014) (VC) were investigated in mice. Male Charles-River-CD1-mice were exposed to 0, 1, 10, 100, 300, or 600 parts per million (ppm) VC, 6 hours per day, 5 days per week, for 4 weeks. Animals were killed immediately, 12 weeks, or 40 weeks after exposure. Animals were systematically autopsied and lungs and other organs were examined with light and electron microscopes. Pulmonary tumors were induced in a dose dependent manner. The first tumor was found in a mouse receiving 600ppm; the mouse died 10 weeks after exposure. At sacrifice, 12 weeks after exposure, 88.8 percent of the 600ppm group and 66.6 percent of the 300ppm group had alveologenic tumors. At the third sacrifice, pulmonary tumors were induced in all groups with the following incidence of tumor production: 600ppm, 85.7 percent; 300ppm, 71.4 percent; 100ppm, 66.7 percent; 10ppm, 33.3 percent; and 1ppm, 11.1 percent. Multiple tumor incidence was 100 percent in the 600ppm group, 60 percent in the 300ppm group, and 50 percent in the 100ppm group. Histological aspects of the tumors were similar to those induced by heavy doses of VC with long exposure. No metastases were observed. Tumors were generally seen in the

00003078

PAGE 40

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

peripheral part of the lung; they were not encapsulated by connective tissue. Neoplastic cells were arranged in tubular, papillary, and adenomatous shapes. Electron microscopically, the neoplastic cells possessed all or some of the ultrastructural characteristics of type 2 cells: microvilli; large round or rod shaped mitochondria; osmiophilic lamellar bodies; junctional structures; multivesicular bodies; and a basement membrane. Intracytoplasmic compartments formed by a membrane structure and glycogen granules were also frequently observed. Hypercellularity of the alveolar lining cells was seen around the induced tumors. The author concludes that the size of the VC induced tumor is related to the dose and recovery time. Latency and incidence are also dose related. Type 2 alveolar cells are the cell type most sensitive to the oncogenicity of VC.

- 71 AU - Spirtas R ; Beebe G ; Baxter P ; Dacey E ; Faber M ; Falk H
 AU - van Kaick G ; Stafford J
 TI - Angiosarcoma As A Model For Comparative Carcinogenesis
 SO - Lancet, page 456, 12 references, 1983
 AB - The latency periods for formation of angiosarcoma of the liver due to exposures to vinyl-chloride-monomer (75014) (VCM) and thorium-dioxide (1314201) were compared. Data on thorium related liver angiosarcomas was obtained from reports issued in West Germany, the United Kingdom, Denmark, and the United States. Incidences of VCM related disease were determined from reports in 12 different countries. Exposures to thorium-dioxide occurred primarily between 1928 and 1955, while exposures to VCM were heaviest in the 1940 through 1960 period. The nature of the exposures was also different: thorium-dioxide exposures were continuous from the time of initial injection, while VCM exposures were intermittent. The median latency periods for angiosarcoma of the liver were 22 years for VCM and 29 years for thorium-dioxide. The authors conclude that the latency period for angiosarcoma of the liver is significantly shorter for VCM exposures compared with thorium-dioxide exposures. This difference appears to reflect differences in the mechanisms of chemical and radiation carcinogenesis, rather than differences in the populations. Cohort analyses of VCM and thorium-dioxide exposed populations are suggested to further clarify differences in the carcinogenic actions of the agents.
- 72 AU - Storetvedt Helldas S ; Langard SL ; Andersen A
 TI - Incidence of cancer among vinyl chloride and polyvinyl chloride workers
 SO - British Journal of Industrial Medicine Feb. 1984, Vol.41, No.1, p.25-30. 21 ref.
 AB - Follow-up study of the incidence of cancer and mortality among 454 workers exposed to vinyl chloride (VC) and polyvinyl chloride in a Norwegian factory between 1950 and 1969. The incidence of lung cancer (5, expected: 2.8) and of malignant melanoma of the skin (4, exp.:0.8) were, despite the low numbers involved, significantly higher than expected, especially for workers with a history of high levels of exposure to VC. Angiosarcoma of the

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

liver, implicated in other studies, occurred in 1 case. It is suggested that VC may act as a multicarcinogen.

LA - Eng

- 73 AU - Radike MJ ; Stemmer KL ; Bingham E
TI - Effect of ethanol on vinyl chloride carcinogenesis.
SO - Environ Health Perspect; VOL 41, 1981, P59-62
AB - Four treatment groups (80 male Sprague-Dawley rats/group) were used in a 2 X 2 factorial design: inhalation of 600 ppm vinyl chloride (VC) 4 hr/day, 5 days/week for 1 year; VC and ingestion of 5% ethanol in water (v/v); filtered air and ethanol; filtered air. Ingestion of ethanol was begun 4 weeks prior to inhalation of VC and continued for life or termination of the study at two and one-half years from the first VC exposure. In this model system, ethanol potentiated the carcinogenic response to VC in the liver and produced an excess of neoplasms in animals receiving ethanol alone. Inhalation of VC induced angiosarcoma of the liver in 23% of the exposed animals; ethanol in addition to VC inhalation increased the incidence to 50%. Concomitant administration of VC and ethanol also produced an excess of hepatocellular carcinoma and lymphosarcoma. Ethanol with or without VC had a strong tumorigenic effect on the endocrine system. These results indicate that ethanol is a cocarcinogen in relation to the carcinogen VC.

LA - Eng

- 74 AU - Suzuki Y
TI - Electron microscopic observations of hepatic and subcutaneous hemangiosarcomas induced in mice exposed to vinyl chloride monomer.
SO - Am J Ind Med; VOL 2, ISS 2, 1981, P103-17
AB - Both subcutaneous and hepatic hemangiosarcomas were induced in mice exposed to vinyl chloride monomer, and for the first time, the ultrastructure of hemangiosarcomas related to vinyl chloride exposure has been described. The subcutaneous hemangiosarcoma developed in a mouse's ear 29 weeks after exposure to 10 ppm vinyl chloride for 4 weeks, and the hepatic hemangiosarcoma was found in a mouse's liver at necropsy 56 weeks after exposure to 600 ppm vinyl chloride for 4 weeks. Both tumors showed a localized, cystic nodular appearance with a dark red tone. Histologically, an angiomatous architecture, the presence of neoplastic mesenchymal cell aggregates, focal necrosis, and hemorrhagic foci were common. Ultrastructurally, two neoplastic cell types, a mesenchymal and a well-differentiated endothelial cell type, were identified in both tumors. In addition, in the hepatic tumor, a pericyte-like neoplastic cell was also present. The incidence of hemangiosarcoma was much lower than that of lung tumors (alveologenic tumor) in mice exposed to vinyl chloride at the same concentrations for the same duration. This study suggests that there is no basic difference in ultrastructure between the vinyl chloride-induced hemangiosarcomas and hemangiosarcomas not related to this chemical exposure.

LA - Eng

R&S 102726

- 75 AU - Popper H ; Maltoni C ; Selikoff IJ
 TI - Vinyl chloride-induced hepatic lesions in man and rodents. A comparison.
 SO - Liver; VOL 1, ISS 1, 1981, P7-20
 AB - Histologic sequences in the liver of rodents exposed by inhalation to gaseous vinyl chloride were compared to the lesions in man exposed to the same agent, mainly in vinyl chloride polymerization plants. An identical sequence, starting with circumscribed proliferation of hepatocytes, soon followed by proliferation of a variety of sinusoidal cells and frequently associated with sinusoidal dilatation, progresses to intralobular and more frequently to trabecular angiosarcoma. Predominantly in young animals and rarely in man, hepatocellular carcinoma develops, but never cirrhosis. The sequence represents a dynamic process of competition between proliferating hepatocytes and sinusoidal cells, of hepatocytes with fibroplasia, between perisinusoidal fibrosis and sinusoidal dilatation, and of proliferation of various sinusoidal cells versus angiosarcoma. The great similarity in the evolution in man and rodents, rarely encountered in other experimental models, supports the prediction of human cancer from animal experiments. The precursor nodules differ from the nodules commonly observed in hepatocarcinogenesis by co-proliferation of sinusoidal cells. The differences in the reactions between man and rodents bespeak a strong fibroblastic reactivity in man. Most important, the precursor lesion of mixed hepatocellular and sinusoidal cell proliferation may be of diagnostic value, being superior to conventional hepatic tests in detection of some initial environmental lesions.
 LA - Eng
- 76 AU - Infante PF
 TI - Observations of the site-specific carcinogenicity of vinyl chloride to humans.
 SO - Environ Health Perspect; VOL 41, 1981, P89-94
 AB - A review of epidemiologic studies of workers exposed to vinyl chloride (VC) was conducted. Some of these studies comprised small cohorts and thus were insensitive in the evaluation of carcinogenic response for sites that do not demonstrate a high relative risk. Other larger studies used methodology and design that precluded an interpretation of the results. Such limitations were acknowledged by some authors. Use of restrictive disease rubrics also lead to the submerging of sites that would have demonstrated significant excesses. For example, some investigators analyzed data for liver cancer deaths with the broad category of digestive system cancer deaths, while others combined data for CNS cancer deaths with the broad category of "other and unspecified cancer," and most studies analyzed information for lymphatic and hematopoietic system cancer deaths with all data combined. Only four of eight studies reviewed could demonstrate a significant excess of liver cancer among VC-exposed workers--a site confirmed in humans by 1974. In contrast, five of eight studies appear to demonstrate a significant excess of CNS

11

00003081

PAGE 43

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

cancer mortality. Workers exposed to VC also demonstrate a significant excess of mortality for lung cancer, while the data for lymphatic and hematopoietic system cancer are suggestive. Interpretation of cancer of the latter systems may have been clarified if investigators had not analyzed their data by broad disease classifications.

LA - Eng

- 77 AU - Groth DH ; Coate WB ; Ulland BM ; Hornung RW
 TI - Effects of aging on the induction of angiosarcoma.
 SO - Environ Health Perspect; VOL 41, 1981, P53-7
 AB - Adult, Sprague-Dawley albino rats of four different ages (6, 18, 32 and 52 weeks) were exposed to 940 ppm vinyl chloride by inhalation for 24 weeks, 5 days/week, 7 hr/day. In each age group, there were 110 to 128 males and the same number of females. The similarly housed control group, which was not exposed to vinyl chloride, consisted of the same number of males and females in each age group. All animals that died spontaneously, or were sacrificed moribund, or were killed at scheduled times (3, 6 and 9 months after initial exposure) were autopsied. All organs were examined grossly, and several tissues from each animal were examined microscopically. The older the rats were when they were first exposed, the greater the incidence of angiosarcomas. The incidences of angiosarcomas in the four age groups (from youngest to oldest) in the exposed males in the nonscheduled sacrifice groups were: 0/37 (0%); 0/44 (0%); 3/45 (6.7%); and 13/55 (24%). Similarly, for the females, these incidences were: 2/38 (5.3%); 7/47 (15%); 23/49 (47%); and 11/54 (20%). Most of the angiosarcomas were highly anaplastic, primary tumors in the livers that metastasized to the lungs. Only one angiosarcoma was seen in all the control rats; that occurred in subcutaneous tissue. This study demonstrated that older adult animals and females are more susceptible to the angiosarcoma-inducing effects of vinyl chloride than young adult animals and males, respectively.

LA - Eng

- 78 AU - Vianna NJ ; Brady J ; Harper P
 TI - Angiosarcoma of the liver: a signal lesion of vinyl chloride exposure.
 SO - Environ Health Perspect; VOL 41, 1981, P207-10
 AB - Vinyl chloride (VCM) induced angiosarcoma of the liver (ASL) is a rare vascular tumor which might be associated with a wide range of disease states. The possibility that this tumor might be a signal lesion is supported by mortality studies suggesting that cancers of the digestive, respiratory, neurological and lymphatic systems have occurred more often than expected in VCM workers. There is also evidence that certain non-neoplastic disorders, such as pneumoconiosis and excess fetal deaths, may be associated with this chemical. It has been suggested that a gradual increase in the incidence of ASL might have occurred in recent years. This could be a reflection of the long latency period and/or the increased recognition of this entity. Several cases of ASL have

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

occurred in people living in the vicinity of VCM plants. This raises the possibility that low-level exposure to this chemical over a long period might induce ASL.

LA - Eng

79 AU - Cooper WC

TI - Epidemiologic study of vinyl chloride workers: mortality through December 31, 1972.

SO - Environ Health Perspect; VOL 41, 1981, P101-6

AB - A population of 10,173 men, employed in 37 plants, was identified as having worked for at least one year in jobs involving probable exposure to vinyl chloride monomer (VCM) prior to January 1, 1973. Of the 9677 men whose vital status was determined, 707 were known to have died. For 699, death certificates were obtained. The standardized mortality ratio (SMR) for all causes was 89, that for all malignancies was 104. The only type of malignancy found in significant excess was in the category of malignant neoplasms of the brain and other parts of the nervous system; 12 deaths occurred where 5.9 were expected, for an adjusted SMR of 203. There were slight but inconclusive upward trends in all malignancies, and for malignancies of the respiratory tract, digestive tract, and central nervous system associated with reported levels of maximum exposure to VCM. When groups in whom less than 20 years had elapsed from the first exposure were compared with those with 20 or more elapsed years, and 25 or more elapsed years, no significantly different SMR's were detected for major primary sites of malignancy. Plans for an updated study of mortality, to include deaths in the period 1973-1979 are briefly discussed.

LA - Eng

80 AU - Thung SN ; Gerber MA

TI - Precursor stage of hepatocellular neoplasms following long exposure to orally administered contraceptives.

SO - Hum Pathol; VOL 12, ISS 5, 1981, P472-4

AB - Hepatic neoplasms and peliosis are known to occur in women taking contraceptives orally. We observed hyperplasia of hepatocytes combined with hypertrophy of sinusoidal lining cells and sinusoidal dilatation with progression to peliosis in the liver of a patient who had been taking such contraceptives for 10 years. These changes resembled the precursor stage in the development of hepatic angiosarcoma induced by vinyl chloride, Thorotrast, and arsenic. In users of orally administered contraceptives these findings may precede the development of hepatocellular neoplasms.

LA - Eng

R&S 102729

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

- 81 AU - Greenberg RA ; Tamburro CH
TI - Exposure indices for epidemiological surveillance of carcinogenic agents in an industrial chemical environment.
SO - J Occup Med; VOL 23, ISS 5, 1981, P353-8
AB - A prospective system for establishing chemical exposure indices was developed and implemented for 22 chemicals used at a Louisville chemical plant. Validation of the indices was done statistically using industry-related cancer (liver angiosarcoma) and worker-matched controls. A rank ordered system for exposures was used to identify a relationship between the occurrence of disease and the presence of a suspect chemical used in the industrial environment.
LA - Eng
- 82 AU - Fortwengler HP Jr ; Jones D ; Espinosa E ; Tamburro CH
TI - Evidence for endothelial cell origin of vinyl chloride-induced hepatic angiosarcoma.
SO - Gastroenterology; VOL 80, ISS 6, 1981, P1415-9
AB - Previous reports of hepatic angiosarcoma have not clearly defined the cellular type from which this tumor arises, as evidenced by the terminology of endothelioma, Kupffer cell sarcoma, endothelial cell sarcoma, and hemangioendothelial sarcoma, etc., which have been used interchangeably. In addition, there has been no consensus on the separate entity of Kupffer and sinusoidal endothelial cells. In the work presented here, evidence for the endothelial cell origin of this tumor is provided by the demonstration of factor VIII, a known endothelial cell marker, in the tumor cells. Fluorescence due to the presence of factor VIII appeared intense in the tumor sinusoidal cells of all four vinyl chloride-associated angiosarcomas studied, whereas normal liver sinusoidal lining cells showed negligible fluorescence.
LA - Eng
- 83 AU - Koischwitz D ; Leibach WK ; Lackner K ; Hermanutz D
TI - [Vinyl chloride-induced angiosarcoma and hepato-cellular carcinoma of the liver (author's transl)]
SO - ROFO; VOL 134, ISS 3, 1981, P283-90
AB - Three patients with industrial exposure to PVC are described, who developed angio-sarcomas of the liver; in one patient this was combined with a multi-lobular primary hepato-cellular carcinoma. The epidemiology, clinical features and diagnosis are discussed, with particular reference to angiography, sonography and computerized tomography. The non-invasive methods, such as computerized tomography and sonography, are the techniques of choice if an angiosarcoma is suspected after long exposure to PVC.
LA - Ger

00003084

PAGE 46

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

-
- 84 AU - Dannaher CL ; Tamburro CH ; Yam LT
 TI - Occupational carcinogenesis: the Louisville experience with vinyl chloride-associated hepatic angiosarcoma.
 SO - Am J Med; VOL 70, ISS 2, 1981, P279-87
 AB - Hepatic angiosarcoma in man was first associated with exposure to vinyl chloride in Louisville, Kentucky, where it was identified in 10 persons from a single vinyl chloride polymerization plant; clinical manifestations are summarized herein. Following prolonged exposure to vinyl chloride, the onset of this disease is insidious and the clinical picture is that of nonspecific hepatic injury with mildly abnormal biochemical liver test results. Carcinoembryonic antigen and alpha fetoprotein are undetectable. Radionuclide and angiographic studies of liver show characteristic but nondiagnostic abnormalities. A definite diagnosis is usually made only by open liver biopsy. Treatment is unsatisfactory but chemotherapy seems to prolong survival. Average survival from diagnosis is about 12 months. Overt liver failure usually occurs only as a preterminal event and was the major cause of death in all of our patients. Preventive measures are now in effect in the plant. This experience illustrates the importance of the clinician in occupationally-related cancer.
 LA - Eng
- 85 AU - Wagoner JK ; Infante PF ; Apfeldorf RB
 TI - Toxicity of vinyl chloride and polyvinyl chloride as seen through epidemiologic observations.
 SO - J Toxicol Environ Health; VOL 6, ISS 5-6, 1980, P1101-7
 AB - In 1974, vinyl chloride (VC) was first reported in the scientific literature to induce angiosarcoma of the liver in animals and humans. Further research has now demonstrated the carcinogenicity of this agent to other organs. Target organs for VC now include the liver, brain, and lung, and probably the lymphohematopoietic system. The carcinogenic risk has been extended to jobs associated with polyvinyl chloride (PVC) exposure. This is evidenced by cases of liver angiosarcoma reported among individuals employed in or residing near PVC fabrication facilities and by epidemiologic study demonstrating a significant association between lung cancer and exposure to PVC dust. An association between PVC dust and pneumoconiosis has been demonstrated. On the basis of these findings, experimental bioassays and epidemiologic studies of the carcinogenicity of PVC are clearly in order. Prudent control of PVC in the industrial setting is also clearly indicated.
 LA - Eng

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

- 86 AU - Smith AH ; Waxweiler RJ ; Tyroler HA
TI - Epidemiologic investigation of occupational carcinogenesis using a serially additive expected dose model.
SO - Am J Epidemiol; VOL 112, ISS 6, 1980, P787-97
AB - The epidemiologic identification of occupational carcinogens is complicated by several problems including worker mobility between jobs, variation over time of chemicals and processes used, and the long latency period between exposure and discovery of a tumor. In the light of these problems, a method using the cumulative dose concept has been developed which involves calculating the expected yearly exposure for each case from work histories of all noncases close to the case in year of birth and year of hire. The data required for use of the method include information concerning exposure to the chemicals being studied for each job in each calendar year of the study. Use of the method is illustrated with a study of angiosarcoma of the liver and vinyl chloride exposure in a polymerization plant. The value of the method lies in the wealth of information generated concerning the association between chemical exposures and cancer, including exposure level relationships, latency information, and the possibility that two chemicals might be acting independently or jointly. The serially additive expected dose model is likely to prove particularly useful in the analysis of data collected by occupational health surveillance systems, as well as retrospective studies of the type illustrated.
LA - Eng
- 87 AU - Baxter PJ ; Anthony PP ; Macsween RN ; Scheuer PJ
TI - Angiosarcoma of the liver: annual occurrence and aetiology in Great Britain.
SO - Br J Ind Med; VOL 37, ISS 3, 1980, P213-21
AB - The annual occurrence of angiosarcoma of the liver (ASL) in Britain from 1963 to 1977 was studied, including clinical and occupational details for those cases agreed as ASL by a panel of histopathologists. Thirty-five cases (28 men, six women, and one infant girl) were agreed as ASL. The increase in the incidence of ASL observed in recent years was attributable to Thorotrast (thorium dioxide) usage (eight cases) and exposure to vinyl chloride (two cases) in the past. In its clinical presentation and prognosis ASL resembled primary liver carcinoma, except that extrahepatic metastases were found in only eight (23%) cases, and haemoperitoneum was more common in those cases due to Thorotrast. The results suggested a possible increased risk of ASL in the electrical and plastics fabrication industries, but information on exposure was inadequate to implicate specific chemicals. The clinical features of one case were indicative of arsenical intoxication, but medications in the other patients did not appear to be of aetiological importance.
LA - Eng

R&S 102732

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

- 88 AU - Taba AH
TI - Problems of occupational carcinogenesis in developing countries.
SO - Cancer Detect Prev; VOL 4, ISS 1-4, 1981, P25-30
AB - An overview of published information on occupational cancer and recorded ongoing occupational cancer research in developing countries is presented. The main cancers reported, of possible occupational origin, are skin carcinoma, leukemia due to exposure to benzene, asbestos-caused mesothelioma, vinyl chloride-induced hepatic angiosarcoma, carcinoma of bilharzial urinary bladder, stomach cancer reportedly associated with nitrogen fertilizers, lung cancer of nickel smelters, and nasopharyngeal and pulmonary carcinoma in workers exposed to the dust of hard wood. The difficulties of developing efficient occupational cancer prevention are discussed. Some options are analyzed regarding legislative, technological, environmental, medical, administrative, and educational cancer control applicable under conditions of developing countries.
LA - Eng
- 89 AU - Emmerich KH ; Norpoth K
TI - Malignant tumors after chronic exposure to vinyl chloride.
SO - J Cancer Res Clin Oncol; VOL 102, ISS 1, 1981, P1-11
AB - Correlations between exposure to vinyl chloride and the development of malignant tumors in the liver have been known since 1974 and have been confirmed by many an experimental investigation. Based on the evaluation of mortality statistics from nine different countries an increased incidence of malignant tumors of the lung, the gastrointestinal tract, and the central nervous system (CNS), and of malignant lymphomas is documented in connection with exposure to vinyl chloride. Statistically significant increases, however, are only found in the incidence of malignant liver tumors. Metabolism and toxicology of vinyl chloride are discussed in detail.
LA - Eng
- 90 AU - Maltoni C ; Lodi P
TI - Results of sputum, cytology among workers exposed to vinyl chloride monomer and to poly(vinyl chloride).
SO - Environ Health Perspect; VOL 41, 1981, P85-8
AB - The results of systematic cytological sputum examinations of 3,380 Italian VC-PVC industry workers and of 2,287 workers in other industries at different potential risk and chosen as control groups are reported. The results indicate an increase in cellular abnormalities and dysplasias in the epithelium of the respiratory tract among VC-PVC workers. These data are in line with experimental results showing that VC produces lung tumors in mice and with early epidemiological evidence among exposed workers.
LA - Eng

R&S 102733

00003087

PAGE 49

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

-
- 91 AU - Lillis R
 TI - Review of pulmonary effects of poly(vinyl chloride) and vinyl chloride exposure.
 SO - Environ Health Perspect; VOL 41, 1981, P167-9
 AB - The contributions of several recent reports to the definition of pulmonary effects of PVC dust inhalation are reviewed. Granulomatous reaction, with inclusion of PVC particles in macrophages and histocytes, and associated interstitial pulmonary fibrosis have been found to lead to exertional dyspnoea, diffuse micronodular chest radiographic opacities and restrictive pulmonary dysfunction. The effects of vinyl chloride (VC) monomer (gas) on proteins and the immunologic mechanisms triggered by the altered protein are possible mechanisms for the development in some cases of interstitial pulmonary fibrosis secondary to VC exposure. Vinyl chloride, a confirmed carcinogen, has been associated with, among other malignant tumors, a significant increase in the incidence of lung cancer. The magnitude of this effect has not yet been completely evaluated.
 LA - Eng
- 92 AU - Waxweiler RJ ; Smith AH ; Falk H ; Tyroler HA
 TI - Excess lung cancer risk in a synthetic chemicals plant.
 SO - Environ Health Perspect; VOL 41, 1981, P159-65
 AB - A standardized mortality ratio of 1.49 for respiratory system cancer (42 observed deaths versus 28.2 expected, p less than 0.01) was observed among a cohort of 4806 males employed at a synthetic chemicals plant since its startup in 1942. Upon review of pathologic material, the excess was found to be limited to adenocarcinoma and large cell undifferentiated lung cancer. Many of the workers had been exposed to vinyl chloride, as well as to chlorinated solvents, poly(vinyl chloride) (PVC) dust, acrylates and acrylonitrile. To evaluate the association between lung cancer and occupational chemical exposures, detailed work histories for each cohort member were combined with exposure ratings for each of 19 chemicals for each job for each calendar year since 1942. A serially additive expected dose model was then constructed which compared the doses of the chemicals observed for the lung cancer cases to the doses expected based on subcohorts without lung cancer individually matched to the cases. PVC dust appeared to be the most likely etiologic agent ($p = 0.037$). Time trends of PVC dust exposure indicated a potential latent period of 5-16 years before death.
 LA - Eng
- 93 AU - Beaumont JJ ; Breslow NE
 TI - Power considerations in epidemiologic studies of vinyl chloride workers.
 SO - Am J Epidemiol; VOL 114, ISS 5, 1981, P725-34 (REF: 16)
 AB - Nine retrospective mortality studies of workers exposed to vinyl chloride were reviewed to determine whether differences in their hypothesis testing results might be due to differences in statistical power. Where possible, the power of each study was

00003088

PAGE 50

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

calculated for cancer of the lung, brain and liver. When power was taken into consideration, the results for liver and brain cancer were found to be consistent with an etiologic role for vinyl chloride. For lung cancer, the data were not consistent with an etiologic role in that two studies with very high power yielded negative results.

LA - Eng

94 AU - Theriault G ; Allard P

TI - Cancer mortality of a group of Canadian workers exposed to vinyl chloride monomer.

SO - J Occup Med; VOL 23, ISS 10, 1981, P671-6

AB - The present study was undertaken to find out whether there was an excess of cancer mortality from causes other than angiosarcoma of the liver among a group of workers heavily exposed to vinyl chloride monomer (VCM). The mortality of 451 workers exposed to VCM for more than five years was compared with that of 870 workers from the same company who had not been exposed to VCM. The relative risk for digestive cancer was significantly higher than 1 (6.25, confidence interval 2.69 to 14.52) in the exposed group. The standardized mortality ratio (SMR) for digestive cancer was also higher (SMR 259.26 p less than 0.01) than that of the general population. No other cancer was in excess. Since the exposed workers are known to have had a cigarette smoking experience similar to that of those who were not exposed, it is concluded that the association between lung cancer and VCM exposure, if present, is indeed rather small.

LA - Eng

95 AU - Pialat J ; Pasquier B ; Pahn M ; Kopp N

TI - (Hepatic lesions caused by vinyl chloride monomer in humans. Study of eight clinicopathological cases (author's transl))

SO - Sem Hop Paris; VOL 56, ISS 25-28, 1980, P1188-202

AB - Six hepatic angiosarcomas, one hepatoma and one hepatic "fibrosis" with portal hypertension in patients chronically exposed to vinyl chloride monomer (VCM) are reported. The industrial methods of synthesis and current knowledge concerning the carcinogenic role of VCM are reviewed. Histogenetic and pathogenetic concepts of "fibrosis" and angiosarcomas of liver are exposed.

LA - Fre

96 AU - Cordasco EM ; Demeter SL ; Kerkay J ; Van Ordstrand HS ; Lucas EV

AU - Chen T ; Golish JA

TI - Pulmonary manifestations of vinyl and polyvinyl chloride (interstitial lung disease). Newer aspects.

SO - Chest; VOL 78, ISS 6, 1980, P828-34

AB - Newer varieties of occupational lung diseases primarily due to the vast increase in industrial technology have been reported recently. Preeminent among such newer agents are vinyl chloride (VC) and polyvinyl chloride. Very few cases have been reported, in Europe only, with descriptive histopathologic changes. To our knowledge, no pathologic studies of VC exposure have been

described in the American literature. The biopsy abnormalities in our patients disclosed desquamation of alveolar macrophages into the alveolar lumina and minor interstitial and alveolar inflammatory changes. Pulmonary function abnormalities included restrictive insufficiency. Preventive therapy consists of the avoidance of further exposures, frequent industrial hygiene monitoring, and total avoidance of tobacco smoke, as well as associated atmospheric pollutants. Thus far, none of these patients has exhibited evidence of pulmonary neoplasms. All three patients survived their occupational injuries, and two are still disabled to varying degrees. Urine and blood levels of phthalic acid derivatives were elevated in two patients, the exact significance of which is not fully known. It probably represents a toxicologic response, but must be further pursued before conclusions can be reached.

LA - Eng

- 97 AU - Lewis JG ; Swenberg JA
TI - Differential repair of O(6)-methylguanine in DNA of rat hepatocytes and nonparenchymal cells.
SO - Nature; VOL 288, ISS 5787, 1980, P185-41
AB - Chronic administration of several chemical carcinogens to laboratory animals induces a variety of tumours which arise from specific cell populations within the liver. In the rat, diethylnitrosamine induces hepatocellular carcinomas, dimethylnitrosamine induces both angiosarcomas and hepatocellular carcinomas, vinyl chloride primarily induces angiosarcomas, and 1,2-dimethylhydrazine induces malignant haemangioendotheliomas. One of the principal mechanisms thought to be involved in initiating carcinogenesis is the alkylation of specific sites on DNA, such as the O(6) position of guanine. Previous investigations of alkylation and repair have, however, analysed DNA prepared from whole liver. This approach does not localize alkylation or repair capacity in the different cell types which give rise to neoplasia. Furthermore, although hepatocytes account for more than 90% of the liver's mass, they only comprise 60-70% of its cells. The nonparenchymal cell (NPC) population, which consists almost entirely of endothelial and Kupffer cells, accounts for the remaining 30-40% and contains 10-20% of the DNA. Therefore, we decided to investigate the alkylation and repair of O(6)- and 7-methylguanine in the target and non-target cells following oral administration of 1,2-dimethylhydrazine. We report here that although initial alkylation was slightly less in NPCs, removal of O(6)-methylguanine was significantly slower. This led to a preferential accumulation of O(6)-methylguanine in NPC 24 h after administering a second daily dose. In contrast, 7-methylguanine decreased at similar rates, resulting in a 28-fold greater O(6)-methylguanine/7-methylguanine ratio in the target cell population.

LA - Eng

R&S 102736

00003090

PAGE 52

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

- 98 AU - Infante PF ; Marlow PB
TI - Evidence For The Carcinogenicity Of Selected Halogenated Hydrocarbons Including Ethylene Dichloride
SO - Ethylene Dichloride: A Potential Health Risk, Banbury Report No. 5, Ames, B., P. Infante, and R. Reitz, Editors; Cold Spring Harbor Laboratory, pages 287-303, 24 references, 1980
AB - Evidence for the carcinogenicities of vinyl-chloride (75014) (VC) and related compounds are reviewed. Related compounds for which information on carcinogenicity is presented are: ethylene-dichloride (107062), ethylene-dibromide (106934), vinylidene-chloride (75354), vinyl-bromide (593602), trichloroethylene (79016), perchloroethylene (127184), epichlorohydrin (106898), chloroform (67663), and carbon-tetrachloride (56235). The overall carcinogenic responses of rats and mice to these ten halogenated hydrocarbons is positive. Seven of the compounds cause cancer in both rats and mice. All of the compounds induce cancer in either rats or mice. Most of the substances induce cancer in more than one organ per species. However, there are considerable variations among species and between different strains of the same species. Route of administration, whether by gavage, inhalation or injection, can also make a difference in tumor sites. In general, the liver is the most common site regardless of route of administration, with the spleen and lung being the next most common. The most common type of tumor is carcinoma. All available epidemiologic studies of the selected hydrocarbons, excluding VC, are discussed. These generally suggest that increased risk of various cancers is associated with exposure to halogenated hydrocarbons. One study of 330 deaths among laundry and dry cleaning workers shows a significant excess of deaths from all types of cancer and from lung and cervical cancer. The authors conclude that an effort should be made to reduce human exposure to all of these substances, beginning at the site of origin.
- 99 AU - Wagoner JK ; Infante PF ; Apfeldorf RB
TI - Toxicity Of Vinyl Chloride And Polyvinyl Chloride As Seen Through Epidemiologic Observations
SO - Occupational Cancer and Carcinogenesis, Vainio, H., M. Sorsa, and K. Hemminki, Editors; Hemisphere Publishing Corporation, Washington, D.C., pages 181-187, 23 references, 1981
AB - The toxic effects of vinyl-chloride (75014) (VC) and polyvinyl-chloride (9002862) (PVC) as determined by epidemiologic studies are described. Several epidemiologic investigations have indicated that occupational exposure to VC is associated with increased risk of angiosarcoma of the liver. Studies of rats administered PVC powder in their diet resulted in changes in the liver. An excess of central nervous system cancer among VC workers has been reported. In nine of ten cases, the cancer was classified as glioblastoma. Inhalation of PVC dust has been associated with pneumoconiosis. The results of X-rayed workers in a PVC production factory suggest that PVC exposure for 5 years or more causes signs of pneumoconiosis. None of the workers in

areas without PVC dust had pneumoconiosis. Lung cancer excesses have been associated with both VC and PVC dust exposure. Some studies suggest that lymphatic system cancers can be found among VC workers. The authors conclude that further studies are needed. In the meanwhile PVC needs to be controlled.

- 100 AU - Falk H ; Baxter PJ
 TI - Hepatic Angiosarcoma Registries: Implications For Rare-Tumor Studie
 SO - Quantification of Occupational Cancer, Banbury Report No. 9, Peto, R., and M. Schneiderman, Editors; Cold Spring Harbor Laboratory, pages 543-551, 34 references, 1981
 AB - The incidence of hepatic angiosarcomas in Great Britain and in the US is reviewed. A search to identify cases of hepatic angiosarcomas conducted by the Centers for Disease Control and the Employment Medical Advisory Service is summarized. Registry data was intended to complement retrospective occupational cohort studies that were simultaneously in progress. The search showed that workers exposed to vinyl-chloride monomer (75014) had a higher risk of developing hepatic angiosarcomas, a type of liver cancer. Additional reasons for establishing the registries were to obtain precise incidence data, to study the pathogenesis of hepatic angiosarcomas in greater detail, and to compare the vinyl-chloride monomer induced cases with cases of unknown etiology. The methodology employed in soliciting information is outlined. The approach in the US was slightly different from that used in Great Britain. About 50 percent of the cases in Great Britain and about 80 percent of the cases in the US were identified from death registries. In the US, time trends for this type of liver cancer are not significant because the numbers are very small. However, four main causative agents have been identified; vinyl-chloride monomers, thorotrast (1314201), arsenic 7440382), and androgenic and anabolic steroids. The authors conclude that registry searches provide unique opportunities for epidemiologic and pathogenic studies of occupational and environmental carcinogens.
- 101 AU - Landrigan PJ ; Rinsky RA ; Waxweiler RJ
 TI - Epidemiologic Assessment Of Occupational Illness Caused By Exposures To Petrochemicals
 SO - Proceedings of the Seventh Alaska Health Congress, May 6-8, 1982, Energy, Health, and the Environment. The Health Impact of Petrochemical Development, pages 84-96, 7 references, 1982
 AB - Four epidemiological surveys in the petrochemical industry were reported. The first assessed the leukemia mortality of 1,006 rubber hydrochloride (7647010) workers (SIC-2822) who had been exposed to benzene (71432). The second study investigated the incidence of brain tumor deaths among petrochemical workers (SIC-2911) who produced ethylene-oxide (75218), vinyl-chloride (75014), acetates, and ethylene-amines. The third study examined the occurrence of acute peripheral neuropathy among workers at a facility that produced plastic coated fabrics (SIC-2295). In the fourth study, infertility of male pesticide workers (SIC-0721)

00003092

PAGE 54

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

who had been exposed to dibromochloropropane (96128) was examined. Seven leukemia deaths occurred among the rubber hydrochloride workers, where 1.25 deaths were expected. Twenty two brain tumor deaths occurred where 10.7 were expected among the petrochemical workers. Forty eight cases of acute peripheral neuropathy occurred among the workers at the plastic coated fabrics plant, and the cases were concentrated in the prints department where there had been in use a print solvent containing methyl-butyl-ketone (591786). Of the male pesticide workers, 13.1 were found to be azoospermic, as opposed to the expected 2.9 percent. Although the unexposed workers showed no symptoms of severe oligospermia, 16.8 percent of the exposed workers were found to have this condition. The authors conclude that these petrochemicals caused diseases or conditions relating to the occupation of the exposed subjects. Epidemiology is useful in evaluating occupational diseases caused by petrochemicals.

- 102 AU - Wallace D ; Nelson N ; Gates T
 TI - Polyvinyl Chloride Wire Insulation Decomposition II. Consideration Of Long Term Health Effects From Chlorinated Hydrocarbons
 SO - Journal of Combustion Toxicology, Vol. 9, pages 105-112, 16 references, 1982
 AB - The long term health effects of polyvinyl-chloride (9002862) (PVC) were investigated. Surveys of fire survivors and firefighters involved in fires where PVC wire insulation had been used were conducted. Twelve females were polled regarding menstrual patterns and unusual reproductive events, and the incidence of cancer in firefighters was studied. All 12 females reported uterine dysfunction. Three fourths complained of heavy or painful menstrual bleeding. One quarter had hysterectomies. Two miscarriages occurred. None of the subjects had reported having problems before the fire. Six cancers were reported among 700 firefighters questioned. These incidences occurred in males at an age younger than expected and at sites different from those generally reported. There were cases of cancer of the larynx, liver, skin, throat, and brain. The authors draw no definite conclusions from the data, except that the age distribution and cancer types appear to be unusual for the population studied. These health effects may be related to production of chlorinated hydrocarbons by decomposition of burning PVC.
- 103 AU - Miller ML ; Radike MJ ; Andringa A ; Bingham E
 TI - Mitochondrial Changes In Hepatocytes Of Rats Chronically Exposed To Vinyl Chloride And Ethanol
 SO - Environmental Research, Vol. 29, No. 2, pages 272-279, 18 references, 1982
 AB - The effects of vinyl-chloride (75014) (VC) exposure on liver mitochondrial cells were investigated in Sprague-Dawley-rats. Groups of rats were exposed to 5 percent ethanol (64175) (EtOH) in drinking water, inhalation of 600 parts per million VC 4 hours per day, 5 days per week, or combined inhalation of VC and ingestion of EtOH. Ingestion of EtOH began 4 weeks before

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

initiation of VC inhalation and continued until death or killing of animals. Animals were treated with VC for 12 months and were killed at 18 months; some animals were killed at 3, 6, 9, or 12 months after initiation of VC inhalation. Tissues were examined by electron microscopy. Mitochondria in all experimental animals demonstrated greater heterogeneity in size and shape than those of untreated controls. Changes and severity of changes increased with duration of exposure and age of the animal. The ratio of surface to volume increased over time. Mitochondria of EtOH treated rats were rounded, with increased numbers of margined cristae and increased heterogeneity in size and shape. The amount of smooth endoplasmic reticulum was increased in cytoplasm of hepatocytes. Inhalation of VC alone did not induce the same mitochondrial changes observed with combined VC and EtOH treatment. Mitochondria were commonly the main component in autophagocytic bodies in cytoplasm of VC treated animals. Mitochondria in the combined treatment groups were predominantly indented and cup shaped; those resulting from VC exposure alone were elongated. Floccular densities were found in mitochondrial matrices in animals given VC alone, and were observed at 6 months and after 18 months of recovery. The authors conclude that no correlation can be made between the structural changes in mitochondria observed after exposure to VC and EtOH and any increased incidence of hepatic angiosarcomas and carcinomas.

- 104 AU - Pond SM
TI - Effects On The Liver Of Chemicals Encountered In The Workplace
SO - Western Journal of Medicine, Vol. 137, No. 6, pages 506-514, 53 references, 1982
AB - The hepatotoxic effects of occupational exposure to chemicals are reviewed. Workplace chemicals that have produced hepatic effects in animals or humans are listed. The process of metabolism of chemicals in the liver and the hepatic processes are described. Hepatic responses range from fatty infiltration to cell death and necrosis; from metabolic changes, such as proliferation of the smooth endoplasmic reticulum, to porphyrias; from infiltration of granulomas to cirrhosis; from vascular lesions of peliosis hepatitis to angiosarcoma; and from parenchymal cell adaptation to neoplasia. Hepatic effects of carbon-tetrachloride (56235), vinyl-chloride (75014), and polychlorinated biphenyls are presented as the prototypes of a number of other compounds. Occupations are listed in which workers may be exposed to xylene (1330207). Some important industrial chemicals, their use in the workplace, and the hepatic responses in humans are noted. The clinical sequence of acute carbon-tetrachloride poisoning is illustrated over a 21 day period. The sequence begins with dizziness, headache, and confusion. This is followed by gastrointestinal pain, nausea and vomiting, and diarrhea; then, necrosis, jaundice, and coma occur, resulting in hepatic death. After this, renal death, pulmonary edema and cardiac failure occur. Exposure to vinyl-chloride is associated with multiple systemic diseases, including acroosteolysis, thrombocytopenia, and liver damage. The general molecular structure of

R&S 102740

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

polychlorinated biphenyls is illustrated, and various chlorine substituents are represented. The author concludes that hepatotoxicity may be only one facet of adverse effects. Liver sensitivity should warn physicians that other organs may also be affected.

- 105 AU - Anonymous
 TI - Pathology Report On The Brains From Mice, Hamsters, And Rats Exposed To Vinyl Chloride In IBT Study 663-03222
 SO - Experimental Pathology Laboratories, Inc., Herndon, Virginia, 40 pages, 1980
 AB - Pathological effects of inhaled vinyl-chloride (75014) on rat, mouse, and hamster brain were evaluated. Brain tissue was obtained from animals exposed to 0, 150, 200, and 2500 parts per million (ppm) vinyl-chloride, 6 hours a day, 5 days a week. Rats and hamsters were exposed for 12 months and mice for 9 months. All animals were kept for their lifetime or were sacrificed when moribund. Brains were fixed in formalin and examined grossly and histologically. A total of 9, 7, and 38 control samples were examined from mice, hamsters, and rats respectively, while 60 specimens were examined from exposed mice, 55 from exposed hamsters, and 114 from exposed rats. Gross examination revealed focal encephalitis in one male hamster brain from the 2500ppm group. Gross lesions in five male rats exposed to 2500ppm included a frontal mass on the brain, gelatinous like focus between anterior frontal half of the brain to the meninges below, firm focal mass in the olfactory region, a soft mass compressing the frontal brain quarter, a mass located between the meninges and skull, and a gelatinous frontal brain area. Histological examination revealed olfactory neuroblastomas in five male and two female rats from the 2500ppm group. A single glioblastoma was found in one male and an astrocytoma in one female of the 200ppm group. Olfactory neuroblastoma showed proliferation of basophilic cells, and numerous mitotic figures. These neoplasms compressed the cerebrum anteriorly and showed presence of infiltration under the meninges. The glioblastoma showed proliferation of a mixture of pleomorphic cells containing large nuclei, giant cells, and mitotic cells. The astrocytoma showed proliferation of well differentiated astrocytes infiltrating the neuropil. Scattered meningoencephalitis, suppurative meningitis, encephalomalacia, and focal encephalitis were found in some rats from control and exposed groups. The incidence of these lesions was low and not compound related. The authors conclude that neuroblastomas result from exposure of vinyl-chloride in rats.
- 106 AU - Atherley G ; Whiting R
 TI - Basic Concepts Of Occupational Cancer
 SO - Canadian Centre for Occupational Health and Safety, Montreal, Canada (Presented at Canadian Labour Congress Conference on Cancer in the Workplace), 14 pages, 8 references, 1981
 AB - Characteristics and concepts of occupational cancer are reviewed. Cancer deaths from workplace exposures are estimated at about 6 percent, with a predicted rate of 20 percent. Compensated cases

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

from exposures to occupational carcinogens are listed and include: nickel (7440020); asbestos (1332214); radiation; tars, soots, and oils; vinyl-chloride (75014), aromatic amines; and benzene (71432). Statistics are cited for compensation for occupational cancer, with 60 cases compensated per year. The disturbance of the normal growth process of the body in critical ways and the unrestricted growth of cells are the main factors of cancer development along with loss of normal function, the invasiveness of the disease, and its ability to spread. The destructive process of cancer cells is described. The diagnosis and treatment of cancers are described; early detection is critical to successful treatment. Methods used for the early detection of cancer include radiography, biopsy or sputum cytology, and detection of abnormal chemicals in the blood. Cancer is a multistage process, and that process is one of the great problems of prevention and detection of occupational cancers because of the latent period between time of exposure and onset of the disease. Cancer mortality is tabulated by affected areas for males and females. Lung cancer affects 27.9 percent of males, and breast cancer affects 22 percent of females; prostate cancer is seen in 11.1 percent of males, with cancer of the large intestine affecting 9.8 percent of males and 14 percent of females. Survival rates for various cancers are discussed. Latent periods are listed as 30 to 50 years for arsenic (7440382), 20 to 40 years for asbestos, 10 to 20 years for chromium (7440473), and 15 to 30 years for nickel exposures. The authors conclude that the problem is complex and solutions must be found to avoid cancer in the workplace.

- 107 AU - Greiser E ; Reinl W ; Weber H
TI - Vinyl chloride exposure and mortality in German chemical workers in comparison to mortality of unexposed chemical workers and PVC fabricators
SO - Zentralblatt für Arbeitsmedizin, Arbeitsschutz, Prophylaxe und Ergonomie Feb. 1982, Vol.32, No.2, p.44-62. 20 ref.
AB - Report of an epidemiological study of 7,021 workers in vinyl chloride (VC) production, 4,910 workers not exposed to VC, and 3,943 workers in polyvinyl chloride fabrication. The two exposed populations showed an elevated total mortality level, due to tumours of the lymphatic and haematopoietic systems, cerebral malignancies, cardiac ischaemia and, especially, malignant hepatic tumours. Given the latency period of the malignant tumours and the high number of hepatic haemangiosarcomas, continued monitoring of the exposed population will be necessary.
LA - Ger

R&S 102742

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

- 108 AU - Machet de la Martinière N
TI - Hepatic fibrosis and development of angiosarcoma following exposure to vinyl chloride
SO - Université de Paris V, Faculté de médecine Necker-Enfants-Malades, Paris, France, 1982. 163p. 85 ref.
AB - This medical thesis attempts to determine whether there is a sequential link between hepatic fibrosis and angiosarcoma. Description of a case of hepatic angiosarcoma in a worker with 16 years exposure to vinyl chloride monomer (VCM). Review of the literature. It seems, although without any scientific certitude, that hepatic fibrosis alone without any changes in adjacent sinusoidal cells, is not precancerous condition but merely one of the VCM-induced lesions. Technical and medical safety measures (review of French legislation). Importance of the occupational physician's role, and the facilities he should have available for detecting early signs and symptoms (biological or other) of hepatic fibrosis (periodic medical examinations, special procedures such as hepatic and splenic echotomography).
LA - Fre
- 109 AU - Henschler D
AD - Wuerzburg Univ. (Germany, F.R.G.). Inst. fuer Toxikologie.
TI - Investigation on the Carcinogenic Effect of Trichloroethylene by Inhalation and Mechanisms of Metabolic Bioactivation.
SO - Govt Reports Announcements & Index (GRA&I), Issue 01, 1983
AB - TD3: Trichloroethylene, one of the most frequently used solvents, was studied as a carcinogen on account of the chemical relationship to vinylchloride. To test this, systematic inhalation experiments were performed on three animal species (mice, rats, hamsters) at 100 ppm and 500 ppm, 6 h/day, 5 days/week for 18 months. In parallel the biochemical level was measured, providing insight into the mechanism of action of the compound. Macroscopic and microscopic evaluation of all tissues of the experimental animals after spontaneous death reveals no increase in the rates of benign and malignant tumors in the exposed group above the controls. In female mice, there is a dose related increase in the rate of malignant lymphomas which is, however, believed to be a nonspecific activation of virus infestation. The results show that long-term inhalation of trichloroethylene, even in high concentrations, renders no indication of a carcinogenic risk. The results of this investigation stand against the worldwide suspicion that trichloroethylene, a very frequently used solvent in the work area as well as in household environments, presents a carcinogenic risk. Final Report, May 1980. In German; English Summary. Sponsored by Bundesministerium fuer Forschung und Technologie.

00003097

PAGE 59

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

- 110 AU - Th'eriault G ; Allard P
 TI - Cancer mortality of a group of Canadian workers exposed to vinyl chloride monomer
 SO - Journal of Occupational Medicine Oct. 1981, Vol.23, No.10, p.671-676. Illus. 25 ref.
 AB - Study undertaken to ascertain if there was an excess of cancer mortality from causes other than angiosarcoma of the liver among a group of workers heavily exposed to vinyl chloride monomer (VCM). The mortality of 451 workers exposed to VCM for more than 5 years was compared with that of 870 unexposed controls. The relative risk for digestive cancer was significantly higher than 1 in the exposed group. The standardised mortality ratio (SMR) for digestive cancer was also higher (SMR 259.26 $p < 0.01$) than that of the general population. No other cancer was in excess. The exposed workers and controls had a similar cigarette smoking experience; the association between lung cancer and VCM exposure, if present, is rather small.
 LA - Eng
- 111 AU - Greenberg RA ; Tamburro CH
 TI - Exposure indices for epidemiological surveillance of carcinogenic agents in an industrial chemical environment.
 SO - Journal of Occupational Medicine May 1981, Vol.23, No.5, p.353-358. Illus. 9 ref.
 AB - Exposure indices which combine the components of work history and job exposure category were developed for 22 chemicals, and the system was validated statistically using industry-related cancer and worker-matched controls. Rank-ordered job exposure categories were assigned after jobs were classified according to area location and work description. The chemical exposure rating is an ordered, six-category ranking assigned to each area-description number for each calendar year. The application of this exposure index system to the incidence of hepatic angiosarcoma showed a clear pattern of high exposure to vinyl chloride over a 30 year period. The data demonstrate that a system of rank-ordered individual exposure indices for highly suspect chemicals can be implemented in an industrial environment and can identify a known causative relationship between exposure and the development of disease.
 LA - Eng
- 112 AU - Anonymous
 TI - Angiosarcoma of the liver: a growing problem?
 SO - Br. Med. J. 282(6263): 504-505 1981 (11 References)
 AB - PESTAB. A description is presented of angiosarcoma of the liver. Fewer than 200 of these tumors having been reported worldwide. It is noted that at least 3 compounds, thorotrast (a colloidal preparation of thorium dioxide), polyvinyl chloride, and arsenic, have been identified as causes of this angiosarcoma. Thorotrast is no longer in use, polyvinylchloride is used under safety regulations, and the use of arsenic pesticides in Britain has diminished. However, it is suggested more cases will appear,

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

since the latent period is 12-29 yr. Presenting symptoms include abdominal pain and swelling, weight loss, enlargement of the liver, and ascites. The prognosis is not good; transplantation or resection are the only cures.

- 113 AU - Anon
AD - National Toxicology Program, Research Triangle Park, NC.
TI - National Toxicology Program Annual Plan for Fiscal Year 1981.
SO - Govt Reports Announcements & Index (GRA&I), Issue 04, 1984
AB - TD3: The National Toxicology Program (NTP) was established in November, 1978, as a Department of Health and Human Services (DHHS) cooperative effort to coordinate and manage the Department's program to develop the scientific information necessary to protect the health of the American public from exposure to hazardous chemicals. Many human diseases can be linked with exposure to chemicals--lung cancer to asbestos, arsenic, and bis(chloromethyl)ether; liver cancer to vinyl chloride and aflatoxins; mesothelioma to asbestos; bladder cancer to benzidine; male sterility to chlordane (Kepone), dibromochloropropane and diethylstilbestrol (DES); neurologic disease to lead, Kepone, methyl mercury and methyl butyl ketone. There are many other chemicals known or suspected to be involved in the causation of human disease. Preventing or limiting exposure to such chemicals will prevent human disease, and disease prevention is a major goal of DHHS. See also PB83-240853.
- 114 AU - Falk H ; Thomas LB ; Popper H ; Ishak KG
TI - Hepatic angiosarcoma associated with androgenic-anabolic steroids.
SO - Lancet; VOL 2, ISS 8152, 1979, P1120-3
AB - A retrospective epidemiological study of deaths from hepatic angiosarcoma (HAS) in the U.S. showed that during 1964--74 there were 168 such cases, of which 37 (22%) were associated with previously known causes (vinyl chloride, 'Thorotrast', and inorganic arsenic) and 4 (3.1%) of the remaining 131 cases with the use of androgenic-anabolic steroids. It is suggested that the long-term use of androgenic-anabolic steroids is the fourth cause of HAS, the majority of cases still being of unknown aetiology. Moreover, the presented cases serve as a link in a spectrum of hepatic disorders recently recognised to be caused by environmental agents such as vinyl chloride, arsenic, and thorotrast, and by contraceptive and anabolic steroids. Similar precursor stages, usually not recognised by clinical laboratory tests and consisting of areas of hyperplasia of hepatocytes and sinusoidal cells and sinusoidal dilatation, lead potentially to hepatic adenoma, carcinoma, peliosis, and angiosarcoma.
- LA - Eng

R&S 102745

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

- 115 AU - Tamburro CH
TI - Health effects of vinyl chloride.
SO - Tex Rep Biol Med; VOL 37, 1978, P126-44, 146-51
AB - Vinyl chloride is a basic chemical for plastics manufacturing and has been used as an anesthetic agent. Vinyl chloride's previously unknown carcinogenic capability appears to be related to the body's ability to convert it from a non-toxic or minimally toxic chemical to a toxic and, with prolonged exposure, cancer-forming agent. Early exposure in animals causes body cells to make adaptive changes which may prepare them for malignant transformation and appear to precede evidence of morphological injury. These findings appear to occur before a low-grade chemical injury occurs. Vinyl chloride chemical injury in man appears to follow the same pattern. Present clinical data in humans now demonstrate evidence of pre-cancer injury and cancer transformation of various types of cells in different organs of the body. Manifestations of pre-cancerous injury to organs other than the liver (such as the lung, heart, spleen, brain and lymphatic system) may also be occurring and require further investigation. Early detection of these pre-cancerous chemical injuries requires a prospective ongoing system of surveillance and the development of diagnostic methods which can identify specific causal agents in the presence of non-specific injury. Such a systematic approach has been developed and is now in operation. Its initial achievements appear to be the foundation for future success in controlling the health effects of industrial chemicals.
- LA - Eng
- 116 AU - Locker GY ; Doroshow JH ; Zwelling LA ; Chabner BA
TI - The clinical features of hepatic angiosarcoma: a report of four cases and a review of the English literature.
SO - Medicine (Baltimore); VOL 58, ISS 1, 1979, P48-64 (REF: 144)
AB - Four cases of hepatic angiosarcoma are reported with a review of 99 other cases in the English literature. Angiosarcoma of the liver is associated with chronic exposure to thorotrast, vinyl chloride, arsenicals, radium and possibly copper and with chronic idiopathic hemochromatosis. Although 40% of patients have hepatic fibrosis or cirrhosis at autopsy, the nature of the association between chronic liver disease and hepatic angiosarcoma is unknown. The clinical presentation of hepatic angiosarcoma is nonspecific with abdominal pain, weakness and weight loss common complaints and with hepatomegaly, ascites and jaundice common findings. Liver function tests are usually abnormal but there is no one liver function test or set of tests specific for the tumor. The occurrence of thrombocytopenia and disseminated intravascular coagulation is characteristic of hepatic angiosarcoma and may be related to local consumption of clotting factors and formed blood elements in the tumor. Catastrophic intraabdominal bleeding is also characteristic and occurs in one-fourth of all cases. This complication is likely related to the high incidence of clotting abnormalities and the vascular

R&S 102746

00003100

PAGE 62

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

nature of the neoplasm. Selective hepatic arteriogram and open liver biopsy are the foundations of diagnostic evaluation. Percutaneous liver biopsy should be avoided. Failure to appreciate the possibility of hepatic angiosarcoma in the proper clinical setting, leading to blind percutaneous biopsy, may result in failure to make the diagnosis at the cost of significant morbidity and mortality. Survival of patients with hepatic angiosarcoma is brief; only 3% live longer than 2 years. Treatment of the tumor to date is empirical. There are probably a few patients who might benefit from radical surgery with curative intent. For all others chemotherapy is indicated. Adriamycin is active against hepatic angiosarcoma, but optimal dose and mode of administration require further investigation. Further study is also required to delineate the cause of hepatic angiosarcoma in the 60% of cases without definite epidemiologic association.

LA - Eng

117 AU - Delorme F

TI - (Association of angiosarcoma of the liver and hepatoma in vinyl chloride worker)

SO - Ann Anat Pathol (Paris); VOL 23, ISS 2, 1978, P105-114

AB - This report deals with a 51 years-old man who, for 23 years and 4 months of his working life, had been exposed to vinyl chloride vapors. Autopsy revealed a hepatoma associated with an angiosarcoma of the liver. The case is the first ever to be reported in the medical literature. This case raises doubts about the theory which suggests that the carcinogenic effect of vinyl chloride in man elicit a tumor of vascular nature.

LA - Fre

118 AU - Popper H ; Thomas LB ; Telles NC ; Falk H ; Selikoff IJ

TI - Development of hepatic angiosarcoma in man induced by vinyl chloride, thorotrast, and arsenic. Comparison with cases of unknown etiology.

SO - Am J Pathol; VOL 92, ISS 2, 1978, P349-69

AB - Examples of human angiosarcoma following exposure to vinyl chloride, Thorotrast, or arsenic (medicinal and industrial) and cases, including children, of unknown etiology were studied to establish diagnostic criteria and to study their evolution. The uniform evolution suggests an environmental factor also in the cases of unknown etiology, which may be established by epidemiologic studies. A precursor stage is characterized by areas of combined hyperplasia of hepatocytes and a variety of sinusoidal and perisinusoidal cells associated with excess of reticulin and with sinusoidal dilatation. The diagnostically useful picture in silver impregnations indicated reticulum formation by the perisinusoidal cells, presumably the fibrocytes. The hepatocytic proliferation suggests a hepatocarcinogenic but usually not fully expressed potential. The mixed hyperplasia of the various sinusoidal cells proceeds to an overgrowth of angiosarcoma cells, presumably derived from endothelial cells. In early stages they are usually in contact with hepatocytes (intralobular growth). A trabecular arrangement results from loosening of the

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

lobular plate arrangement by dilatation of sinusoids, leading to primary peliosis. With disappearance of the hepatocytes, various growth patterns develop, terminating in nodular, solid angiosarcoma composed of either spindle-shaped or polyhedral cells which undergo necrosis or hemorrhage (secondary peliosis). The interaction between hepatocytes and sinusoidal cells requires elucidation.

LA - Eng

- 119 AU - Delorme F ; Th'eriault G
TI - Ten cases of angiosarcoma of the liver in Shawinigan, Quebec.
SO - J Occup Med; VOL 20, ISS 5, 1978, P338-40
AB - Ten cases of angiosarcoma of the liver have been diagnosed in Shawinigan, Quebec since 1955. All have occurred in men who worked in a vinyl chloride polymerizing plant. Cigarettes and alcohol do not seem to be associated with this tumor. The amount of vinyl chloride to which these people were exposed, according to information obtained through questionnaires, appears elevated. Angiosarcoma of the liver is accompanied by a fibrosis of the liver which may precede its appearance. In describing the Canadian cases of angiosarcoma, this study attempts to shed more light upon the causal relationship between vinyl chloride monomer and angiosarcoma of the liver and thus to provide some clues to understanding the pathogenesis of this disease.

LA - Eng

- 120 AU - Veltman G ; Lange CE ; Stein G
TI - [The vinyl-chloride disease]
SO - Hautarzt; VOL 29, ISS 4, 1978, P177-82 (REF: 35)
AB - Workers engaged in the PVC-production, who were long-term exposed to the gaseous base vinyl chloride exhibit a complex pattern of damages. Changes of the skin, vascular and bone system, as well as thrombocytopenia, liver fibrosis with portal hypertension, disturbances of the porphyrin metabolism and alterations of the central nervous system were observed. Moreover vinyl chloride is oncogenic and may cause angiosarcoma of the liver. By directed occupational medicine supervision, improvement of the production conditions and introduction of new processing techniques health risks at the workplace could be eliminated to a far extend.

LA - Ger

- 121 AU - Infante PF
TI - Mutagenic and carcinogenic risks associated with halogenated olefins.
SO - Environ Health Perspect; VOL 21, 1977, P251-4
AB - Recent experimental evidence indicates that structural analogs of vinyl chloride namely, vinylidene chloride and trichloroethylene, are mutagenic. Carcinogenic response also has been observed in experimental animals following exposure to vinylidene chloride, trichloroethylene, and perchloroethylene. More recent observations demonstrate low-level vinyl chloride-induced mammary carcinoma. An additional chlorinated olefin, chloroprene, has demonstrated a mutagenic response in several test systems.

R&S 102748

00003102

PAGE 64

 VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

Likewise, several studies have indicated significant excesses of chromosomal aberrations as well as adverse effects on reproductive function following male exposure to chloroprene. Although reports have indicated an increased incidence of lung and skin cancer among workers occupationally exposed to chloroprene, adequately designed studies have not been carried out which would allow the development of valid inferences regarding its carcinogenicity. The question facing the scientific community and society is whether observations in subhuman species are adequate to institute prudent public health practice by controlling these agents as carcinogens or mutagens or whether, once again, epidemiologic enumeration of the toll will be required.

LA - Eng

- 122 AU - Fox AJ ; Collier PF
 TI - Mortality experience of workers exposed to vinyl chloride monomer in the manufacture of polyvinyl chloride in Great Britain.
 SO - Br J Ind Med; VOL 34, ISS 1, 1977, P1-10
 AB - Identification particulars were obtained for over 7000 men who were at some time between 1940 and 1974 exposed to vinyl chloride monomer in the manufacture of polyvinyl chloride. Approximately 99% of these men have been traced and their mortality experience studied. The overall standardised mortality ratio, 75-4, shows a significant reduction compared with the national rates. Four cases of liver cancer were found. Two of these have been confirmed by a panel of liver pathologists as angiosarcoma and two as not angiosarcoma. There is no evidence to support the hypothesis that cancers other than those of the liver are associated with exposure to vinyl chloride monomer. The two cases of angiosarcoma were found in men who had been exposed to high concentrations of the monomer although the second man died only eight years after first exposure. The industry in Great Britain has expanded considerably since the second world war with over 50% of men having entered within the last decade. Conclusions drawn about the effect of vinyl chloride monomer on the mortality experience of men in this industry must consequently be tempered by the reservation that the full impact may not yet be in evidence.

LA - Eng

- 123 AU - Feron VJ ; Spit BJ ; Immel HR ; Kroes R
 TI - One-year time-sequence inhalation toxicity study of vinyl chloride in rats. III. Morphological changes in the liver.
 SO - Toxicology; VOL 13, ISS 2, 1979, P143-54
 AB - Wistar rats were exposed to atmospheres containing 0 (control) or 5000 ppm vinyl chloride monomer (VCM), 7 h/day, 5 days/week, for a period of 52 weeks. After 4, 13, 26 and 52 weeks each time 10 rats/sex/group were killed and subjected to extensive examinations. The present paper describes the morphological changes found in the liver. The major parenchymal changes comprised swelling and malformation of mitochondria, an increased amount of smooth endoplasmic reticulum, necrosis, nuclear and

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

cellular polymorphism of hepatocytes, "foci of cellular alteration", neoplastic nodules and hepatocellular carcinomas. A reduced glucose-6-phosphatase activity in hepatocytes and a strong sinusoidal activity of alkaline phosphatase were found within "foci of cellular alteration". The non-parenchymal alterations included focal dilatation of sinusoids, focal proliferation of atypical sinusoidal cells and multicentric angiosarcomas. The effects of VCM on the hepatic parenchyma seemed to precede those on the hepatic stroma.

LA - Eng

- 124 AU - Lee CC ; Bhandari JC ; Winston JM ; House WB ; Dixon RL ; Woods JS
TI - Carcinogenicity of vinyl chloride and vinylidene chloride.
SO - J Toxicol Environ Health; VOL 4, ISS 1, 1978, P15-30
AB - Exposure of mice to 50, 250, or 1000 ppm of vinyl chloride (VC) in the air for 6 h/d, 5 d/wk, caused a high incidence of bronchioloalveolar adenoma, mammary gland tumors, and hemangiosarcoma. Mammary gland tumors occurred in the females and included ductular adenocarcinoma and squamous and anaplastic cell carcinomas with metastasis to the lung. Hemangiosarcoma occurred in the liver and, to a lesser extent, in various other organs. The incidence and severity of these tumors increased with the concentration of VC and the length of exposure. Malignant lymphoma involving various organs was observed in several mice. Rats were more resistant to the carcinogenic effects of VC. Exposure of rats to 250 or 1000 ppm of VC caused hemangiosarcoma in the liver. Many rats with hepatic hemangiosarcoma also developed hemangiosarcoma in the lung. Extrahepatic hemangiosarcoma also occasionally occurred in other organs. Exposure to 55 ppm of vinylidene chloride (VDC) caused hepatic hemangiosarcoma and probably bronchioloalveolar adenoma in mice. Hemangiosarcoma also occurred in the mesenteric lymph node or subcutaneous tissue in two rats exposed to 55 ppm of VDC.

LA - Eng

- 125 AU - Nicholson WJ
TI - Cancer following occupational exposure to asbestos and vinyl chloride.
SO - Cancer; VOL 39, ISS 4 Suppl, 1977, P1792-801 (REF: 39)
AB - A review is presented of the various factors important in the identification of carcinogenic disease from occupational and environmental exposure to asbestos and vinyl chloride. The long lapsed period, usually of 20 or more years from first exposure to these materials, is discussed, as well as the requirement for sufficiently long observation periods in prospective epidemiological studies. The multiple-factor etiology of lung cancer involving cigarette smoking and asbestos exposure is illustrated. The risks of asbestos-related cancers to other than those directly working with the material are discussed in a variety of circumstances, and finally the effectiveness of control procedures for vinyl chloride and asbestos are compared.

LA - Eng

R&S 102750

00003104

PAGE 66

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

- 126 AU - Chiazze L Jr ; Nichols WE ; Wong O
 TI - Mortality Among Employees Of PVC Fabricators
 SO - Journal of Occupational Medicine, Vol. 19, No. 9, pages 623-628, 9 references, 1977
 AB - A study was carried out among employees of polyvinyl-chloride (9002862) (PVC) fabricators to identify angiosarcoma deaths. The study was based on 4,341 deaths of current or former employees of 17 companies engaged in PVC fabrication during a 10 year period (1964 to 1973). The distribution of deaths by cause was also calculated. No angiosarcoma deaths were found in this particular group. Among the 3,248 white males nearly 60 percent of the deaths were from diseases of the circulatory system as compared to 46 percent of the 601 white females. Thirty one percent of all the cancer deaths were due to digestive system cancer. Digestive and respiratory cancers accounted for almost 66 percent of all cancer deaths among white males. Among white females, slightly over 50 percent of the cancer deaths were from cancers of the breast and digestive system. The authors conclude that while there is an excess of cancer deaths, particularly of the digestive system, there is no excess of liver, lung or brain cancer. They recommend caution in interpreting results which are arrived at using the proportionate mortality ratio based on an external standard.
- 127 AU - Anonymous
 TI - Criteria For A Recommended Standard. Occupational Exposure To Vinyl Halides
 SO - Division of Criteria Documentation and Standards Development, NIOSH, U.S. Department of Health, Education and Welfare, 296 pages, 356 references, 1979
 AB - An exposure standard is proposed for the vinyl halides and evidence gathered to support the standard is reviewed. It is proposed that employee exposure to vinyl halides in the workplace be controlled by adherence to the provisions for vinyl-chloride (75014), which are appended. The recommended standard applies to workplace exposure to the monomers vinyl-chloride, vinylidene-chloride (75354), vinyl-bromide (593602), vinyl-fluoride (75025), and vinylidene-fluoride (75387), including any unreacted monomer that may remain in polymers of these halides. The biologic effects of exposure to humans, including epidemiologic studies and historical reports of exposure are reviewed. Studies of animal toxicity and metabolism of these compounds, structure activity considerations, and correlation of exposure and effect are examined. Studies of carcinogenicity, mutagenicity, teratogenicity, and reproductive effects are described. Results show the biologic effects of vinyl halide exposure to include changes in behavior, cardiovascular abnormalities, degenerative changes in the liver and bones, and the induction of malignant neoplasms, especially angiosarcomas of the liver. Sampling and analytical procedures for airborne vinyls in occupational environments are described. Results of vinyl-chloride production workplace hygiene studies

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

are reported. Engineering controls to eliminate the potential for exposure to vinyl halides are discussed. Closed system operations are recommended as providing the best means of elimination of employee exposure, but ventilation systems are also examined. Safe work practices and personal protection are discussed. The basis for previous vinyl halide standards and the recommended standard are examined. It is noted that only vinyl-chloride is a known human carcinogen at this time, but animal studies suggest the possible efficacy of the other vinyl halides in this regard. Research needs on biological effects of exposure to vinyl halides include epidemiological studies, examination of human toxic effects, and development of sampling and analysis practices, particularly for vinyl halides other than vinyl-chloride. A substantial bibliography is appended.

R&S 102752

- 128 AU - Anonymous
TI - Vinylidene Chloride And Vinylidene Chloride-Vinyl Chloride Copolymers
SO - IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans: Some Monomers, Plastics and Synthetic Elastomers, and Acrolein, Vol. 19, pages 439-459, 76 references, 1979
AB - The toxic and carcinogenic effects of vinylidene-chloride (75354) (VC) and vinylidene/chloride-vinylchloride copolymers (VCVCC) are evaluated. Chemical and physical data on VC and VCVCC is listed. Production methods and manufacturing uses are reviewed. The occurrence of each found in air, water, and other sources is summarized. Procedures in the analysis of VC and VCVCC are discussed. Animal carcinogenicity studies on VC are reviewed. Occurrences, due to exposure to VC, of carcinomas, adenocarcinomas, bronchioloalveolar adenomas, angiosarcomas, hepatomas, and keratoacanthomas are described. No such data is available for VCVCC. Reports on toxic effects of VC are highly variable. The lethal concentrations are dependent on dietary parameters and on the hepatic glutathione content. No teratogenic effects of VC in rats or rabbits have been identified. Evidence of embryotoxicity and fetotoxicity is observed in VC exposure by inhalation. Metabolic and excretory pathways are discussed. A review of VC exposure health effects in humans shows central nervous system depression and narcosis, liver and renal dysfunction, skin irritation, conjunctivitis, and transient corneal injury. An epidemiological study among a cohort of 138 workers exposed to VC reports no statistically related findings. However, a preliminary mortality study reports the incidence of malignant tumors and bronchial carcinomas. There is no embryotoxicity, teratogenicity, carcinogenicity, metabolic, or mutagenicity data on VCVCC. The authors conclude that more information is needed to make an evaluation of the carcinogenicity of VC and VCVCC, although experimental evidence indicates a similarity to vinyl-chloride (75014).

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

- 129 AU - Griciute L
TI - The Carcinogenicity Of Vinyl Chloride
SO - Environmental Carcinogens, Selected Methods of Analysis, Vol. 2, Methods for the Measurement of Vinyl Chloride in Poly (Vinyl Chloride), Air, Water and Food Stuffs, IARC Scientific Publication No. 22, pages 3-11, 34 references, 1978
AB - The carcinogenicity of vinyl-chloride (75014) is reviewed. Vinyl-chloride is carcinogenic in humans and animals. Pathological conditions are outlined; chronic exposures in animals cause hepatic lesions and bone changes. Tumors induced by vinyl-chloride in animal liver, lung, intestine, kidney, skin, mammary gland, and forestomach are discussed. Tumors observed in workers in the polyvinyl-chloride (9002862) industry are generally liver angiosarcomas. Histological studies made by British scientists on the primary angiosarcomas of the liver are described. Estimated individual exposures to vinyl-chloride are presented. The European standards for concentrations of vinyl-chloride in the workplace environment are between 1 to 5 parts per million, time weighted average. The concentrations at some sites in an industrial facility can be greater than at others. Hazardous conditions may result from leakage of vinyl-chloride, caused by mechanical breakdown or malfunction of manufacturing equipment. The regulations set by 13 European countries for pollution of the workplace environment by vinyl-chloride are discussed. The author concludes that to reduce vinyl-chloride concentrations in the workplace, the use of modern technology to promote industrial and general hygiene is crucial.
- 130 AU - Anonymous
TI - Vinyl Chloride, Polyvinyl Chloride And Vinyl Chloride-Vinyl Acetate Copolymers
SO - IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans: Some Monomers, Plastics and Synthetic Elastomers, and Acrolein, Vol. 19, pages 377-438, 256 references, 1979
AB - Data relevant to the evaluation of the carcinogenic risk to humans from vinyl-chloride (75014) (VC), polyvinyl-chloride (9002862) (PVC), and VC/vinyl-acetate (108054) copolymers is reviewed. Chemical and physical properties of the compounds are presented. Their production, use, occurrence, and analysis are described. VC is reported to have been detected in ambient air, water, and food in the US. Research is reported which shows VC carcinogenicity tested in rats by oral, subcutaneous, and intraperitoneal administration and in mice, rats, and hamsters by inhalation exposure. Following inhalation exposure, VC was carcinogenic in all three species, producing tumors at different sites, including angiosarcomas of the liver. Research is also cited which showed VC to be carcinogenic in rats following prenatal exposure. A dose/response effect is reported. The mutagenicity of VC vapor to Salmonella strains with and without bioactivation is reported. Induction of local sarcomas in rats

R&S 102753

00003107

PAGE 69

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

following subcutaneous and intraperitoneal implantation is reported; the incidence of tumors varied with the size and form of the implant. Studies indicate an elevated proportion of digestive system cancer in PVC workers and breast and urinary tract cancer in female workers. Implantation of VC/vinyl-acetate copolymers as films in rats is reported which produced similar results. Studies in humans are examined which show exposure to VC results in increased carcinogenic risk involving in the liver, brain, lung, and hemolymphopoietic system. Epidemiological studies of VC indicate a possible mutagenic effect in human germ cells. Chromosomal aberrations are reported in lymphocytes of VC exposed workers. Increased rates of birth defects among children of parents residing in communities where VC/PVC processing facilities are located are also described. The authors conclude that VC is a human carcinogen. Evidence of its mutagenicity and teratogenicity is also available. Available studies are insufficient to evaluate the carcinogenicity of PVC.

- 131 AU - Gehring PJ ; Watanabe PG ; Park CN
 TI - Resolution Of Dose-Response Toxicity Data For Chemicals Requiring Metabolic Activation: Example Vinyl Chloride
 SO - Toxicology and Applied Pharmacology, Vol. 44, pages 581-591, 22 references, 1978
 AB - The nature of dose/response relationships in carcinogenicity studies involving active metabolites was studied in rats exposed to vinyl-chloride (75014) (VC). Sprague-Dawley-rats inhaled labeled VC in concentrations from 1.4 to 4600 parts per million (ppm) for 6 hours. Immediately after exposure, the rats were killed, and total body radioactivity was determined as a measure of metabolized VC. Data was analyzed using a transformation of the Michaelis and Menten equation. The results were applied to a previous experiment to correlate VC exposure, metabolism, and induction of hepatic angiosarcoma in rats exposed to 50 to 10000ppm VC 4 hours per day, 5 days per week for 12 months. The ratio of VC metabolized in 6 hours to VC in 1 liter of air ranged from 8.33 to 10.52 at exposure concentrations up to 109ppm, and then decreased as concentrations rose, dropping to 0.79 at 4600ppm. The data was found to fit both a linearized transformation of the Michaelis and Menten model and the original nonlinear model. Using the equations and calculated constants, the data from the previous experiment was extrapolated to predict that exposure to 4.6ppm VC for 4 hours daily, 5 days per week for 1 year would produce one angiosarcoma per 10000 rats. The authors conclude that experiments assessing the effects of low doses of toxic or carcinogenic compounds must incorporate in their design dose dependent, Michaelis and Menten type, pharmacokinetic parameters. Also, extrapolation of data below the range of exposures causing a discernible response may be expected to overestimate the projected incidence, due to the possibilities of threshold effects and longer than lifetime latencies.

00003108

PAGE 70

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

- 132 AU - Anonymous
 TI - Review, Summarization, And Evaluation Of Literature To Support The Update And Revision Of Criteria Documents. VIII. Vinyl Chloride
 SO - NIOSH, Rockville, Maryland, Contract No. 210-76-0167, 95 pages, 140 references, 1977
 AB - Recent literature on occupational health standards for vinyl-chloride (75014) (VC) is reviewed. Analytical methods are discussed. The NIOSH recommended method of sampling and analysis is described. This method can be improved either by modifying the carbon-disulfide desorption procedure or by using a thermal desorption method. Alternative analytical methods are summarized. The human effects of VC exposure are discussed. The clinical symptoms of VC poisoning are described. Epidemiological surveys and case reports are presented. Epidemiological surveys have confirmed the existence of excess liver cancer mortality among workers exposed to VC. More than 38 cases of hepatic angiosarcoma attributed to VC have occurred since 1974. Animal studies of the pharmacodynamics and metabolism, biochemical effects, toxicity, mutagenicity, and carcinogenicity of VC are considered. Prolonged inhalation at concentrations of 50 parts per million has caused cancers in various animal species. Positive mutagenic results have occurred in *Salmonella-typhimurium* incubated with VC in the presence of liver microsomes. Work practices and engineering controls are discussed. Current techniques of medical surveillance are described. Long term bioassays in several species need to be conducted to determine if there is a safe dose of VC. Research is also needed to determine possible effects of VC on reproductive functions.
- 133 AU - Watanabe PG ; Hefner RE Jr ; Zempel JA ; Pegg DG ; Park CN
 AU - Gehring PJ
 TI - Summary of the Studies Conducted on the Pharmacokinetics/Metabolism of Vinyl Chloride in Rats
 SO - Toxicology Research Laboratory, Health and Environmental Research, Dow Chemical, U.S.A., Midland, Michigan, 16 pages, 1977
 AB - Vinyl-chloride (75014) (VC) metabolism and pharmacokinetic studies conducted on rats are summarized. During inhalation exposure of 1000 parts per million (ppm) or oral exposure at 100 milligrams per kilogram, the metabolism of VC is extensive, and the urinary metabolites consist mainly of cysteine conjugates. The toxification of VC at exposure concentrations below 10ppm is more efficient than at higher concentrations (50 to 2000ppm), which depress hepatic glutathione, diminishing the detoxification of VC metabolites, and resulting in their disproportionate increase. The diminished ability to detoxify VC at higher concentrations correlates with the induction of hepatic angiosarcoma. Studies with radioactive VC show that the total amount of radioactivity bound to macromolecules in the liver does not increase proportionately with increases in VC exposure concentrations. There is no indication of a threshold for the

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

reaction of VC metabolites with total intracellular macromolecules; however, at exposure concentrations exceeding 50ppm, the covalent binding of VC metabolites to macromolecules correlates well with the percentage incidence of hepatic angiosarcoma in rats. Results of repeated exposure to VC (6 hours per day, 5 days per week for 7 to 8 weeks) show no change in the biotransformation or the rate of elimination of VC; however, the increase in binding of VC metabolites to hepatic macromolecules after repeated exposure (versus single exposure) indicates that repeated treatment augments the reaction of electrophilic metabolites of VC with macromolecules, and this may be expected to enhance the potential for toxicity (including carcinogenicity).

- 134 AU - Lee CC ; Bhandari JC ; Winston JM ; House WB ; Dixon RL ; Woods JS
TI - Carcinogenicity of Vinyl Chloride and Vinylidene Chloride
SO - Journal of Toxicology and Environmental Health, Vol. 4, No. 1, pages 15-30, 26 references, 1978
AB - The carcinogenic effects of inhalation exposure to vinyl-chloride (75014) (VC) and vinylidene-chloride (75354) (VDC) were examined in mice and rats. Groups of albino-CD-1-mice and CD-rats were exposed to 50, 250, or 1000 parts per million (ppm) VC, 55ppm VDC, or room air for 6 hours a day, 5 days a week. Laboratory tests and gross and histopathologic examinations were performed at the end of 1, 2, 3, 6, and 9 months. Exposure to VC was highly carcinogenic in mice. Bronchioloalveolar adenomas, mammary gland tumors, and hemangiosarcomas developed in these mice. Mammary gland tumors were observed only in female mice starting at 6 months. Observations of this tumor suggested the tumor originated as ductular adenocarcinoma and underwent anaplastic and squamous cell metaplasia. The incidence and severity of mammary gland tumors appeared to be greater in mice exposed to higher VC doses and for longer periods of time. Only a few mice exposed to VDC developed bronchioloalveolar adenomas. Hepatic hemangiosarcomas were observed in three mice exposed to VDC. The severity of these tumors and the mammary gland tumors in females exposed to VC probably contributed to the deaths of most of the mice. Rats were more resistant to the carcinogenic effects of VC and VDC. Hepatic hemangiosarcomas were observed in rats exposed to 250 or 1000ppm VC starting at 9 months. In contrast to the mice, many of the rats with hepatic hemangiosarcomas also developed hemangiosarcomas in the lung. VC did not cause any other tumors in rats. The authors question the significance of bronchioloalveolar adenomas in VDC mice, and conclude that rats are more resistant to the effects of VC and VDC than mice.

00003110

PAGE 72

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

- 135 AU - Nicholson WJ ; Hammond EC ; Seidman H ; Selikoff IJ
 TI - Mortality Experience of a Cohort of Vinyl Chloride-Polyvinyl Chloride Workers
 SO - Annals of the New York Academy of Sciences, pages 225-230, 8 references, 1977
 AB - The mortality status of workers occupationally exposed to vinyl-chloride (75014) (SIC-3079) was investigated. Company records of workers exposed to vinyl-chloride (9002862) production for at least 5 years subsequent to 1946 were examined. Work and medical histories of 255 workers were documented. Work practices were reviewed to estimate exposure concentrations and individuals were divided according to these values. Peak exposure was estimated to have often reached 1000 parts per million (ppm) and to have approached 10,000ppm at times in the production facility. Of the 255 workers, 24 had died; 18 deaths were reported from cancer, and 3 deaths were due to hemangiosarcoma of the liver. Workers who died from hemangiosarcoma all worked in polyvinyl-chloride production prior to 1951. Other cancers listed as cause of death included 1 glioblastoma, 1 lymphosarcoma, and 1 reticulum cell sarcoma. One death from cirrhosis of the liver was reported in an individual who did not drink. The authors conclude that at least 17 percent of the deaths examined casually related to vinyl-chloride exposure. Continuation of these mortality studies is recommended.
- 136 AU - Anonymous
 TI - Epidemiological Study of Vinyl Chloride Workers Final Report
 SO - Equitable Environmental Health, Inc., Maryland, 49 pages, 8 references, 1978
 AB - The incidence of mortality among workers exposed to vinyl-chloride (75014) and its polymers was surveyed. A total of 10,173 workers from 37 factories were studied of which 9,677, or 95.1 percent, were traced through available employment records, histological materials and death certificates. Individuals had worked for at least 1 year in a job which exposed them to vinyl-chloride. Active, terminated, retired and deceased workers were included. The observed mortality was compared to the male population of the United States during the time period of the study. There were 669 certified deaths available for analysis. Even though the Standardized Mortality Ratio (SMR) for malignancies at various sites was lower, there was still some support for the theory that exposure to vinyl-chloride increased the incidence of cancer in sites other than the liver. This observation was based on the incidence of lung cancer and miscellaneous cancers which appeared in individuals during long periods of maximum exposure to vinyl-chloride. The excess of brain tumors was noted but no relation was found to exist between either the intensity of exposure or duration of exposure to vinyl-chloride. The author concludes that another study should be conducted within a five year period to include measurements on longer periods of exposure to vinyl-chloride and observation on the incidence of cancers in sites other than the liver.

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

- 137 AU - Anon
AD - National Inst. for Occupational Safety and Health, Cincinnati, OH.
AD - Occupational Safety and Health Administration, Washington, DC.
TI - Current Intelligence Bulletin 28. Vinyl Halides Carcinogenicity: Vinyl Bromide, Vinyl Chloride, and Vinylidene Chloride.
SO - Govt Reports Announcements & Index (GRA&I), Issue 04, 1985
AB - TD3: The National Institute for Occupational Safety and Health (NIOSH) and the Occupational Safety and Health Administration (OSHA) jointly recommend that vinyl bromide and vinylidene chloride be considered in the workplace as potential carcinogens to humans and controlled with the same degree of prudence as vinyl chloride, another vinyl halide currently regulated as a carcinogen by OSHA. This recommendation is based on the results of recent studies indicating that exposure to vinyl bromide and to vinylidene chloride causes angiosarcoma of the liver and other cancers in laboratory animals. Safe levels of exposure to carcinogens have not been demonstrated, but lowered exposure to carcinogens may in general decrease the probability of cancer development. Prepared in cooperation with Occupational Safety and Health Administration, Washington, DC.
- 138 AU - Anon
AD - National Toxicology Program, Research Triangle Park, NC.
TI - National Toxicology Program Annual Plan for Fiscal Year 1980.
SO - Govt Reports Announcements & Index (GRA&I), Issue 24, 1983
AB - TD3: The National Toxicology Program (NTP) aims to develop scientific information which can be used to protect the health of the American public from damage by exposure to environmental chemicals. Many human diseases can be traced to chemical exposure--lung cancer to asbestos, arsenic, bis(chloromethyl) ether and others; liver hemangiosarcoma to vinyl chloride; mesothelioma to asbestos; male sterility to kepone and dibromochloropropane; neurologic disease to kepone, methyl mercury, lead and methyl butyl ketone. Preventing human exposure to such chemicals will prevent human disease. The Department of Health, Education, and Welfare is responsible for safeguarding the public's health, and the prevention of human exposure to toxic chemicals remains a keystone in the Department's efforts to prevent disease and promote health.
- 139 AU - Winell M ; Holmberg B ; Kronevi T
TI - Biological effects of vinyl chloride: an experimental study.
SO - Environ Health Perspect; VOL 17, 1976, P211-6
AB - Plasma activities of alkaline phosphatase, (AP), transaminases and total lactate dehydrogenase (LDH) with isoenzymes were determined in mice inhaling 50 and 550 ppm vinyl chloride (VC). The animals were also autopsied and the tissue pathology was studied. The total LDH activity was elevated in both dose groups along with a shift to cathodic enzymes. AP was increased in animals exposed to 500 ppm and transaminases were not at all changed. Enzyme changes occurred after the appearance of tumors. Alveogenic adenomas occurred in all animals at the higher

R&S 102758

dosage and in about half of the animals inhaling the lower dose. Subperitoneal and subcutaneous hemangiosarcomas were frequent in both dose groups; but especially among 50 ppm animals. Only one animal had a hemangiosarcoma of the liver. No liver fibrosis was seen. All primary subperitoneal and subcutaneous tumors were located in fat tissue. Telangiectasis was observed in two animals in the 500 ppm series. The importance of blood vessel changes in the toxicology of vinyl chloride is discussed.

LA - Eng

- 140 AU - Gokel JM ; Liebezeit E ; Eder M
TI - Hemangiosarcoma and hepatocellular carcinoma of the liver following vinyl chloride exposure. A report of two cases.
SO - Virchows Arch [Pathol Anat]; VOL 372, ISS 3, 1976, P195-203
AB - A report is given of the clinical and autopsy findings of two men who died from malignant liver neoplasm following occupational exposure to vinyl chloride. The first patient was a 44-year-old man with an hemangiosarcoma of the liver, the second patient a 67-year-old man with an hepatocellular carcinoma. So far an hepatocellular carcinoma due to vinyl chloride has not yet been observed in man. Its occurrence, however, has been suggested from the results of animal experiments. The connection of hepatocellular carcinoma with exposure to vinyl chloride is discussed.

LA - Eng

- 141 AU - Sarić M ; Kulčar Z ; Zorica M ; Gelić I
TI - Malignant tumors of the liver and lungs in an area with a PVC industry.
SO - Environ Health Perspect; VOL 17, 1976, P189-92
AB - The incidence of malignant tumors of the lung and bronchus and of cytologically confirmed primary malignant tumor of the liver was analyzed for a 4-yr period in a city with several factories, including a PVC industry. Prior to the study two cases of angio-sarcoma of the liver were diagnosed in workers employed in PVC production. The total incidence of analyzed tumors was only slightly higher than predicted. The tumors of the liver recorded did not show any dependence on place of work or residence. During the period of observation, malignant tumors of the bronchus (lung) were not recorded in the PVC industry. Their rate in the area in which the PVC industry is situated was approximately the same as that for the entire city area. The study does not indicate that the occurrence of malignant tumors other than angiosarcoma is associated with exposure to vinyl chloride.

LA - Eng

- 142 AU - Byr'en D ; Engholm G ; Englund A ; Westerholm P
TI - Mortality and cancer morbidity in a group of Swedish VCM and PCV production workers.
SO - Environ Health Perspect; VOL 17, 1976, P167-70
AB - The cohort of workers employed in a Swedish vinyl chloride/poly(vinyl chloride) plant since its start in the early 1940's has been followed for mortality and cancer morbidity patterns. Only 21 of the 771 persons could not be traced. Difficulties in establishing exposure levels at different work areas in the past makes an evaluation of dose-effect relationships impossible. A four- to fivefold excess of pancreas/liver tumors was found, including two cases later classified as angiosarcomas of the liver. The number of brain tumors and suicide do not deviate significantly from expected. Cardiovascular and cerebrovascular diseases, on the other hand, differ significantly from the expected. The discrepancies between previous reports on VCM/PVC workers and this report are discussed. The possible etiology of the cardiovascular deaths is also discussed.
LA - Eng
- 143 AU - Infante PF ; Wagoner JK ; Waxweiler RJ
TI - Carcinogenic, mutagenic and teratogenic risks associated with vinyl chloride.
SO - Mutat Res; VOL 41, ISS 1 spel. no, 1976, P131-41
AB - The data presented demonstrate clearly that vinyl chloride (VC) is related to a significant excess of mortality from cancer of the liver, lung and brain among workers occupationally exposed to VC. The risk of dying from cancer of the lymphatic and hematopoietic system also appears to increase with an increase in latency. These cancer sites could have been predicted by the animal bioassay conducted by Maltoni. With regard to the liver, even the histopathologic type of cancer (angiosarcoma) was observed first in experimental animals. A study of cancer mortality among populations residing proximate to VC polymerization facilities also demonstrated an increased risk of dying from CNS and lymphatic cancer. These latter findings raise cause for concern about out-plant emissions of VC, but without further study these cancers obviously cannot be interpreted as being related to out-plant exposure to VC. Various test systems now have elicited a positive mutagenic response to VC. Thus, our observations of a significant excess of fetal mortality among the wives of males, who were occupationally exposed to VC, raise public health concern that VC may be mutagenic in humans. With regard to the teratogenicity of VC, observations of a significant excess of children born with birth defects were reported among populations residing proximate to VC polymerization facilities. Additional epidemiologic study is needed to determine whether a repeated pattern of excessive numbers of children born with birth defects can be observed in other communities with VC polymerization facilities.
LA - Eng

00003114

PAGE 76

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

- 144 AU - Fox AJ ; Collier PF
TI - Low mortality rates in industrial cohort studies due to selection for work and survival in the industry.
SO - Br J Prev Soc Med; VOL 30, ISS 4, 1976, P225-30
AB - Occupational groups are often described as being relatively healthy because their mortality rates are lower than those of the national average. Although correct this confuses the issue for those who are interested in assessing the effects of exposure to a particular chemical. In a further analysis of data collected in a study of all men ever exposed to vinyl chloride monomer in the manufacture of polyvinyl chloride in Great Britain, three factors have been shown to contribute to the low mortality rates that were observed. The three factors: the selection of a healthy population for employment, the survival in the industry of the healthier men, and the length of time that this population has been pursued, have been quantified. The mortality experience within five years of entering this industry was shown to be as low as 37% of that expected; for circulatory disease and respiratory disease it was as low as 21%. There was a progressive increase in standardized mortality ratio with the length of time since entry so that the effect had almost disappeared 15 years after entry. To avoid confounding the selection effect with the survival effect the latter was measured by separating men who survived 15 years after entering the industry according to whether or not they were still in the industry after this period. Those who had left experienced an overall standardized mortality ratio some 50% higher than those still in the industry. This effect, although consistent in the age groups between 25 and 74 years and for all cause groups studied, was greatest in those aged between 25 and 44 years and for lung cancer and respiratory disease.
LA - Eng
- 145 AU - Blyghton AC
TI - The trade unionist's view of occupational cancer.
SO - IARC Sci Publ, ISS 13, 1976, P425-9
AB - The Transport and General Workers' Union (UK) has an active programme devoted to monitoring the health of its 1.8 million members. Files on members who died of bladder cancer after exposure to beta-naphthylamine go back to the late 1920's. From the same period came data on members suffering from asbestosis which included some cases of lung cancer before the industrial cause of the disease was recognized. These and other more recent examples including Nonox S and vinyl chloride amply justify the need for setting up registers of all workers who are at risk from industrial exposure. The scientific community has a responsibility for communicating data regarding hazards both to employers and employees who can then ensure that all who have been exposed can be notified and screened. The trade unions have a part to play in ensuring that industry accepts conditions of greater control under the new regulations in the United Kingdom. There must be a continuing tripartite discussion between industrial management,

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

R&S 102762

- trade unions and the responsible government official.
- LA - Eng
- 146 AU - Morl M
TI - [Liver tumors. Laparoscopic aspects]
SO - Fortschr Med; VOL 94, ISS 32, 1976, P1876-8
AB - A review is given on laparoscopic possibilities in the differentiation of tumours of the liver. Benign lesions are rare and usually discovered by chance. Primary cancer of the liver can be verified ante finem in a maximum of 40% of the cases. Characteristic is the endoscopic picture in the case of haemangiosarcoma after arsenic, Thorotrast, vinyl chloride (marked capsular fibrosis, net-like marking, "restless" surface of the liver). All the tumours need to be confirmed histologically. A tumour-like appearance is presented by echinococcus alveolaris and coarse-nodular granulomatous changes (sarcoidosis, lymphogranulomatosis, etc.).
- LA - Ger
- 147 AU - Berk PD ; Martin JF ; Young RS ; Creech J ; Selikoff IJ ; Falk H
AU - Watanabe P ; Popper H ; Thomas L
TI - Vinyl chloride-associated liver disease.
SO - Ann Intern Med; VOL 84, ISS 6, 1976, P717-31
AB - Although polyvinyl chloride has been produced from vinyl chloride monomer for more than 40 years, recognition of toxicity among vinyl chloride polymerization workers is more recent. In the mid 1960s, workers involved in cleaning polymerization tanks were found to have acro-osteolysis. In 1974, the same population of workers was found to be at risk for an unusual type of hepatic fibrosis and angiosarcoma of the liver. We describe two cases of vinyl chloride-associated liver injury, one of hepatic fibrosis and one of angiosarcoma. Histologic features of these lesions are similar to the hepatic fibrosis and angiosarcomas resulting from chronic exposure to inorganic arsenicals. Preliminary studies suggest that the toxicity of vinyl chloride may result from formation, during high-dose exposure, of active metabolites by mixed function oxidases of the liver. Epidemiologic studies indicate an increased incidence not only of liver disease, but also of cancers of the brain, lung, and possibly other organs.
- LA - Eng
- 148 AU - Whelan JG Jr ; Creech JL ; Tamburro CH
TI - Angiographic and radionuclide characteristics of hepatic angiosarcoma found in vinyl chloride workers.
SO - Radiology; VOL 118, ISS 3, 1976, P549-57
AB - Hepatic angiosarcoma, recently discovered in a large series of vinyl chloride workers, demonstrates characteristic angiographic and radionuclide changes. Tumors exhibiting central hypovascularity with puddling are usually surrounded by a peripheral stain. A negative peripheral defect is demonstrated on hepatic scan. Healing hepatic infarction secondary to wedged hepatic venography creates a false-positive lesion on angiography similar to angiosarcoma. Splenomegaly and systemic venous

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

hypertension develop in a number of these patients.
LA - Eng

- 149 AU - Mark L ; Delmore F ; Creech JL Jr ; Ogden LL II ; Fadell EH
AU - Songster CL ; Clanton J ; Johnson MN ; Christopherson WM
TI - Clinical and morphologic features of hepatic angiosarcoma in vinyl chloride workers.
SO - Cancer; VOL 37, ISS 1, 1976, P149-63
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 to 58 years (average 47.5 years). Their exposure time ranged from 4 to 27.8 years (average 16.9 years). The most common presenting symptoms were fatigue, weight loss, and abdominal pain. Hepatomegaly followed by splenomegaly were the most common physical findings. Biochemical profiles yielded variable results and proved to be of little value in the 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. The reduction of industrial chemical exposure has already been achieved and will hopefully eliminate this chemically related tumor in the future. There is, however, a significant group of previously exposed workers who will require careful monitoring to detect functional abnormalities of the liver and possible early neoplastic changes.
LA - Eng
- 150 AU - Withey JR
TI - Pharmacodynamics and uptake of vinyl chloride monomer administered by various routes to rats.
SO - J Toxicol Environ Health; VOL 1, ISS 3, 1976, P381-94
AB - Finding at least 2-3 ppm and occasionally as much as 10-20 ppm of vinyl chloride monomer in a wide range of foodstuffs has prompted concern for a possible human health hazard. The recognition of vinyl chloride as a carcinogen to humans in April 1974, following the discovery of angiosarcoma as the cause of death in at least 25 workers who had been engaged in the manufacture of polyvinyl chloride, enhanced this concern with respect to the presence of vinyl chloride monomer in foods. 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

R&S 102763

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

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 biexponential. 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 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. The precise kinetic coefficients that describe the distribution and elimination rates of vinyl chloride from the blood compartment were also determined from the blood concentration data after the administration of an intravenous dose of aqueous or vegetable oil solution.

LA - Eng

- 151 AU - Chabalko JJ ; Fraumeni JF Jr
TI - Blood-vessel neoplasms in children: epidemiologic aspects.
SO - Med Pediatr Oncol; VOL 1, ISS 2, 1975, P135-41
AB - In a search for etiologic leads to blood-vessel neoplasms, we examined 111 death certificates of U.S. children who died from 1960 to 1968 of angiosarcoma, hemangioendothelioma, and hemangiopericytoma and 127 medical records of similar cases from 12 institutes. The available data provided no leads to environmental agents (vinyl chloride, thorotrast, arsenic) that can produce vascular liver tumors in adults, but 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.

LA - Eng

- 152 AU - Trieff NM ; Corrigan GE
TI - Contemporary work-related environmental diseases.
SO - Tex Rep Biol Med; VOL 33, ISS 1, 1975, P107-44 (REF: 43)
AB - This paper is a general review of occupational diseases with particular emphasis on contemporary work-related diseases. Reasons for the difficulties in diagnosis and treatment of industrial disease are given. The basic principles of occupational health are reviewed. The particular occupational diseases discussed in detail are the clinical pneumoconioses, and the contemporary diseases: angiosarcoma from exposure to vinyl chloride and respiratory carcinoma from bichloromethyl ether exposure. Numerous other environmental hazards are mentioned. The role of the Occupational Safety and Health Administration (OSHA) is discussed, as is the role of the physician from the point of view of taking an appropriate medical history from an

00003118

PAGE 80

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

- occupational vantage and medical diagnosis of occupational disease. Attitudinal aspects are emphasized.
- LA - Eng
- 153 AU - Ludwig J ; Hoffman HN
 TI - Hemangiosarcoma of the liver. Spectrum of morphologic changes and clinical findings.
 SO - Mayo Clin Proc; VOL 50, ISS 5, 1975, P255-63
 AB - Analysis of four cases of hemangiosarcoma of the liver and review of the literature indicate that these tumors are either predominantly cystic and fairly well differentiated or are more solid and poorly differentiated. Well-differentiated hemangiosarcomas may resemble peliosis hepatis or other benign conditions. The tumor was associated disseminated intravascular coagulation and fibrinolysis syndrome in one of our cases. One of our patients had received thorium dioxide (Thorotrast) but none seemed to have been exposed to arsenicals or to vinyl chloride.
- LA - Eng
- 154 AU - Biersack HJ ; Lange CE ; Ebinger H ; Marsteller HJ ; Leibach WK
 AU - Veltman G ; Winkler C
 TI - [Sequential scintigraphy of liver and spleen in patients with polyvinyl chloride disease (author's transl)]
 SO - Dtsch Med Wochenschr; VOL 100, ISS 12, 1975, P615-7
 AB - Occurrence of severe liver damage including angiosarcoma in polyvinyl chloride production workers necessitates regular control investigations of liver and spleen. Radioisotope techniques with small irradiation doses which give valid results should be used. Investigations of 15 patients with PVC-induced liver disease showed that hepatic perfusion as demonstrated by ^{99m}Tc pertechnetate does not correlate with the uptake of sulphide colloid in the hepatic reticuloendothelial system. This provides evidence that in VC disease specific damage of the reticuloendothelial system of the liver occurs. Sequential scintigraphy also proved that the liver perfusion quotient can be considered as a measure of portal pressure. In practice this may be used for follow-up controls. Vascularized tumours described in VC disease can also be demonstrated by scintigraphy.
- LA - Ger
- 155 AU - Thomas LB ; Popper H ; Berk PD ; Selikoff I ; Falk H
 TI - Vinyl-chloride-induced liver disease. From idiopathic portal hypertension (Banti's syndrome) to Angiosarcomas.
 SO - N Engl J Med; VOL 292, ISS 1, 1975, P17-22
 AB - Histologic examination of liver tissue (eight autopsy and 18 biopsy specimens) and five spleens from 20 workers with vinyl chloride polymerization showed hepatic angiosarcomas in 15. In addition, a peculiar pattern of progressive portal-tract, inconspicuous intralobular and conspicuous capsular fibrosis was observed in the five workers without angiosarcoma, in all the seven patients with angiosarcoma from whom tumor-free portions of the liver were available, and in two tumor-free biopsies from patients subsequently found to have angiosarcoma. The fibrosis

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

was accompanied by splenomegaly. Hypertrophy and hyperplasia of both hepatocytes and hepatic and splenic mesenchymal cells were also seen. The histologic similarity to chronic inorganic arsenical poisoning, in which angiosarcomas also occur, and to idiopathic portal hypertension (Banti's syndrome) suggests that the latter syndrome at times results from unknown toxic, possible environmental, chemicals.

LA - Eng

- 156 AU - Maltoni C
TI - Carcinogenicity Of Vinyl-Chloride: Current Results. Experimental Evidence
SO - Advances in Tumor Prevention, Detection and Characterization, Vol. 3, pages 216-237, 7 references, 1976
AB - The carcinogenicity of vinyl-chloride (75014) monomer was investigated in rats, hamsters, and mice. Adult Sprague-Dawley-rats were exposed by inhalation 4 hours per day, 5 days per week, for up to 52 weeks to vinyl-chloride at doses from 0 to 10,000 parts per million (ppm). In some cases exposures were begun when rats were 19 weeks or 1 day old, or pregnant females were exposed beginning on gestation day 12. Wistar rats were also exposed to determine the effects of animal strain. Swiss-mice and male Golden-hamsters were exposed by inhalation to doses from 0 to 10,000ppm 20 hours per week for 30 weeks. Additionally Sprague-Dawley-rats ingested up to 3.33 milligrams per kilogram for 52 or 104 weeks. Tumors were induced in all three species, although the range of induced tumors varied extensively. In Sprague-Dawley-rats, liver angiosarcoma incidence was related to dose, increasing from 2 percent of animals inhaling 50ppm to 22 percent of those at the highest doses. Zymbal gland carcinomas were seen in animals inhaling 500ppm or more; 26 percent of those receiving 10,000ppm developed such tumors. Nephroblastomas affected approximately 9 percent of Sprague-Dawley-rats receiving 250ppm or more. A few cases of ossifying angiosarcomas, and tumors of the skin, mammary glands, forestomach, uterus, scrotum, ovaries, brain, salivary gland, neck, and Harderian gland were also seen. The incidence of angiosarcomas and nephroblastomas was increased with increasing exposure. In Wistar-rats, angiosarcomas showed a dose response effect similar to that in Sprague-Dawley-rats, but other tumor types were significantly reduced in this strain. Four extra hepatic angiosarcomas, a nephroblastoma, and four Zymbal gland carcinomas occurred in the offspring of dams exposed during pregnancy. Administered by stomach tube, vinyl-chloride induced angiosarcomas of the liver and other sites, as well as Zymbal gland carcinomas. The author concludes that vinyl-chloride is carcinogenic in doses as low as 50ppm, and acts transplacentally.

R&S 102766

- 157 AU - Anonymous
TI - Vinyl Chloride-Associated Liver Disease
SO - Annals of Internal Medicine, Vol. 84, No. 6, pages 717-731, 51 references, 1976
AB - Liver disease associated with exposure to vinyl-chloride (75014) is reviewed. Polyvinyl-chloride (9002862), the most widely used synthetic plastic, has been manufactured for more than 40 years by the polymerization of vinyl-chloride monomer gas. Toxicity among workers has only recently been recognized with the reports of hepatic fibrosis, splenomegaly and portal hypertension from Germany and the recognition of increased cases of hepatic angiosarcoma among workers. Specific case reports of the occurrence of hepatic fibrosis and angiosarcoma of the liver represent those being recognized. Workers found to be at risk of acroosteolysis in the 1960s are now being recognized as at risk for liver diseases. Tests of liver function have potential in identifying employees at risk of liver problems. Epidemiological studies have established that cancer induced by vinyl-chloride has a long period of clinical latency. Studies of the metabolism of vinyl-chloride suggest that its toxicity may result from the formation of active metabolites by the mixed function oxidases of the liver. The potential of the reactive products to bind with intracellular macromolecules requires further elucidation. The histological features of hepatic fibrosis induced by vinyl-chloride have been indicated as resembling those induced by chronic exposure to inorganic arsenicals. Angiosarcoma induced by vinyl-chloride appears to develop multicentrically, beginning with precursor lesions of sinusoidal cell proliferation and atypia. Again, there is a resemblance to the hepatic angiosarcomas induced by the inorganic arsenicals. The authors conclude that significant progress has been made toward clarification of the liver diseases resulting from vinyl-chloride exposure considering that only 1 year has gone by since first recognition.
- 158 AU - Hoffmann D ; Wynder EL
TI - Smoking And Occupational Cancers
SO - Preventive Medicine, Vol. 5, No. 2, pages 245-261, 105 references, 1976
AB - Epidemiologic evidence and experimental studies concerning the relative importance of tobacco smoking as a cofactor in occupational cancers are reviewed. Industrial carcinogens for which data is available for smokers and nonsmokers are examined: uranium (7440611), asbestos (1332214), nickel (7440020), arsenicals, chromate (11104599), and chloromethyl ethers. Epidemiological data demonstrates significantly higher risks of cancer for uranium miners who smoke than for nonsmoking miners; the increased yield of pulmonary tumors in hamsters simultaneously exposed to alpha radiation and benzo(a)pyrene (50328) support the possibility of such a synergistic effect. Epidemiologic findings are also given showing that asbestos induces mesothelioma of the pleura and peritoneum but not, by

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

itself, of the bronchus, but that cigarette smoke and asbestos dust combined are carcinogenic to the bronchial epithelium, and that their combined effect induces a higher incidence rate of bronchogenic carcinomas than cigarette smoke alone. Experimental data is lacking, but the strong absorptive powers of asbestos are suggested as a factor. Nickel compounds in cigarette smoke may play a role in tobacco carcinogenesis, but it is suggested that cigarette smoking was only a minor factor for earlier increased risk of lung cancer in nickel workers, for whom industrial hygiene is now much improved. No experimental studies are reported for combined effects of arsenic and smoking, but epidemiological studies suggest such a synergism. Similar connections are suspected for chromate but experimental evidence is lacking. Studies show bis-(chloromethyl)-ether in concentrations as low as 0.1 part per million induces bronchogenic carcinomas and esthesioneuroepitheliomas in rats, findings, substantiating epidemiologic investigations. Possible cocarcinogenicity of cigarette smoke and vinyl-chloride (75014), coke fumes, and coal fumes is also discussed. Effects of cigarette smoking on bladder cancer are considered. The authors conclude that future studies of occupational carcinogenesis must include detailed data on all factors that could affect the risk for a given cancer.

- 159 AU - Whelan JG Jr ; Creech JL ; Tamburro CH
TI - Angiographic And Radionuclide Characteristics Of Hepatic Angiosarcoma Found In Vinyl Chloride Workers
SO - Radiology, Vol. 118, pages 549-557, 32 references, 1976
AB - Angiographic and radionuclide characteristics of hepatic angiosarcomas found in vinyl-chloride (75014) polymerization workers were described. Liver scans were conducted on 1,180 workers in a vinyl-chloride polymerization facility (SIC-2821) in Louisville, Kentucky. Fifty of these individuals were subsequently followed with hepatic and splenic angiography, transjugular hepatic venography, venous pressure studies, and liver biopsies. Four workers were found to have hepatic angiosarcomas. The case histories were summarized. The patients worked at the facility for 12 to 20 years. Angiographic characteristics of the tumors included hypervascular changes around the periphery of the tumor, peripheral tumor skin, puddling of contrast agent extending from the mid arterial phase up to 34 seconds, and some degree of central hypovascularity within the tumor. Subcapsular fibrosis, portal fibrosis, sinusoidal dilatation and endothelial lining cell hyperplasia were associated with the tumors. Angiosarcomas appeared as negative defects on liver scans when gold-198, iodine-131 labeled rose-bengal or a technetium-99m-sulfur colloid were used. Most lesions appeared initially as a single focus. Half of the vinyl-chloride workers with tumors had splenic enlargement. Systemic venous hypertrophy developed in two of the cases.

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

- 160 AU - Holmberg B ; Kronevi T ; Winell M
TI - The Pathology Of Vinyl Chloride Exposed Mice
SO - Acta Veterinaria Scandinavica, Vol. 17, No. 3, pages 328-342, 25 references, 1976
AB - The effects of exposure to vinyl-chloride (75014) were studied in outbred albino-mice. Mice were exposed to 50 parts per million (ppm) or 500ppm by inhalation 6 hours a day, 5 days a week for 52 and 26 weeks, respectively. Weight was recorded for all exposed groups and a control group. Four of each sex from each group were killed and tissues were examined at 26 weeks. Four other animals were killed for examination after a year and other animals were examined at spontaneous death. Histological examinations were made of spleen, lung, liver, kidney, and brains and any visible tumors. Exposed animals did not gain weight as rapidly as controls and eventually lost weight. There were three tumors among 48 control animals. Of animals exposed to 50ppm, 71 percent developed tumors. Thirteen of this group had histologically benign alveologenic lung adenomas. Five of these had hemangiosarcomas in fat or other tissues. Inhalation of 500ppm induced multiple alveologenic adenomas in lungs of all animals. Eight of these had hemangiosarcomas of the abdomen. Only one angiosarcoma of the liver was noted and no liver fibrosis was found. The authors conclude that vinyl-chloride has a dose dependent carcinogenic effect on animals.
- 161 AU - Berk PD
TI - Vinyl Chloride-Associated Liver Disease
SO - Annals of Internal Medicine, Vol. 84, No. 717-731, (1976), 1976
AB - Case history, industrial screening, and epidemiologic information on liver diseases induced by exposure to polyvinyl-chloride (9002862) is reviewed. Histologic features of hepatic fibrosis and angiosarcoma in human patients are described. The authors conclude the toxicity of polyvinyl-chloride may result from formation, during high dose exposure, of active metabolites by mixed function oxidases of the liver. Epidemiologic studies indicate an increased incidence not only of liver disease, but only of cancers of the brain, lung, and possibly other organs.
- 162 AU - Anonymous
TI - Vinyl Chloride Toxicity And The Use Of PVC For Packaging Foodstuffs
SO - European Council of Chemical Manufacturers' Federations, Brussels, 68 pages, 9 references, 1976
AB - The possibility of a risk of carcinogenesis from ingestion of vinyl-chloride (75014) from food packaging is reviewed. The carcinogenicity of vinyl-chloride is summarized. The frequency of angiosarcomas of the liver is discussed for humans and animals. Absorption concentrations of vinyl-chloride in food are infinitesimally small and many orders of magnitude lower than current safe limits in production facilities. Assessment of risk has been extrapolated from incomplete data. In general, the presence of vinyl-chloride in foodstuffs does not constitute a

00003123

PAGE 85

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

hazard. Limits must be set on a technological, not toxicological, basis. In occupational situations where exposure is below 0.5 parts per million, vinyl-chloride is not considered hazardous. Concepts and principles of control are discussed. It is not possible to achieve a below detectable limit. Other limits depend on the accuracy and precision of measurement. Control may be exercised on the foodstuff or on the package. Current legislative positions are summarized for seven nations. Industry is able to operate a nominal maximum limit of 0.050 milligrams per kilogram. To achieve this in real terms requires limits of a few parts per thousand million. The authors conclude that public exposure to vinyl-chloride through foodstuffs is 100 to 500 times lower than exceptionally conservative estimates of safety.

- 163 AU - Adams GL
TI - Toxic Substance Control: Vinyl Chloride
SO - Masters Thesis, Sever Institute of Technology, Washington University, St. Louis, Missouri, 253 pages, 256 references, 1976
AB - The control of vinyl-chloride (75014) (VC) in industry is discussed. The physical and chemical properties of VC are reviewed, along with emission sources, occupational exposures, and industrial uses. Polyvinyl-chloride (9002862) physical and chemical properties, occupational exposures, emission sources, and fabrication processes also are described. The biological effects of VC exposure are described, such as acroosteolysis, cancer, hepatotoxicity, and mutagenicity, and possible mechanisms of action are considered. A historical review is included on the discovery and investigation of the toxicity of VC and general workplace exposures. Occurrences of angiosarcoma of the liver among exposed workers at a rubber company first reported around 1973 are noted. Steps taken to control workplace exposures to VC are described, including recommendations made and actions taken by the Manufacturing Chemists' Association and by various federal agencies concerning acceptable exposure limits and monitoring responsibilities. The technologies used to control VC emissions and exposures are discussed, and the economic impact of legislated control requirements is reviewed in relation to production rates, operating costs, and consumer costs. Proposed substitute polymers are listed. The contributions of science toward the control of toxic substances in general, and VC in particular, are discussed, along with the ability and willingness of both industry and the government to control worker exposures. The author concludes that the technologies exist to control occupational exposures to VC and other toxic substances, but delays have been caused by lack of information and lack of incentives and policies to foster effective control. These problems could be eliminated by establishing a central data system for toxic substances and by establishing public policies on balancing the risks, costs, and benefits of the use and control of toxic substances.

- 164 AU - Bolt HM ; Kappus H ; Kaufmann R ; Appel KE ; Buchter A ; Bolt W
TI - Metabolism of 14C-Vinyl Chloride In Vitro and In Vivo
SO - INSERM Symposia Series, Vol. 52, IARC Scientific Publications No. 13, pages 151-163, 32 references, 1976
AB - The metabolism of vinyl-chloride (75014) (VC) was investigated in rat liver microsomes and in Wistar-rats. Carbon-14 (C-14) labeled VC at a concentration of 140 parts per million was administered in atmosphere to rats for 5 hours. Binding of radioactivity to microsomes and metabolites to proteins were determined. Tissue homogenates were examined for metabolites and unchanged VC. Radioactivity of organs was determined. Rat liver microsomes with a reduced nicotinamide-adenine-dinucleotide-phosphate (NADPH) regenerating system were incubated in an atmosphere containing labeled VC. Incubations were also performed in a superoxide generating system. In microsomes, irreversible binding of labeled VC to albumin occurred in both the NADPH and the superoxide systems. In rats, significant amounts of radioactivity were irreversibly bound to liver microsomal protein but the majority was readily extractable from cytoplasm. The bulk of radioactivity was excreted in urine within 24 hours. Metabolites were irreversibly bound to lung, intestine, spleen, and liver and kidneys. Proteins were the major target for irreversible binding of VC metabolites to macromolecules. The authors conclude that the most important reaction in the carcinogenicity of VC is the irreversible binding to DNA and RNA.
- 165 AU - Baxter PJ
TI - Epidemiological Studies of PVC Manufacturers and Fabricators, and Primary Angiosarcoma of the Liver
SO - Proceedings of the Royal Society of Medicine, Vol. 69, pages 297-299, 1 reference, 1976
AB - Epidemiological survey procedures are described for polyvinyl-chloride (9002862) (PVC) manufacturers, PVC fabricators, and a retrospective study of primary angiosarcoma of the liver. For PVC manufacturers, the objective is to evaluate the effects of exposure in terms of mortality and cancer rates, and should include all past workers in every PVC factory as well as present and future workers. Workers alive at the start of the survey are identified and death certificates are then obtained. Statistical comparisons are to be made using sex and age standardized rates. For PVC fabricators, mortality and cancer rates in each sector of the industry are determined as to whether or not they are related to PVC. Samples of workers, their employment records, and exposures are monitored. Followup and analysis is similar to procedures used for PVC manufacturers. For the retrospective study of angiosarcoma, all death certificates with possible diagnosis of angiosarcoma are evaluated. All diagnosed cases of primary angiosarcoma of the liver are identified and verified, and the association of exposure to vinyl-chloride is evaluated. The verified cases of angiosarcoma are registered together with occupational histories

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

and medical records in order to obtain a true estimate of the incidence of angiosarcoma. The frequency of vinyl-chloride exposure to angiosarcoma cases are compared with unexposed workers. The author concludes that these procedures for epidemiological surveys provide a comprehensive assessment of risk of exposure to vinyl-chloride.

- 166 AU - Berk PD ; Martin JF ; Young RS ; Creech J ; Selikoff IJ ; Falk H
 AU - Watanabe P ; Popper H ; Thomas L
 TI - Vinyl Chloride-Associated Liver Disease
 SO - Annals of Internal Medicine, Vol. 84, No. 6, pages 717-731, 51 references, 1976
 AB - The effects of occupational exposure to vinyl-chloride (75014) were examined in two workers with liver injury. One case was a 30 year old male who had cleaned polymerization tanks for 5.5 years. A heptosplenomegaly with mildly elevated serum bilirubin and serum glutamic-oxalacetic-transaminase concentrations, and abnormal plasma bromsulphalein (BSP) retention were found. Intense portal fibrosis with bile ductular proliferation, capsular and intrasinusoidal fibrosis, activated sinusoidal lining cells, and marked anisocytosis hepatitis were evident on liver biopsy. An enlarged spleen was removed. Lymphoid and reticuloendothelial proliferation was found histologically. At followup 2.5 years later, physical examination was normal, but a mild restrictive pulmonary function was evident. All liver functions were normal. Nodules were again seen on biopsy. Bilirubin and BSP retention were normal. Bile acid disappearance test results were abnormal. The second case, a 42 year old male, worked for 20 years in the polymerization of vinyl-chloride to polyvinylchloride (9002862) (PVC). High alkaline-phosphatase and abnormal bilirubin concentration were observed. Liver cirrhosis or tumor was verified by angiogram and biopsy. Alcohol consumption had been heavy for 6 years. Surgery was rejected due to the liver cirrhosis. Adriamycin was given intravenously. With alcohol abstinence, liver function returned to normal. Two months later, the size of persistent lesions was unchanged. Liver function tests were normal except for BSP retention. Cyclophosphamide was administered, but the patient died 5 months later. Death was due to a ruptured cyst in the liver. Extensive angiosarcoma of the liver and metastases in the lymph nodes and lungs were found on autopsy. The authors conclude that vinyl-chloride associated hepatic fibrosis persists after the patient has been removed from exposure. Lesions may be quite extensive even though liver function tests have normalized.
- 167 AU - Makk L ; Dalmore F ; Creech JL Jr ; Ogden IL ; Fadell EH
 AU - Songster CL ; Clanton J ; Johnson MN ; Christopherson WM
 TI - Clinical and Morphologic Features of Hepatic Angiosarcoma in Vinyl Chloride Workers
 SO - Cancer, Vol. 37, No. 1, pages 149-163, 23 references, 1976
 AB - Fifteen cases of primary angiosarcoma of the liver among male workers exposed to vinyl-chloride (75014) (VC) were investigated. Data on duration of VC exposure, early symptoms and clinical

00003126

PAGE 88

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

findings, and biopsy and autopsy results were obtained and summarized. Subjects were 36 to 58 years old and had been exposed to VC for 4 to 28 years. Early symptoms were nonspecific and included fatigue, abdominal pain, and weight loss; two subjects were asymptomatic. Clinical laboratory findings were also nonspecific to this neoplasma. The gamma-glutamyltranspeptidase test was the most sensitive in detecting patients with liver lesions, but was shown to have a high false positive rate. Tumors were usually hemorrhagic, cystic, and necrotic with reactive fibrosis. Tumor extension to nearby tissues was found in four cases. Cases treated with chemotherapy or radiotherapy survived 5 to 22 months after onset. Untreated cases survived 2 to 8 months. The authors conclude that hepatic angiosarcoma development in these patients may be related to the higher VC concentrations prevalent in the polyvinyl-chloride industry in its early years.

- 168 AU - Smith PM ; Williams DMJ ; Evans DMD
 TI - Hepatic Angiosarcoma in a Vinyl Chloride Worker
 SO - Bulletin of the New York Academy of Medicine, Vol. 52, No. 4, pages 448-452, 2 references, 1976
 AB - Hepatic angiosarcoma was diagnosed in a 36 year old white male who had worked for 3.5 years as a cleaner of polymerization vessels in a factory where vinyl-chloride (75014) monomer (VCM) gas was processed. The patient was initially admitted to the hospital for the surgical treatment of a recurrent ulcer. On examination at this time, the only abnormal physical sign was a liver palpable to 6 centimeters. A year after this surgery, the patient showed no abnormal physical signs apart from the enlarged liver, although liver function tests showed a further rise in the serum alkaline phosphatase concentration and an elevated bilirubin value. Four months later, the patient showed dyspepsia, ascites, ankle edema, and jaundice and looked ill and wasted. Liver function tests were grossly abnormal, bilirubin continued to rise, and hepatic arteriogram revealed a widespread pathological circulation, with multiple areas of tumor blush suggestive of a highly vascular multicentric hepatic neoplasma. At necropsy, there was edema of both lungs and evidence of hemorrhages; the liver was greatly enlarged by a vascular tumor, and the spleen was very congested and firm. Microscopy showed replacement of much hepatic parenchyma by hemorrhagic and necrotic tumor tissue. The authors conclude that this case is remarkable because of the age of the patient, the brevity of the exposure period (3.5 as compared to an average of 16 years) and the short duration of the latent period (8 as compared to a mean of 17 years).

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

R&S 102774

- 169 AU - Maltoni C ; Lefemine G
TI - Carcinogenicity Bioassays Of Vinyl Chloride: Current Results
SO - Annals of the New York Academy of Sciences, Vol. 246, pages 195-218, 2 references, 1975
AB - Carcinogenicity bioassays of vinyl-chloride (75014) (VC) were examined. A series of 15 experiments studying the effects of VC administered through different routes at different concentrations, for varying periods of time by continuous or intermittent treatment, on different species and strains of animals was conducted. Experiments used mainly Sprague-Dawley-rats, Wistar-rats, Swiss-mice, and hamsters. Short term exposures up to 250 parts per million (ppm) VC were studied in rats. Long term exposures up to 10,000ppm VC were administered to determine exposure effects in rats, mice, and hamsters. An experiment was initiated to assess whether VC acted on tissues directly or through metabolites. In another experiment all animals were kept under observation until spontaneous death. All detectable gross pathological changes were recorded. All animals were autopsied, and histological examinations were performed. Results showed that different types of tumors can be present in the same animal. Zymbal gland carcinomas were bilateral. Nephroblastomas were often bilateral, metastasizing to the liver, spleen, lung, and brain. Angiosarcomas and angiomas were at more than one site in the same animal. Skin carcinomas in treated rats appeared to rise from sebaceous glands. Hepatomas in treated rats were usually well differentiated. Lung adenomas in treated mice were usually multicentric. Several tumors produced by VC, liver angiosarcomas, nephroblastomas and neuroblastomas, had never spontaneously occurred in rats. The authors conclude that VC produces tumors in experimental animals; the range of induced tumors varies between species. VC shows a dose/response relationship for angiosarcomas and nephroblastomas. A transplacental effect of VC is indicated.
- 170 AU - Holmberg B ; Molina G
TI - The Industrial Toxicology Of Vinyl Chloride. A Review
SO - Work, Environment, Health, Vol. 11, No. 3, pages 138-144, 49 references, 1974
AB - The industrial toxicology of vinyl-chloride (75014) is reviewed. Since the discovery that vinyl-chloride is a carcinogen in humans, the chemical has caused great concern in the area of occupational hygiene. The physical properties of vinyl-chloride and its industrial use as a monomer in the manufacture of plastics are outlined. In 1973, the threshold limit value (TLV) was in the range of 10 to 500 parts per million (ppm). In the United States the TLV for vinyl-chloride is 200ppm. Recently the TLV for vinyl-chloride was reduced to 1ppm for 15 minutes in view of its carcinogenicity; the upper limit is 5ppm. Studies of industrial facilities and the contamination of vinyl-chloride in these areas are described. The acute and chronic toxicity of vinyl-chloride is discussed. Cancer of the liver caused by acute

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

exposure to vinyl-chloride is characterized by angiosarcoma. Epidemiological studies on liver cancer caused by the chemical in various countries are summarized. Toxicity studies in animals are described. The authors conclude that vinyl-chloride exposure occurring in polyvinyl-chloride production facilities is a serious health hazard.

- 171 AU - Lloyd JW
TI - Angiosarcoma Of The Liver In Vinyl Chloride/Polyvinyl Chloride Workers
SO - Journal of Occupational Medicine, Vol. 17, No. 5, pages 333-334, 1975
AB - Cases of angiosarcoma of the liver in vinyl-chloride (75014) and polyvinyl-chloride (9002862) workers are reviewed. In January, 1974, three cases of angiosarcoma of the liver were reported among employees of a single vinyl-chloride polymerization facility. Subsequently 29 additional cases were recognized from the United States and nine other nations. All but three were diagnosed within the 7 years preceding 1975. An exact estimate of the incidence of angiosarcoma of the liver among polymerization workers cannot be determined but it is apparent that these workers are at high risk. About 5,600 workers are currently employed at 36 facilities in the United States. All the facilities from which angiosarcoma of the liver have been reported have been in operation more than 25 years. So far, 15 cases of liver angiosarcoma have been reported in the United States. Nine cases have been found in a facility employing fewer than 300 workers. The average latent period from first exposure to diagnosis is about 19 years. Consequently, most cases are appearing in the older facilities. It appears that these workers are also at high risk for other malignant neoplasms. Cases of angiosarcoma have been reported in other workers with exposure to vinyl-chloride. The relative youth of these workers in comparison with workers in the general population with liver cancer suggests a common etiology although the cause and effect relationship to vinyl-chloride exposure cannot be established. The author concludes that polymerization workers may not be the only industrial population at risk from exposure to vinyl-chloride or polyvinyl-chloride.
- 172 AU - Viola PL
TI - Vinyl Chloride Disease
SO - Medicina del Lavoro, Vol. 65, No. 3-4, pages 81-99, 45 references, 1974
AB - The toxic effects of vinyl-chloride (75014) (VC) are reviewed. The physicochemical properties of VC are described. It is noted that commercial grade VC contains 0.1 to 3 percent impurities, consisting of chlorinated hydrocarbons. The effects of human exposure to VC are described. Acute exposure causes general malaise, headache, dizziness, asthenia and, occasionally, nausea, vomiting, and chills. Concentrations of 100,000 parts per million can cause unconsciousness, narcosis, and death due to cardiorespiratory insufficiency. Chronic poisoning results in

R&S 102775

00003129

PAGE 91

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

asthenia, dizziness, digestive disturbances, pathological changes in the bone structure of the hands, circulatory disturbances of the extremities, liver enlargement, and impaired hepatic function. Histopathological changes induced by VC include degenerative changes of collagen bundles, elastic fibers, peripheral arteries, bone structure, and hepatic cells. Liver cell changes resemble those for chronic hepatitis. Experimental animal studies are summarized. It is noted that rats exposed to VC vapor develop malignant tumors of the skin, lungs, bone, liver, and intestine. The occupational health aspects are discussed. The author recommends periodic electrocardiogram examinations and monitoring of the urine and liver function for all exposed workers. (Italian)

- 173 AU - Block JB
 TI - Vinyl Chloride And Angiosarcoma
 SO - Journal of the Kentucky Medical Association, Vol. 72, No. 9, pages 483-485/505, 31 references, 1974
 AB - The relationship between occupational exposure to vinyl-chloride (75014) (VC) and angiosarcoma of the liver is reviewed. Seven confirmed cases of the disease among VC workers in a Kentucky factory are reported. Pathogenesis of this rare type of tumor is discussed. Early diagnosis is considered difficult if not impossible because of the insidious onset and silent course of the tumor. Liver function tests are shown to be of little value in screening against angiosarcoma because extensive liver damage must occur before there is significant functional impairment. Alpha-fetoprotein is suggested as a possible screening test for VC workers, but its value has not yet been established. Photoscanning and arteriography are valuable for identifying the tumor and planning for surgery. Biopsy is not recommended because the vascular nature of the tumor increases the possibility of hemorrhage. Surgery is viewed as the only cure for carcinoma of the liver but is successful only when the lesion is well localized. Radiation therapy and chemotherapy are considered palliative only and do not significantly prolong survival time. The author recommends that any VC worker exhibiting symptoms of gastric ulcer be examined for possible angiosarcoma of the liver.
- 174 AU - Anonymous
 TI - Standard Support And Environmental Impact Statement: Emission Standard For Vinyl Chloride
 SO - Office of Air Quality Planning and Standards, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina, NTIS PB-249-703, Report No. EPA-450/2-75-009, 450 pages, 46 references, 1975
 AB - The establishment of an emission standard for vinyl-chloride (75014) from ethylene-dichloride (107062) and polyvinyl-chloride (9002862) facilities is reviewed. Vinyl-chloride is implicated as a cause of angiosarcoma, other cancers, and a number of noncarcinogenic disorders in humans with occupational exposure and in animal studies. Extrapolation from these studies

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

contribute to the classification of vinyl-chloride as a hazardous air pollutant. Nine basic sources of emissions including fugitive emissions, reactor opening loss, stripper losses, monomer recovery systems, slurry blend tanks, centrifuges, dryers, bagging and bulk resin storage areas, and safety relief valve discharges from reactors are discussed. Engineering measures which can be used to control vinyl-chloride emissions are described for each source. Purging, ventilation, adsorbers, incineration, and refrigeration are a few of the techniques mentioned. The primary and secondary impacts of alternative controls are discussed. The major secondary impacts of the controls on air, water, solid waste, noise, radiation, and energy are detailed. Economic impacts of controls are analyzed. Cost analyses of alternative emission control systems are discussed. The rationale for selecting the emission sources, emission limits, testing, reporting, and recordkeeping requirements included in the proposed standards is presented. The proposed standard would limit employee exposure to 1 part per million (ppm) with a ceiling of 5ppm during an 8 hour work day. In addition, requirements for monitoring, protective clothing, regulated areas, and respiratory protection will be included in the proposal.

- 175 AU - Holder BB
TI - Mortality Studies Of Vinyl Chloride Workers
SO - Chemicals, Human Health and the Environment, Vol. 1, pages 90-98, 1975
AB - Mortality due to malignancy was studied among 594 vinyl-chloride (75014) workers exposed between 1942 and 1968. Exposure categories were rated as low, intermediate, and high based on exposure to less than 22 parts per million (ppm) per 8 hour time weighted average (TWA), 25 to 200ppm, and 200 to 300ppm, respectively. Duration of exposure was classified as less than 1 year and 1 year and over. Mortality findings for malignancy were compared with deaths expected based on national averages. Dose response relationships were estimated. A subgroup of those exposed to arsenicals in the past was considered separately. Observed deaths among all workers were 91 percent of expected deaths. Of ten deaths among workers exposed to arsenicals and vinyl-chloride, seven were due to malignancy. Thirteen malignancies were found among workers studied after excluding those exposed to arsenicals; 9 of the 13 were in the high exposure groups, and 8 of these 9 were found in those with more than 15 years of exposure. The distribution of malignant neoplasms suggested a dose response relationship. No angiosarcomas of the liver were found. The author concludes that in those exposed above 200ppm TWA there is a statistically significant increase in overall malignancy. No adverse effect in terms of malignancy occurred at exposure below 200ppm TWA.
- Dow*

R&S 102777

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

- 176 AU - Anonymous
TI - Vinyl Chloride
SO - IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man, Vol. 7, pages 291-320, 71 references, 1974
AB - Chemical and physical properties and uses and hazards of vinyl-chloride (75014) are reviewed. Worldwide production and trade of vinyl-chloride-monomer is discussed. The product is used in a number of household and consumer goods and packaging materials. It is no longer used as an aerosol propellant, a risk to the public having been identified by the government. The dangers of occupational exposure have been recognized for some time. Up until 1974 1300 milligrams per cubic meter of air were allowed but since 1940, the standard has been dropped to allow employee exposure to no traces detectable by approved analytical methods. Vinyl-chloride can be an air pollution problems as caused by emissions from a manufacturing facility. It has been banned in containers for alcoholic beverages though it is still used in other food packaging materials. Analysis of concentrations of vinyl-chloride can be by thin layer chromatography, infra red spectroscopy, and gas and gas liquid chromatography. Carcinogenicity has been studied extensively in animals. Among tumors produced there have been angiosarcomas of the liver. Chemical signs in humans of chronic vinyl-chloride exposure include Reynaud's Syndrome and acroosteolysis, and degeneration of the finger tips. Expected cases of angiosarcoma of the liver are far exceeded by those found in vinyl-chloride workers. The authors conclude that vinyl-chloride is carcinogenic in mice and rats, and that, in humans, there is a casual relationship between vinyl-chloride and angiosarcoma of the liver. Production, use, occurrence, and hazards of vinyl-chloride polymers and vinyl-chloride/acetate copolymers need also be considered.
- 177 AU - Anonymous
TI - Chronic Vapor Inhalation Toxicity Study With Vinyl Chloride (Ethylene Derived) In Albino Rats, Albino Mice And Golden Hamsters
SO - Manufacturing Chemists Association, Report No. IBT-663-03222, 96 pages, 1975
AB - Data tables are presented from a study of the effects of vinyl-chloride (75014) exposure in mice, rats, and hamsters. The animals were exposed for up to 2 years to vinyl-chloride vapor; specific exposure concentrations and schedules are not included. Some animals were killed during exposure, and others were maintained after exposure for observation. The data in this report covers 23 months. Information is included on the following parameters: mean body weight; mortality rates; leukocyte and erythrocyte count, hemoglobin, and hematocrit; numbers of lymphocytes, monocytes, eosinophils, and basophils; and tumor incidence in liver, spleen, lung, skin, and miscellaneous organs.

00003132

PAGE 94

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

- 178 AU - Moore JW
TI - The Vinyl Chloride Story
SO - Chemistry, Vol. 48, No. 6, pages 12-16, 8 references, 1975
AB - The carcinogenic, mutagenic, and teratogenic effects of vinyl-chloride (75014) (VC) are reviewed. Rats exposed to VC in air develop liver cancer; epidemiological studies show that workers engaged in the polymerization of polyvinyl-chloride (9002862) (PVC) develop angiosarcoma of the liver. A cause and effect relationship between VC and human angiosarcoma is generally accepted. High rates of lung cancer and brain cancer are also recorded among VC workers. The early detection of the carcinogenic effect of VC is hampered by its long latent period which averages 19 years, with a range of 15 to 40 years. Chronic exposure is not necessary, although there is evidence that increasing the dose of the carcinogen increases the incidence of the disease. However, the detection of VC induced cancer is facilitated by the rarity of the condition, so that even a single case is highly noticeable. Furthermore, PVC workers constitute a well defined group with well known exposure to VC.
- 179 AU - Warren HS ; Huff JE
TI - Vinyl Chloride Monomer: A Literature Condensation
SO - Toxicology Information Response Center, Oak Ridge National Laboratory, Oak Ridge, Tennessee, pages 11-32, 33 references, 1975
AB - The hazards of vinyl-chloride-monomer (75014) (VCM) are reviewed. The physicochemical properties of VCM are summarized. The production and uses of VCM are discussed. Potential routes of exposure are considered. The chief source of environmental and occupational exposure to VCM is in the manufacturing process, particularly during polymerization. Consumer contact with VCM occurs primarily through the use of fabricated polyvinyl-chloride (9002862) products. VCM has also been used as an aerosol propellant. It is noted that a 30 second release of VCM aerosol would result in a VCM concentration of 400 parts per million (ppm) in the air of a closed room. Leakage of unreacted VCM from finished products, such as food packaging, water conduit and pipe linings, floor coverings, and wearing apparel, is described as significant. The biological effects of VCM exposure are discussed. Human effects are considered. Acroosteolysis is described as a common result of VCM intoxication. The carcinogenic activity of VCM is discussed. Animal studies are cited that show that VCM induces angiosarcomas in the liver. Cases of liver angiosarcoma have occurred in workers exposed to VCM. Current standards are discussed. The current OSHA standard is 1ppm for an 8 hour time weighted average and 5ppm peak exposure for any 15 minute period.

- 180 AU - Delorme F ; Makk L
TI - Angiosarcomas Of The Liver Among Workers Exposed To Prolonged Contact With Vinyl Chloride-Morphological Description Of The Lesions
SO - L'Union Medicale du Canada, Vol. 104, No. 12, pages 1836-1844, 6 references, 1975
AB - The morphological features of neoplastic and nonneoplastic lesions were studied in workers exposed to vinyl-chloride (75014). Pathological examinations were made of 18 cases of liver angiosarcoma among workers exposed to vinyl-chloride for an average of 17 years. Tumors presented specific characteristics in development, histology, and behavior. Within the hepatic parenchyma, a certain number of benign, nontumorous modifications appeared to precede tumor development. The chronological sequence of hepatic lesions caused by vinyl-chloride seemed to act on a sinusoidal cell with multiple potentialities, later transformed and activated, which resulted in appearance of perisinusoidal fibrosis and proliferation of sinusoidal cells. Proliferating sinusoidal cells were transformed, yielding pronounced atypia or dysplastic and neoplastic cells that formed a tumor with morphological aspects resembling an angiosarcoma. The authors conclude that the connection between angiosarcoma of liver and vinyl-chloride represents an important step for researchers and clinicians concerned with noxious effects of modern chemicals on humans. (French)
- 181 AU - Turchi G
TI - Environmental Mutagenesis: Coinciding Scientific and Social Welfare Problems
SO - Atti Associazione Genetica Italiana, Vol. 20, pages 46-47, 1975
AB - The mutagenicity of vinyl-chloride (75014) (VC) is reviewed. Studies on the effects of VC on microorganisms are cited. The danger of exposure to VC by large numbers of workers is stressed. Diagnosis of 24 cases of angiosarcoma of the liver is noted among exposed workers. The difference between determination of environmental mutagenesis and research based on acquisition of data is discussed. The need for interdisciplinary studies due to the multiple aspects of the VC exposure problem is stressed. The author concludes that the VC study serves as a model for the application of research to specific problems to be examined and confronted on a wider scale; the scientific area is only one phase of the efforts. The value of joint action consists of establishment of a basis for more consistent and effective collaboration aimed at global intervention to settle problems of the occupational environment. The VC information is significant because of the involvement of workers in the synthesis, polymerization, and transformation of VC into a finished product and their concomitant exposure to its mutagenic and carcinogenic properties. (Italian)

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

- 182 AU - Bartsch H ; Montesano R
TI - Mutagenic and Carcinogenic Effects of Vinyl Chloride
SO - Mutation Research, Vol. 32, No. 2, pages 93-113, 100 references, 1975
AB - The toxicology of vinyl-chloride-monomer (75014) (VCM) in humans is reviewed. Liver damage and acroosteolysis (a sclerotic syndrome) is discussed as the major nonneoplastic disease seen in humans. The neoplastic disease, angiosarcoma is reported to occur only in persons exposed to VCM. Carcinomas of the brain and lungs have also been reported in persons exposed to VCM. Chromosome aberrations in workers exposed to VCM, and experimental evidence of the mutagenic effects of VCM are thoroughly described. The possible metabolic routes of VCM in experimental animals are considered. Available data concerning the biological hazards of VCM show that the compound is toxic, mutagenic, and carcinogenic in humans, as well as in animals. The various adverse biological effects appear to be dependent on the metabolic conversion of VCM into chemically reactive metabolites. Polymerization workers are at a very high risk of developing angiosarcoma of the liver. Another potentially dangerous source of human exposure is in food and beverages packed in polyvinyl-chloride (9002862) containers. Since knowledge of chemical carcinogenesis cannot allow the establishment of a safe exposure concentrations for VCM, every effort should be made to prevent human exposure, and therefore minimize the risk.
- 183 AU - Janerich DT ; Lawrence CF
TI - Epidemiological Strategies for Identifying Carcinogens
SO - Mutation Research, Vol. 33, pages 55-63, 20 references, 1975
AB - The current status of the epidemiological approach to the study of occupational cancer is reviewed. The limitations of the epidemiological approach, and the social implications of experimental intervention to the study of human cancers is described. A detailed examination of investigative procedures which resulted in the discovery of an association between diethylstilbesterol (56531) (DES) to vaginal cancer in adolescents due to maternal ingestion of DES during pregnancy is reported. Sufficient epidemiologic data has now been accumulated to show that the timing of the prenatal exposure to DES is an important modifying risk factor in this disease. Examples of other epidemiologic studies such as intrauterine X-ray exposures (which increase the risk of leukemia during the first decade of life) and vinyl-chloride (75014) (which induces angiosarcoma of the liver) are reported. Systematic surveillance programs for the detection of environmentally induced cancers, and continual monitoring of birth defects in New York State are specified. A mathematical model for analyzing cancer data is presented, and results of the analyses with reference to colon, pancreatic, and gall bladder cancers is reported. Major alternative approaches for conducting epidemiologic studies are offered. The prospective and retrospective cohort methods are recommended.

R&S 102781

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

The authors suggest that epidemiology studies should be used to complement and supplement laboratory or clinical findings, and should involve the participation of an interdisciplinary task force.

- 184 AU - Alrenga DP
TI - Primary Angiosarcoma of the Liver
SO - International Surgery, Vol. 60, No. 4, pages 198-203, 50 references, 1975
AB - The clinical and experimental literature concerning primary angiosarcoma of the liver is reviewed. Incidence, etiology, clinical features, pathological findings, and related conditions are described. The best known causative agent of hepatic angiosarcoma is thorium-dioxide (1314201). Other causative agents are gamma radiation, arsenic (7440382), and vinyl-chloride (75014). Thorium-dioxide has been used for arteriography, chiefly cerebral angiography. Angiosarcoma has comprised slightly more than one third of all reported cases of thorium-dioxide induced liver malignancies. Hepatic angiosarcoma, otherwise a rare tumor, has become an important issue in environmental pathology after being discovered in industrial workers exposed to vinyl-chloride. At present, about 6,000 workers are involved in producing vinyl-chloride and related products (SIC-3079). The consumer public has been exposed to a vast array of polyvinyl-chloride (9002862) based products for about three decades. In addition, about 300 million pounds of vinyl-chloride gas escapes annually into the atmosphere in the United States. Treatment and clinical behavior of patients with angiosarcoma are discussed. The author concludes that angiosarcoma of the liver has an unfavorable prognosis once it is discovered.
- 185 AU - Anonymous
TI - Vinyl Chloride and Cancer
SO - British Medical Journal, Vol. 1, No. 5908, pages 590-591, 11 references, 1974
AB - The possible association between exposure to vinyl-chloride (75014) and angiosarcoma of the liver is discussed. The need for simple, inexpensive tests of the carcinogenicity of molecules is emphasized. Studies are cited which implicate vinyl-chloride in angiosarcoma of the liver and in a sclerotic syndrome which has been called vinyl-chloride disease. The manufacture of polyvinyl-chloride (9002862) (PVC) is described, and opportunities for vinyl-chloride exposure during PVC manufacture are noted. Although PVC should not be regarded as a carcinogen, PVC contains traces of monomeric vinyl-chloride which may be liberated on heating. The possibility of screening all old and new substances for carcinogenicity is limited by the lack of trained personnel or facilities, the expense of animal tests, and impurities and variability in batches of industrial chemicals. Carcinogenicity testing using mutagenesis of microorganisms in-vitro and unscheduled synthesis of DNA in-vivo are cited as alternatives in cancer determination.

R&S 102782

00003136

PAGE 98

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

- 186 AU - Anonymous
TI - Report of a Working Group on Vinyl Chloride
SO - International Agency for Research on Cancer, Report No. 74/005, Lyon, France, pages 1-55, 70 references, 1974
AB - The effects of vinyl-chloride (75014) (VC) on man are reviewed. Experimental evidence of VC carcinogenicity, the pathology of lesions in humans, and occupational and nonoccupational VC exposures are discussed. Epidemiological studies and reports for 13 cases of angiosarcoma are described. Confirmed cases of liver angiosarcomas among workers exposed to VC or polyvinyl-chloride (9002862) (PVC) are tabulated. Cancer registries as an epidemiological resource are considered. The need for international coordination is stressed for the epidemiology, toxicology, industrial hygiene, and analytical methods connected with the risk of VC. There is a need for improvement of working conditions in VC and PVC factories and to eliminate or reduce exposures. Recommendations of the working committee include: setting up a clearinghouse for collection and dissemination of VC information; establishing a panel of pathologists to review histological material from exposed workers and to maintain a library of duplicate and reference sections; coordinating epidemiological studies; and, evaluating screening techniques to identify and diagnose VC related conditions. Chemical and physical data; production, use, occurrence and analysis; biological data for evaluation of carcinogenic risk to man; and comments on human and animal data are appended.
- 187 AU - Anonymous
TI - Vinyl Chloride, P.V.C., and Cancer
SO - The Lancet, Vol. 1, No. 1870, pages 1323-1324, 6 references, 1974
AB - The carcinogenic effects of vinyl-chloride (75014) are reviewed. A case is reported of a 71 year old male who worked as a polyvinyl-chloride (9002862) (PVC) processor for 20 years, and died of angiosarcoma of the liver. Various experiments are cited in which rats develop cancers in acoustic duct, lungs, bones, and other sites after exposures to high concentrations of vinyl-chloride. The establishment of exposure standards for vinyl-chloride in PVC manufacturing facilities is discussed, as is the formulation of a guidance document for PVC processors. The mechanism of vinyl-chloride exposure in PVC manufacture is described. Unreacted vinyl-chloride present in newly manufactured PVC may be released during various stages: in storage or upon heating during manufacture; during compounding processes such as dry blending, roll mill compounding, extrusion compounding, paste mixing; and during fabrication processes, such as extrusion, colandering, and paste spreading. Carefully planned ventilation is recommended at appropriate locations in PVC processing facilities. The need for information is stressed for the safety of PVC food wrapping materials. Reports of intermittent heavy exposure to vinyl-chloride resulting in the development of angiosarcomas are presented. Exposures ranged from 12 to 27 years and most dated back to the early days of PVC

00003137

PAGE 99

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

manufacture, before many health hazards were recognized. The author concludes that chemical manufacturers cannot assume that a chemical is carcinogenically safe. Systematic evaluation of industrially used chemicals is necessary for the protection of workers.

- 188 AU - Heath CW Jr ; Falk H ; Creech JL Jr
 TI - Characteristics of Cases of Angiosarcoma of the Liver Among Vinyl Chloride Workers in the United States
 SO - Annals of the New York Academy of Sciences, pages 231-236, 3 references, 1975
 AB - Thirteen cases of liver angiosarcoma among workers occupationally exposed to vinyl-chloride (75014) were detailed. The relationship of vinyl-chloride exposure was established because of the otherwise rare occurrence of this cancer. The age range of the 13 workers was from 36 to 60 years at diagnosis, and the exposure to vinyl-chloride prior to diagnosis ranged from 12 to 29 years. Many of the cases were not diagnosed prior to autopsy. Abnormalities in liver function tests were not clear until the terminal phase of illness. Symptoms of the illness varied greatly, and included abdominal mass, gastrointestinal bleeding, fatigue, and weight loss. No abnormal findings were detected in two cases. In addition, three or four vinyl-chloride workers who developed nonmalignant liver disease required splenectomies. The authors conclude that any industrial exposure to vinyl-chloride-monomer is potentially harmful, with the possibility of inducing hepatic fibrosis and eventually angiosarcomas. Liver function tests are not good indicators in the early stages of the disease.
- 189 AU - Warren H ; Huff JE
 TI - Health Effects of Vinyl Chloride Monomer. An Annotated Literature Collection
 SO - Environmental Health Perspectives, Vol. 11, pages 251-319, 1975
 AB - A compilation of the literature concerning the health effects of vinyl-chloride-monomer (75014) (VCM) is reviewed. The deaths of four vinyl-chloride polyvinyl-chloride (9002862) (PVC) workers from angiosarcoma of the liver are discussed in terms of the intensive epidemiological and toxicological researches conducted as the result of those cancers. VCM is described as a colorless gas with a sweet odor, which is produced at 5 billion pounds per year. The polymer, PVC, is a powdery white crystal that forms the basis for a vast plastics industry with an annual growth of more than 14 percent. The reactive VCM is suspected as the toxic agent and carcinogen; the point of greatest worker exposure is in the polymerization processes. Hand cleaning of polymerization reactors has been established as a causal factor of acroosteolysis, a symptom of vinyl-chloride disease, that appears among reactor cleaners. Improvements in processing procedures, and the control of monomer losses are noted. An OSHA standard for an exposure limit of 1 part per million (ppm) over an 8 hour period and a ceiling of 5ppm over any period not exceeding 15 minutes is cited for VCM. Annotated literature compiled on the

health aspects and some historical background of vinyl-chloride, which is a part of the data base of Oak Ridge National Laboratory's Information Center, is presented.

- 190 AU - Selikoff IJ ; Hammond EC
TI - Workshop on Toxicity of Vinyl Chloride-Polyvinyl Chloride
SO - Transactions of the New York Academy of Sciences, Vol. 37, pages 59-61, 1975
AB - Topics discussed at the New York Academy of Sciences Workshop on the Toxicity of Vinyl-Chloride (75014) and Polyvinyl-Chloride (9002862) are reviewed. A study involving clinical manifestations of vinyl-chloride exposure in 70 individuals is cited. Reference is made to screening procedures used in a clinical survey of workers employed by the Goodrich Rubber Company. Data from a morbidity study conducted by the American Cancer Society and the Mount Sinai School of Medicine involving a polymerization facility is presented. The review cites an analysis done on clinical and occupational histories of cases of liver hemangiosarcoma in the United States. Animal carcinogenicity bioassays of vinyl-chloride done in Italy and the United States are also noted. The review refers to a seminar regarding possible metabolic pathways of vinyl-chloride and their relationship to human cancer. The possible extension of vinyl-chloride health effects from the workplace into the community is also considered. The authors conclude that the conference was a milestone in the history of occupational and environmental health. They emphasize the fact that the carcinogenic effects from vinyl-chloride were not identified until 40 years after its commercial polymerization, and speculate on the backlog of diseases that may continue for decades.
- 191 AU - Anonymous
TI - Report of a Working Group on Epidemiological Studies on Vinyl Chloride Exposed People
SO - World Health Organization International Agency for Research on Cancer, IARC Internal Technical Report, No. 75/001, 15 pages, 4 references, 1975
AB - Data presented and discussed at a meeting of the International Agency for Research on Cancer (IARC) was reported. The working group was concerned with epidemiological studies on persons exposed to vinyl-chloride (75014) (VC). A total of 43 cases of angiosarcoma of the liver were reported; 37 of these were polymerization workers, 2 were fabrication workers, and 2 were exposed to vinyl-chloride-monomer. In addition, two cases occurred in persons with no occupational exposure to VC, but exposure to polyvinyl-chloride (9002862) (PVC) material. Thirteen epidemiological studies currently in progress in several countries including Italy, France, United Kingdom (UK), and the United States (US), were discussed. The data collected to date indicated an excess of brain and lung tumors among PVC workers. The UK and US established review panels of pathologists, and nationwide registers of angiosarcomas of the liver. The IARC committee stressed the responsibility of industry for maintaining

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

an appropriate system of records of exposure and medical status of their workers. They also stated that this investigation could serve as a prototype for future collaborative studies on occupational cancer.

- 192 AU - Seymour RB
TI - The VCM-PVC Syndrome
SO - Australian Plastics and Rubber, Vol. 25-26, Nos. 12-1, pages 9-11, 1974
AB - The dangers associated with the manufacture of polyvinylchloride (9002862) (PVC) and the efforts of manufacturers to limit these dangers are examined. Statistics on the manufacture of PVC, and its vinyl-chloride-monomer (75014) (VCM) are provided. It is estimated that more than 100,000 metric tons of VCM and 25 metric tons of PVC are discharged annually into the environment in the United States. It is now recognized that VCM in concentrations greater than 50 parts per million is a carcinogen. Research into the adverse health effects of VCM is reviewed. Russian results indicating hepatitis like changes in the livers of PVC workers are cited. International research on the incidence of malignant tumors in the livers of rats exposed to high concentrations of VCM is discussed. However, it is noted that PVC is an essential product in modern technology. In British manufacturing facilities, airborne concentrations of VCM have been reduced from 2000 to 150 parts per million in the past 20 years. Nevertheless, a total of 24 deaths of VCM or PVC workers throughout the world have been reported. Liver defects resulting from exposure to PVC or VC, including angiosarcoma of the liver are described. Reports on the prevalence of lung, brain, and liver cancer, and liver and lung abnormalities are cited. Recent experiments involving rat exposures to various products related to PVC are summarized.
- 193 AU - Falk H ; Creech JL Jr ; Heath CW Jr ; Johnson MN ; Key MM
TI - Hepatic Disease Among Workers at a Vinyl Chloride Polymerization Plant
SO - Journal of the American Medical Association, Vol. 230, No. 1, pages 59-63, 10 references, 1974
AB - The incidence and correlates of hepatic disease were studied among workers at a vinyl-chloride (75014) polymerization facility in Louisville, Kentucky. Because of concern aroused by the discovery of hepatic angiosarcoma in workers, a medical screening program aimed at detecting hepatic abnormalities was instituted, and all employees, whether exposed to polyvinyl-chloride (9002862) (PVC) polymerization products or not, were examined. As a result of this program, two additional cases of angiosarcoma of the liver were diagnosed, both in PVC workers. Among the seven patients with angiosarcoma, ages at diagnosis ranged from 36 to 58 years. Among the four patients with nonmalignant hepatic disease, ages at diagnosis ranged from 28 to 56 years. The durations of employment for the two groups were 12 to 28 years and 5 to 29 years, respectively. All of the workers with hepatic diseases had worked exclusively or predominantly in one

R&S 102786

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

or more of the PVC polymerization buildings. Both tumor and nontumor cases of portal fibrosis and atypical sinusoidal lining cells were found. The authors conclude that a direct causal relationship exists between exposure to vinyl-chloride-monomer and liver pathology.

- 194 AU - Anonymous
TI - Preliminary Assessment of the Environmental Problems Associated with Vinyl Chloride and Polyvinyl Chloride. Report on the Activities and Findings of the Vinyl Chloride Task Force
SO - Office of Toxic Substances, Environmental Protection Agency, Washington, D.C., 34 pages, 9 references, 1974
AB - Environmental Protection Agency (EPA) findings on the environmental hazards of vinyl-chloride (75014) (VC) and polyvinyl-chloride (9002862) (PVC) are reviewed. Details are provided on the cancer deaths of four PVC workers at facility, which triggered EPA interest in VC and PVC. Environmental exposure to VC/PVC is of particular interest to EPA, including the use of VC as a propellant in pesticide sprays, discharges from VC/PVC industrial facilities, and unreacted vinyl-chloride-monomer entrapped in PVC products. Hazardous health effects of VC are outlined, including anesthetic effects of acute exposure, acroosteolysis, liver function abnormalities, and liver angiosarcoma. The persistence of VC in the atmosphere, and the ecological effects of VC on the aquatic environment are considered. VC and PVC production in the United States is described. EPA regulatory concerns are discussed regarding registration of pesticides containing VC, air pollution, water pollution, solid waste disposal, ocean dumping, and drinking water. OSHA standards for VC exposure in the workplace are reviewed. Some areas involving major industrial commitments are outlined, including the reduction of VC discharges, medical surveillance of VC and PVC workers, fence line monitoring for chemical discharges, toxicological testing, testing for persistence and environmental fate of VC and PVC resins and products. EPA recommendations for regulatory and supportive actions are listed.
- 195 AU - Thomas LB ; Popper H
TI - Pathology of Angiosarcoma of the Liver Among Vinyl Chloride-Polyvinyl Chloride Workers
SO - Annals of the New York Academy of Sciences, Vol. 246, pages 368-277, 4 references, 1975
AB - Observations on the gross and microscopic features of angiosarcomas of the liver among vinyl-chloride (75014) and polyvinyl-chloride (9002862) workers were reported. Nine of the 13 patients in the study had died, and livers were obtained at autopsy. In addition, seven liver specimens were obtained by surgical or needle biopsy. All of the nine livers obtained were massively involved with cystic, blood filled tumors which had replaced most of the liver. These angiosarcomas produced bulging masses on the surface of the liver. Microscopically, all specimens showed irregular infiltration of angiosarcoma into

R&S 102787

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

R&S 102788

adjacent hepatic tissue with envelopment of hepatic cord cells and proliferating bile ducts. Sinusoidal structure pattern was observed in 11 of the 13 specimens. Papillary and cavernous growth patterns were also present. A few of the angiosarcomas had nodular areas of solid tumor which were composed of anaplastic sarcoma cells. Two of the patients underwent a complete autopsy; angiosarcoma was found in the duodenum of one; and angiosarcoma of the lungs, myocardium, epicardium, kidney, peritoneum, muscularis of the small intestine and mesenteric lymph node was found in the other. The authors conclude that histological studies are of major importance in understanding the relationship of the development of angiosarcomas and the vinyl-chloride and polyvinyl-chloride industries.

- 196 AU - Tabershaw IR ; Gaffey WR
TI - Mortality Study of Workers in the Manufacture of Vinyl Chloride and Its Polymers
SO - Journal of Occupational Medicine, Vol. 16, No. 8, pages 509-518, 11 references, 1974
AB - The effects of occupational exposure to vinyl-chloride (75014) (VC) on mortality rates were examined in 8384 workers from VC factories (SIC-2821). The mortality of the VC workers was compared to that of the general population, and mortality patterns among VC workers were compared based on estimated exposure to VC. All subjects had worked at least 1 year in a job involving exposure to VC. Cause of death was determined from death certificates. An estimated exposure history for each worker was summarized by calculating an Exposure Index (EI). No relationship was found between EI score and duration of exposure. The overall mortality of the study group was lower than that of the general male population. For malignant neoplasms as a whole, the risk of death increased with increased exposures to VC, whether measured by exposure concentrations or duration. There was an increase in mortality from cardiovascular and renal diseases with an increase in VC exposure. Mortality from digestive cancer, respiratory cancer, cancer of the brain, and lymphomas appeared to be related to exposure. Cancers of the buccal cavity and pharynx were represented in the study group at a higher rate than in the general population, but only in workers with low and short exposures. The authors note that workers with long exposures followed by a long latent period are not adequately represented in the study.
- 197 AU - Block JB
TI - Angiosarcoma of the Liver Following Vinyl Chloride Exposure
SO - Journal of the American Medical Association, Vol. 229, No. 1, pages 53-54, 8 references, 1974
AB - The relationship of vinyl-chloride (75014) exposure to angiosarcoma of the liver was investigated in rubber workers. Six workers exposed to vinyl-chloride for 12 to more than 20 years in the same tire factory had died of angiosarcoma of the liver. All diagnoses were confirmed by pathologists at the National Institutes of Health. A nonalcoholic form of cirrhosis

00003142

PAGE 104

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

was found in four of the cases. In the general population there were only 43 cases of liver angiosarcomas reported as of 1974, none of which were attributed to vinyl-chloride. All cases had been exposed to high concentrations of vinyl-chloride when cleaning vats containing residues. In the six cases reviewed, three had neoplasms resulting from vinyl-chloride exposure. These were first diagnosed as gastric ulcers. All cases had enlarge livers. The author concludes that the subjects developed the angiosarcoma from low exposures over a period of years. Preexisting cirrhosis due to other causes may play a role in the genesis of vinyl-chloride angiosarcoma. New cleaning techniques and industrial hygiene practices have reduced exposures to the chemical.

- 198 AU - Barr RJ ; Bonin M
 TI - Polyvinyl Chloride
 SO - Journal of the American Medical Association, Vol. 231, No. 9, page 914, 7 references, 1975
 AB - A potential early detection indicator of human hemangiosarcoma was discovered. During an autopsy in a case of primary hemangiosarcoma due to occupational exposure to polyvinyl-chloride (9002862), alcian-blue dye at pH 2.5 was used to stain mucopolysaccharides in the liver. This technique has previously been used as a diagnostic aid in characterizing malignant vascular tumors of the skin. When alcian-blue was applied to the liver hemangiosarcoma tissue, a strongly positive result was obtained. The results of this technique were consistent with an increase of production of sulfated acid mucopolysaccharides, which is characteristic of malignant vascular tumors of the skin. The authors suggest that researchers who are currently investigating polyvinyl-chloride produced hemangiosarcomas attempt to qualitate and quantitate the production of acid mucopolysaccharides in the neoplasms, serum, and urine of polyvinyl-chloride workers. The mucopolysaccharide urine spot test is suggested as a gross screening test which can be used as an initial examination for polyvinyl-chloride exposed workers.
- 199 AU - Kay K
 TI - Conference on toxicology-epidemiology-health effects of pesticides. A review of the problem.
 SO - Clin. Toxicol. 8(3): 289-300; 1975.(60 references)
 AB - PESTAB. Six developments occurring in 1974 related to pesticides are reviewed: the vinyl chloride case; the regulation of 14 carcinogens under OSHA; the banning of aldrin and dieldrin; cancer among U.S. arsenic workers; the relation of neurotoxicity and carcinogenicity; human poisoning due to chlorinated-p-dioxins; and the encapsulation of pesticides. The findings of cases of hemangiosarcoma of the liver among workers in polyvinyl chloride demonstrated that there is a need to retest older pesticides and associated materials that have never been adequately assessed on a long-term basis to disclose carcinogenicity. Of the 14 carcinogenic chemicals brought under

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

R&S 102790

control on Feb. 11, 1974 by the OSHA, only two, beta-propiolactone and ethyleneimine, could be considered pesticidal. They constitute a potential occupational hazard for an extremely small percentage of workers exposed to pesticides. In 1974 dieldrin and aldrin were established as carcinogens. Large numbers of workers have been exposed to occupational contact with these carcinogens before. Hemangioendothelioma of the liver was diagnosed in vineyard workers. Last year there leukemia was reported in a U.S. worker using arsenic pesticides. Studies of workers manufacturing arsenical sheep dip have strongly suggested that lung cancer occurs in higher than expected rates in these arsenic exposure occupations. Pesticides as a class of compounds appears to strengthen the idea of a relation between neurotoxicity and carcinogenicity. For a time, toxicologic test procedures were not adequately modified to avoid marketing products which contained high toxicity contaminants. A technique has been developed for the microencapsulating of pesticides to provide slow controlled release. Two years of field trials are cited during which the encapsulated methyl parathion diffusing through the pores of the polyamide microspheres maintained levels on crops for much longer than did conventional methyl parathion treatment. Residues of the encapsulating polyamide are inert and nontoxic in certain food crops. Microcapsules can be readily sprayed on as a water slurry. Caution is advised as the vinyl chloride case has alerted the health-related professions to the occurrence of unreacted monomers and additives in seemingly nonreactive plastics. Even smaller nylon type polymer spheres are available. These could be inspired into the periphery of the lung where release of unreacted monomers and additives would presumably ensue.

- 200 AU - Viola PL ; Bigotti A ; Caputo A
TI - Oncogenic Response of Rat Skin, Lungs, and Bones to Vinyl Chloride
SO - Cancer Research, Vol. 31, pages 516-522, 12 references, 1971
AB - The oncogenic response of rats exposed for 12 months to vapors of vinyl-chloride (75014) (VC) were studied. Three month old male Wistar-rats were exposed to airborne concentrations of 3 percent VC. At the end of treatment, surviving rats were killed. All rats were subjected to histological examination. Almost all animals developed tumors of the skin and lungs while very few developed bone tumors. Skin tumors were the most common, accounting for 65 to 70 percent of the total. The tumor that developed most frequently in the para auricular region was the epidermoid carcinoma, although papillomas and occasional mucoepidermoid carcinomas occurred. In all cases, the neoplasms were of epithelial nature. Warty sub auricular growths occurred in some rats. The tumors in the respiratory tract were mainly adenocarcinomatous. When tumors were seen in their early development, they occasionally consisted of cubic or columnar cells arranged as regular or irregular tabular and papillary elements. In other cases, glandular structures were imperfectly formed. In the metacarpal and metatarsal regions of the limbs, a large proliferation of cartilaginous tissues arose outward from

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

the periosteum and seemed to derive directly from the cortical bone. None of the control rats developed tumors or lesions. The authors conclude that the cutaneous system is the most susceptible to the oncogenic effects of VC. The salivary glands may be involved in the excretion of VC or some of its active decomposition products.

- 201 AU - Selikoff IJ
 TI - Testimony Presented At Public Hearing On Proposed Standard For Occupational Exposure To Vinyl Chloride
 SO - Presented at U.S. Department of Labor, Washington, D.C., June 25, 1974
 AB - Testimony at a Department of Labor public hearing on a proposed standard for occupational exposure to vinyl-chloride (75014) is presented. Findings among workers in vinyl-chloride polymerization factories are reviewed. Such workers demonstrate a significant prevalence of liver abnormalities, peripheral vascular changes, and lung abnormalities. The lung problems may reflect exposure to polyvinyl-chloride (9002862) dust, rather than to monomer gas. A disproportionate number of deaths from hemangiosarcoma of the liver occur among these workers. The proposed standard for employee exposure is supported. The standard is set at a no detection limit, based on a sampling method capable of detecting 1 part per million (ppm) vinyl-chloride. Animal experiments in which cancer can be produced by exposure to 50ppm vinyl-chloride are discussed. The technical difficulties that a no detection limit may create for industry are recognized, but it is also recognized that industrial hygiene engineers can attain this goal. A decrease in exposure to vinyl-chloride will cause a sharp decline in the neoplastic risk. The possible elevation of alkaline-phosphatase activity and the palpable enlargement of liver and spleen that can occur at vinyl-chloride doses that may be too low to have a malignant effect are discussed. Problems that may result from inhalation of polyvinyl-chloride resin particles and that are unrelated to the monomer are noted. Because it has been shown that polyvinyl-chloride particles can pass through the placenta, and because vinyl-chloride has been shown to have teratogenic effects in rats, the author concludes that females of childbearing age should be prohibited from working with any form of vinyl-chloride.
- 202 AU - Suzuki Y
 TI - Neoplastic Effect Of Vinyl Chloride In Mouse Lung Lower Doses And Short-Term Exposure
 SO - NIOSH, U.S. Department of Health and Human Services, Cincinnati, Ohio, Grant No. OH-00681, 27 pages, 21 references
 AB - The neoplastic pulmonary effects of vinyl-chloride (75014) (VC) were studied in mice. Male CD1-mice were exposed to VC vapor at concentrations of 2500 or 6000 parts per million (ppm) for 5 to 6 months. Animals were then killed and studied for histopathological changes. CD1-mice were exposed to 0.1, 10, 100, 300, or 600ppm VC for 4 weeks and were observed for at least

00003145

PAGE 107

VINYL CHLORIDE, POLYVINYL CHLORIDE / CANCER-RELATED

41 weeks. Animals were killed at intervals up to 41 weeks after exposure and lungs were studied for histopathological changes. Ninety six percent of the mice exposed to 2500 or 600ppm VC developed pulmonary tumors. These tumors were alveologenic and were characterized by large irregularly shaped mitochondria, tight junctions between adjacent cells, and lack of mucinous secretory granules and cilia. In mice exposed to VC for 4 weeks, the tumor incidence was 5 percent at 1ppm, 16 percent at 10ppm, 37.5 percent at 100ppm, 68.4 percent at 300ppm, and 92 percent at 600ppm. Induction times of the tumors was also dose related, ranging from 10 weeks at 600ppm to 40 weeks at 1, 10, and 100ppm. The author concludes that alveologenic tumors arose as a result of a transformation of type II epithelium through a hyperplastic form.

- 203 AU - Neal J ; Rigdon RH
 TI - Stomach Cancer and Air Pollution: An Experimental Study in a Petrochemical Area
 SO - Texas Reports on Biology and Medicine, Vol. 27, No. 3, pages 787-793, 14 references, 1969
 AB - Induction of gastric tumors by ingestion of air pollutant particulates was investigated in mice. Benzo(a)pyrene (50328) (BaP) was collected on air filters and extracted with double distilled benzene. Recovery was 1.1 to 2.3 micrograms BaP per 1000 cubic meters of air per month. The filters also contained styrene monomer (100425), vinyl-chloride (75014), acrylonitrile monomer (107131), polyethylene (9002884), methanol (60154009), tertiary-butylamine (75649), detergent bases, resins, high octane gasoline, and carbon blacks. CFW-mice received 50 milligrams (mg) thermal carbon-black (7440440) or lamp-black, 1.5mg particulate matter plus 21mg filter, or 21mg filter per gram (g) of food. Average consumption was 4g of food per day for 1 year. Animals were sacrificed and examined for tumors. No significant increases in stomach or lung tumors were found as compared to controls. Weight was not significantly affected. The authors conclude that this experimental model would be useful in clinical and epidemiological studies of gastric cancer in areas of air pollution. The induction of gastric cancers by feeding air particulate matter is more significant than a statistical relationship between gastric cancers and air pollutants.

* * * * * END OF OFFLINE PRINT * * * * *