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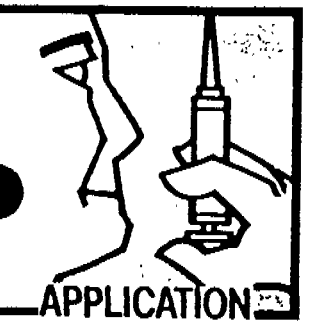
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R&S 111206



A SERVICE OF THE
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R&S 111207

ONCOLOGY OVERVIEWS are a service of the International Cancer Research Data Bank (ICRDB) Program of the National Cancer Institute. Each *ONCOLOGY OVERVIEW* represents a survey of the literature associated with a selected area of cancer research. It contains abstracts of articles which have been selected and organized by researchers associated with the field. The purpose of this *OVERVIEW* is to facilitate and promote the exchange of information between cancer scientists by keeping them aware of literature related to their research being published by other laboratories throughout the world.

The material published in *ONCOLOGY OVERVIEWS* is obtained from CANCERLINE, an on-line cancer information system created by the ICRDB Program in cooperation with the National Library of Medicine. Abstracts from the CANCERLINE database, which is updated monthly with new articles abstracted from over 3000 journals, can be retrieved via on-line computer terminals at more than 800 locations in the U.S. and other countries. Any organization linked to the MEDLARS/MEDLINE system at the National Library of Medicine has access to the CANCERLINE database.

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R&S 111208

Selected Abstracts

On

THE CARCINOGENICITY OF VINYL CHLORIDE AND RELATED COMPOUNDS

Benjamin L. Van Duuren, Sc.D.
Consulting Reviewer

R&S 111209

A Service of the International Cancer Research Data Bank (ICRDB) Program
of the National Cancer Institute

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INTRODUCTION

This ONCOLOGY OVERVIEW on the carcinogenicity of vinyl chloride and related compounds includes abstracts selected from the CANCERLINE data base, referencing articles published mainly during 1975-79. Selected information dating back to 1970 is included for historical perspective. These abstracts are currently available in the CANCERLINE computerized data base. The strategy used to retrieve these abstracts can be requested from the CIDAC and entered on any MEDLARS/MEDLINE terminal system to update references in this area.

The scope of this OVERVIEW includes articles on the carcinogenicity, teratogenicity, and mutagenicity of vinyl chloride and related compounds including chloroprene, vinylidene chloride, tri- and dichloroethylene, and other analogous halogenated hydrocarbons. Studies of the chemistry and analysis, pharmacokinetics, biological effects in animals and humans, chemical structure and biological activity of vinyl chloride and its analogs are included. Also included are epidemiological investigations as well as public health issues, occupational safety and regulations. Studies of halogenated aromatics and of anesthetics are specifically excluded from this OVERVIEW.

This OVERVIEW was prepared by Benjamin L. Van Duuren, Sc.D. (Editor) of the New York University Medical Center, Institute for Environmental Medicine, and Harriet Glaser Hill, M.S., of the CIDAC for Carcinogenesis Information, The Franklin Research Center.

R&S 111211

EDITORIAL COMMENTARY

Short-chain halogenated hydrocarbons, both saturated and unsaturated, have been synthesized, manufactured and used, mainly in industry, for many decades. In some instances the toxicology of these compounds has been studied sporadically for many years.

The demonstration of the carcinogenicity of vinyl chloride (VC) by Viola and associates (1) and the subsequent intensive studies of Maltoni and associates (2) on the inhalation carcinogenicity of VC spurred widespread studies on VC and its analogs.

These compounds as a group are very heavily used in industry; several of them are gaseous or volatile liquids, and hence pose potential occupational hazards via inhalation. Skin contact and hence systemic absorption is another route of possible exposure. Because of the relative stability of these compounds and thus their possible environmental dispersion and persistence, they need also to be considered as general environmental pollutants. It is, therefore, not surprising that a number of halohydrocarbons related to VC have been found in air, water and in foodstuffs, although usually at low levels (3,4).

These factors have generated interest in these compounds in laboratory studies, in the industrial setting, which includes epidemiologic studies, and in governmental regulatory agencies. For VC and some of its analogs, the U.S. Occupational Safety and Health Administration has set health standards and maximum permissible levels of these agents in the workplace. The U.S. Environmental Protection Agency is actively pursuing the sources and elimination of halogenated hydrocarbon contamination in drinking water supplies and in polluted air.

In laboratory studies, some work was done on the predictive value of chemical structure as related to biological activity, particularly carcinogenicity. This particular approach is well exemplified by the prediction that trichloroethylene will be carcinogenic based on its possible metabolism to an epoxide which is an alpha-chloroether (5); several compounds in the alpha-chloroether series are carcinogens, the most notable of which is the human carcinogen bis(chloromethyl)ether (6). Subsequent animal studies proved this prediction concerning the carcinogenicity of trichloroethylene to be correct (7). The use of chemical structure, reactivity and possible metabolic pathways as a predictive method for carcinogenicity has been reviewed (6,8).

Other methods of predicting animal or human carcinogenicity include the study of chromosomal effects in animals, mutagenicity in bacterial systems and *Drosophila*, and the effects of these chemicals in mammalian cell culture. In many instances some of these tests have proven to be valuable indicators of potential animal and human carcinogenicity (3,4,9). Teratogenicity studies and studies of mammalian cell culture transformation with halogenated hydrocarbons have been limited. Transformation in cell culture can be a useful short-term assay for predicting carcinogenicity. This has been borne out in studies with other carcinogens (10).

Of particular interest is that chromosomal aberrations and the use of cytology as indicators of potentially deleterious health effects in humans exposed to VC have given informative results. This point is relevant and important in medical surveillance of workers exposed to suspect chemicals.

Studies on the metabolism of halohydrocarbons have been extensive and postulated mechanisms of action even more plentiful (3,4,11). Many studies suggest that these compounds are indirect-acting carcinogens, unlike carcinogenic epoxides and haloethers which are direct-acting agents (12,13). Indirect-acting agents that are carcinogenic need to be metabolized to activated carcinogenic intermediates. The most frequently proposed activated carcinogenic intermediates for VC and related compounds are epoxides (3,4,11) although peroxides, free radicals and other species of electrophilic intermediates have also been suggested (3,4,11).

Binding studies using halogenated hydrocarbons, usually in *in vitro* experiments, have been done with a variety of tissue constituents, e.g., DNA, RNA and proteins. However, it is at present unclear which of these covalent interactions are critically important in accounting for the carcinogenicity of a given agent.

The same, however, holds true for many other indirect-acting carcinogens such as the nitrosamines, aflatoxins, aromatic amines, etc., some of which have been under study for 30 years or more. In some instances activated carcinogenic intermediates (ultimate carcinogens) have been suggested for these carcinogens. These proposed intermediates are supported by extensive experimental evidence (14). Such studies still need to be pursued more extensively with VC and its analogs.

One of the subject categories in this ONCOLOGY OVERVIEW deals with modifying factors, i.e., materials which enhance or diminish the carcinogenicity of halohydrocarbons. The paucity of information in this area suggests the need for increased emphasis on this aspect. This applies not only for the compounds under discussion but for many other carcinogens. This subject has not received the attention it deserves probably because of the complexity of the problem. It is, nevertheless, of great importance in cancer causation since multiple factors are frequently involved in chemical carcinogenesis (15).

It is noteworthy that in spite of the hundreds of thousands of workers exposed to VC and the extensive epidemiologic studies, the list of workers with angiosarcomas of the liver clearly linked to exposure to VC is only 65 in number (16). This number is taken from results of epidemiologic studies in eleven or more countries and it is probably impossible to estimate how many hundreds of workers have been exposed to VC for 20 years or more. This raises the question of the carcinogenic potency of VC relative to such potent carcinogens as bis(chloromethyl)ether, beta-naphthylamine and benzidine. In fact, the epidemiologic data available to date suggest that it is a weak carcinogen compared to these carcinogens.

Epidemiologic studies have been carried out on the potential occupational hazard of chloroprene and trichloroethylene as carcinogens. In neither case has the evidence been convincing.

Three recent volumes deal in part or in toto with halohydrocarbons (11,17,18). Two recent reviews cover the carcinogenicity, mutagenicity, other biological effects and epidemiology of VC and seven of its analogs (3) and analogous saturated halohydrocarbons (4).

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1. Viola, P.L., Bigotti, A., and Caputo, A.: Oncogenic response of rat skin, lungs, and bones to vinyl chloride. *Cancer Res.* 31: 516-522, 1971.
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3. Fishbein, L.: Potential halogenated industrial carcinogenic and mutagenic chemicals. I. Halogenated unsaturated hydrocarbons. *Sci. Total Envir.* 11: 111-161, 1979.
4. Fishbein, L.: Potential halogenated industrial carcinogenic and mutagenic chemicals. II. Halogenated saturated hydrocarbons. *Sci. Total Envir.* 11: 163-195, 1979.
5. Van Duuren, B.L.: On the possible mechanism of carcinogenic action of vinyl chloride. *Ann. N.Y. Acad. Sci.* 246: 258-267, 1975.
6. Van Duuren, B.L.: Structural prognostication of carcinogenicity and tumor-enhancing activity in various chemicals. In: Niebergs, H.E. (editor): *Prevention and Detection of Cancer. Part I, Prevention, Vol. 2, Etiology*, New York and Basel, Marcel Dekker, Inc., 1978, pp. 2071-2084.
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8. Ashby, J.: Structural analysis as a means of predicting carcinogenic potential. *Brit. J. Cancer.* 37: 904-923, 1978.
9. Ames, B.N.: Identifying environmental chemicals causing mutation and cancer. *Science* 204: 587-593, 1979.
10. DiPaolo, J.A. and Castro, B.C.: In Vitro carcinogenesis with cells in early passage. In: *Third Decennial Review Conference on Cell Tissue and Organ Culture; Gene Expression and Regulation in Culture Cells*, U.S. National Cancer Institute Monograph, 48, pp. 245-259, Bethesda, Md., U.S. National Cancer Institute, 1978.
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12. Van Duuren, B.L., Goldschmidt, B.M. and Seidman, I.: Carcinogenic Activity of di- and trifunctional alpha-chloro ethers and of 1,4-dichlorobutene-2 in ICR/Ha Swiss mice. *Cancer Res.* 35: 2553-2557, 1975.

13. Henschler, D.: Metabolism and mutagenicity of halogenated olefins - A comparison of structure and activity. *Envir. Hlth. Perspect.* 21: 61-64, 1977.
14. Searle, C.E. (ed.), *Chemical Carcinogenesis*. American Chemical Society Monograph No. 173, American Chemical Society, Washington, D.C., 1976, 788 pp.
15. Van Duuren, B.L., and Goldschmidt, B.M.: Cocarcinogenic and tumor-promoting agents in tobacco carcinogenesis. *J. Natl. Cancer Inst.* 56: 1237-1242, 1976.
16. Spirtas, R., and Kaminski, R.: Angiosarcoma of the liver in vinyl chloride - polyvinyl chloride workers: 1977 Update of the NIOSH register. *J. Occup. Med.* 20: 427-429, 1978.
17. Selikoff, I.J., and Hammond, E.C. (eds.): *Toxicity of vinyl chloride - polyvinyl chloride*. Ann. N.Y. Acad. Sci, 337 pp., Vol. 246, 1975.
18. Saffiotti, U., and Wagoner, J.K. (eds.): *Occupational carcinogenesis*. Ann. N.Y. Acad. Sci., Vol. 271, 516 pp., 1976.

R&S 111214

I. CHEMISTRY AND ANALYSIS OF VINYL CHLORIDE AND RELATED COMPOUNDS

1. A PRACTICAL METHOD FOR THE MEASUREMENT OF VINYL CHLORIDE MONOMER (VCM) IN AIR.

Murdoch IA, Hammond AR
Standard Telecommunication Lab. Limited, Harlow,
Essex, England
Ann Occup Hyg; 20(1):55-61 1977

A new method for the determination of vinyl chloride monomer in air is described which uses gas chromatography and a sealable trap sampling system. For practical purposes the detection limit is 0.1 vol/million, since below this level there is a possibility of peaks from minor impurities. (3 Refs)

2. MEASUREMENT OF SOME POTENTIALLY HAZARDOUS MATERIALS IN THE ATMOSPHERE OF RUBBER FACTORIES.

Nutt A
Dunlop Res. Centre, Birmingham, England
Environ Health Perspect; 17:117-123 1976

The measurement of chlorinated monomers in polyvinyl chloride (PVC) and polychloroprene, and the measurement of benzopyrene (BP) in factory air, particularly in the tire industry, are outlined. BP is present in trace quantities in the mineral oils and carbon blacks used in tire manufacture. Measurements taken daily over a 2-yr period showed no significant concentrations of BP in the atmosphere within the tire plant as compared to an outside air station. (6 Refs)

3. MIGRATION OF VINYL CHLORIDE FROM PVC PACKAGINGS.

VomBruck CG, Eckert WR, Rudolph FB
Unilever Gesellschaft mbH, Hamburg, West Germany
Fette Siefen Anstrichm; 78(8):334-337 1976

Gas chromatographic assay of vinyl chloride (VC) migration in polyvinyl chloride (PVC) or fat simulant HB 307 was made by Puschmann's method with a sensitivity of 0.00001% (0.1 mg/kg) for PVC and 0.000001% (0.01 mg/kg) for HB 307. VC migration from PVC was directly proportional to the initial VC concentration. In two separate PVC samples the VC level fell from 0.006% to 0.002% and from 0.0017% to 0.0006% after 35 days. At 20 C a linear relation was also obtained for the VC flow into HB 307 for 100 days. At 40 C a max VC concentration was reached in HB 307 in 50-60 days, after which the level gradually fell. The appearance of a max suggests a reflux from HB 307 through PVC into the ambient atmosphere. On the average, an adult will consume about 1 kg of packaged food per day. Since only a small fraction of that kilogram is in PVC packaging, the threat of VC contamination, even at a 0.006% concentration in PVC, is very small. (4 refs)

4. VAPOR INFRARED SPECTROPHOTOMETRIC IDENTIFICATION OF CHLOROFORM, HALOTHANE, METHOXYFLURANE, TETRACHLOROETHYLENE, AND TRICHLOROETHYLENE.

Schwartzman G
Pharmaceutical Res. and Testing, Food and Drug
Admin., Washington, DC, 20204
J Assoc Off Anal Chem; 61(5):1306-1308 1978

The use of vapor phase infrared spectrophotometry for identification of chloroform, halothane, methoxyflurane, tetrachloroethylene, and trichloroethylene is described. The curves obtained by this technique are unique and characteristic for each material, obviating the need for other physical or chemical tests in the identification of these compounds. (4 Refs)

5. GAS CHROMATOGRAPHIC ANALYSIS OF HALOGENATED HYDROCARBONS IN SILICONE HALIDES.

Rath HJ, Schmidt D, Wimmer J
Wacker-Chemitronic, Gesellschaft fur Elektronik-
Grundstoffe mbH, Postfach 1140, D-8263 Burghausen,
W. Germany
Fresenius Z Anal Chem; 295(4):266-268 1979

A method for analyzing silicone halide complexes for small amounts of contaminating halogenated hydrocarbons is described. After hydrolysis of the matrix, the hydrocarbons are enriched in the nitrogen phase of a nitrogen-water mixture, and gas chromatography is used to detect the hydrocarbons. Transdichloroethene, 1,1-dichloroethane, 1,1,1-trichloroethane, and trichloroethylene are detectable at concentrations of 1 ppm (by wt). (6 Refs)

6. GAS-LIQUID CHROMATOGRAPHIC DETERMINATION OF TRICHLOROETHYLENE METABOLITES IN URINE.

Nomiyama H, Nomiyama K, Uchiki H
Dept. Environmental Health, Jichi Medical Sch.,
Minamikawachi-machi, Tochigi-ken 329-04, Japan
Am Ind Hyg Assoc J; 39(6):506-510 1978

A gas-liquid chromatography technique using an electron capture detector was developed to determine all the urinary metabolites of trichloroethylene (TCE) on a single column. With urine from TCE-exposed rats, detection limits were as low as 0.1-5 nanograms. (10 Refs)

7. ETHYLENE DIBROMIDE IN URBAN AIR.

Leinster P, Perry R, Young RJ
Public Health and Water Resource Engineering Section,
Imperial Coll. Science and Technology, London S.W.7,
England
Atmos Environ; 12(12):2383-2387 1978

A procedure for the rapid sampling of ethylene dibromide, a potential carcinogen, in ambient air is described. Ambient levels in London air were in the range 0.001-0.17 ug/m³, and levels on a garage forecourt were 1.2 and 1.8 ug/m³. Ethylene dibromide was also measured in car exhaust, a calculation relating levels of organic lead to those of ethylene dibromide is presented. (9 Refs)

8. REACTIONS OF EPOXY-1,1,2-TRICHLOROETHANE WITH NUCLEOPHILES.

Kline SA, Van Duuren BL

Lab. Organic Chemistry and Carcinogenesis, Inst.
Environmental Medicine, New York Univ. Medical
Center, New York, NY, 10016

J Heterocycl Chem; 14(3):455-458 1977

The reactions of epoxy-1,1,2-trichloroethane with nucleophiles were studied. Epoxy-1,1,2-trichloroethane was synthesized by UV or benzoyl peroxide initiated autoxidation of trichloroethylene. The epoxide intermediate of 1,1,2-trichloroethylene (TCE) has been proposed as the activated carcinogenic intermediate of the compound. The reactivity of epoxy-1,1,2-trichloroethane toward sulfhydryl nucleophiles was determined since the SH moiety is a likely target for its covalent reactions with protein. It reacted readily with 2-mercaptobenzimidazole, 1-methyl-2-mercaptoimidazole, p-nitrothiophenol, and 3,4-dichlorothiophenol forming 2-chloro-2-(benzimidazole-2-thio) acetic acid, 2-chloro-2-(1-methylimidazole-2-thio) acetic acid, 2-chloro-2-(4-nitrothiophenoxy)-4-nitrophenylthioacetate, and 2-chloro-2-(3,4-dichlorothiophenoxy)-3,4-dichlorophenylthioacetate, respectively. Base hydrolysis of 2-chloro-2-(4-nitrothiophenoxy)-4-nitrophenylthioacetate yielded 2,2-di(4-nitrothiophenoxy)acetic acid. Adduct 2-chloro-2-(4-nitrothiophenoxy)-4-nitrophenylthioacetate decomposed on silica gel yielding p-nitrophenyldisulfide. (11 Refs)

9. SYNTHESIS AND REACTIONS OF CHLOROALKENE EPOXIDES.

Kline SA, Solomon JJ, Van Duuren BL

Lab. Organic Chemistry and Carcinogenesis, Inst.
Environmental Medicine, New York Univ. Medical
Center, New York, NY, 10016

J Org Chem; 43(18):3596-3600 1978

The chloroalkene epoxides, vinyl chloride oxide (1), trichloroethylene oxide (2), tetrachloroethylene oxide (3), cis- and trans-1-chloropropene oxide (4 and 5), and cis- and trans-1,3-dichloropropene oxide (6 and 7), were synthesized from their respective chloroalkenes via either autoxygenation (in the case of 2 and 3) or m-chloroperbenzoic acid oxidation (in the case of 1 and 4-7). Dichlorobenzene was a byproduct in the synthesis of both 6 and 7. In the case of 6, its formation was determined to be a result of bimolecular reaction involving an intermediate in the synthesis of 6. Kinetics of hydrolysis at pH 7.4 and 37 C were determined for compounds 2-7. Kinetics of thermal decomposition in dilute hydrocarbon soln were determined for compounds 2, 4, 5, and 7. The hydrolysis and thermolysis rates are discussed with respect to structure and mechanism of product formation. (Author abstract) (21 Refs)

10. A HIGHLY STEREOSELECTIVE SYNTHESIS OF VINYL BROMIDES AND CHLORIDES VIA DISUBSTITUTED VINYLSILANES.

Miller RB, McGarvey G

Dept. Chemistry, Univ. California, Davis, CA, 95616
J Org Chem; 43(23):4424-4431 1978

A detailed study of the utility of vinylsilanes as intermediates in a stereoselective synthesis of vinyl halides is described. The requisite vinylsilanes are readily available from alkynes by hydroalumination-protonolysis or hydrosilation. Various methods of desilicohalogenation of intermediate dihalides from vinylsilanes 2a and 3a are compared. The effect of the alkyl substituent on the vinylsilane upon yield and stereoselectivity of the overall halogenation-desilicohalogenation sequence is studied. When the substituent is a primary or secondary alkyl group, the vinylsilanes are converted in good yields with high stereoselectivity to the vinyl chlorides and bromides; the overall reaction involves

replacement of the trimethylsilyl group by halogen with inversion of stereochemistry about the double bond. When the substituent is a phenyl group the stereochemical outcome is retention about the double bond. When the alkyl substituent is tert-butyl, both isomeric vinylsilanes give cis-1-halo-3,3-dimethyl-1-butene as the product. (Author abstract) (32 Refs)

11. VOLATILE CARCINOGENS: OCCURRENCE, FORMATION AND ANALYSIS. (PP. 1943-1949)

Hoffmann D, Schmeltz I, Hecht SS, Brunnemann KD, Wynder EL

Naylor Dana Inst. Disease Prevention, American Health Foundation, Valhalla, NY, 10595

Prevention and Detection of Cancer, Proceedings of the Third International Symposium on Detection and Prevention of Cancer Held by the International Study Group for the Detection and Prevention of Cancer in New York, April 26 - May 1, 1976. Vol. 2(Part 1), International Study Group for the Detection and Prevention of Cancer, New York, NY, 2404 pp., 1978.

Carcinogenicity data (humans and animals); levels in occupational environments, polluted air, and cigarette smoke; and analytical methods for several volatile chemical carcinogens, including vinyl chloride, chlorinated hydrocarbons, bis(chloromethyl) ether, N-nitrosamines, and hydrazines, are reviewed. (33 Refs)

II. PHARMACOKINETICS

A. Uptake, Distribution, and Metabolism of Vinyl Chloride and Related Compounds in Experimental Animals

1. Uptake and Distribution of Vinyl Chloride and Related Compounds in Experimental Animals

12. DISPOSITION OF 1,2¹⁴C VINYL CHLORIDE IN THE RAT.

Bolt HM, Kappus H, Buchter A, Bolt W

Institut für Toxikologie der Universität, Wilhelmstr. 56,
D-7400 Tübingen, West Germany
Arch Toxicol (Berl); 35(3):153-162 1976

Three male Wistar rats, 200-250 g, were exposed to (1,2¹⁴C)-vinyl chloride in an all-glass closed system of 10.3 l volume. To avoid saturation of the metabolizing enzymes, concentrations below 100 ppm were applied. In preliminary experiments, it was found that only about 40% of inspired vinyl chloride is absorbed by the lungs. Uptake of vinyl chloride by the rats was completely blocked by acute pretreatment with potent inhibitors of cytochrome P-450-dependent microsomal drug metabolism (i.e., by 35 mg/kg 3-bromophenyl-4(5)-imidazole or 50 mg/kg 6-nitro-1,2,3-benzothiadiazole in 0.6 ml/kg dimethyl sulfoxide, DMSO). A weaker inhibition was observed after pretreatment with 2-diethylaminoethyl-2,2-diphenylvalerate:HCl (SKF-525A) or 5,6-dimethyl-1,2,3-benzothiadiazole (50 mg/kg in 0.6 ml/kg DMSO). Metapyrone did not cause inhibition. Uptake of vinyl chloride was increased by pretreatment with 1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane (DDT) and, to a lesser extent, with clotrimazole. No significant stimulation of uptake was observed after pretreatment with phenobarbital, 3-methylcholanthrene, rifampicin, or chronic ethanol treatment. Immediately after exposure, highest radioactivity levels were observed in liver and kidney; the radioactive metabolites were rapidly excreted, mainly in the urine (69.4% ± 2.6% within 24 hr).

13. FATE OF ¹⁴C VINYL CHLORIDE FOLLOWING INHALATION EXPOSURE IN RATS.

Watanabe PG, McGowan GR, Madrid EO, Gehring PJ
Toxicology Res. Lab., Health and Environmental Res.,
Midland, MI 48640

Toxicol Appl Pharmacol; 37(1):49-59 1976

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

14. PRELIMINARY STUDIES OF THE FATE OF INHALED VINYL CHLORIDE MONOMER (VCM) IN RATS.

Hefner RE, Watanabe PG, Gehring PJ
Health and Environmental Res., Dow Chemical U.S.A.,
Midland, Mich. 48640

Environ Health Perspect; 11:235-242 1975

Male Sprague-Dawley rats were exposed to vinyl chloride monomer gas (VCM) in a closed recirculating system. The rate at which VCM was removed from the system via metabolism was determined for rats exposed to initial concentrations of VCM ranging from 50-1167 ppm. Upon exposure to initial concentrations of 50-105 ppm, the rate of metabolism was 8.04 plus or minus 3.40 X 10⁻³ min⁻¹. Upon exposure to initial concentration ranging from 220 to 1167 ppm, the rate constants were less; the mean value being 2.65 plus or minus 1.35 X 10⁻³ min⁻¹. Regardless of concentration, the disappearance followed apparent first order kinetics. Pretreatment of rats with pyrazole (320 mg/kg) prior to exposure to 65 and 1234 ppm VCM caused 71 and 87% reductions, respectively, in the rate of metabolism. Ethanol (5 ml/kg, 95%) caused 96% and 83% reductions in the rate of VCM metabolism by rats exposed to 56 and 97 ppm VCM, respectively. Ethanol was less effective in blocking the rate of metabolism by rats exposed to high concentrations of VCM; 46 and 36% in rats exposed to 1025 and 1034 ppm VCM. In rats exposed to 65 ppm VCM, SKF-525-A AA(75 mg/Kg) administration caused no inhibition of the rate of VCM metabolism; however, a 19% inhibition was seen in rats exposed to 1038 ppm. The nonprotein sulfhydryl content of the liver (glutathione and cysteine) of rats exposed to 50-15,000 ppm VCM was reduced without a relationship to dose. With repeated daily exposure, the degree of reduction was reduced. Preliminary results indicate that the primary metabolites of VCM react with the non-protein sulfhydryl.

Final metabolic products excreted in the urine appear to be S-(2-hydroxyethyl)cysteine and S-(2-carboxymethyl)cysteine and the respective N-acetyl derivatives. Monochloroacetic acid was identified as another potential metabolite. The results suggest that VCM is readily and extensively metabolized. Metabolism via the primary pathway, postulated to involve alcohol dehydrogenase, is swamped by exposures to concentrations exceeding 220 ppm. In rats exposed to concentrations at and exceeding this level, metabolism occurs via a secondary pathway(s), postulated to be epoxidation and/or peroxidation. These results are considered pertinent in assessing the potential hazard at low-level exposures to VCM.

15. FATE OF ¹⁴C VINYL CHLORIDE AFTER SINGLE ORAL ADMINISTRATION IN RATS.

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Toxicol Appl Pharmacol; 36(2):339-352 1976

Male Sprague-Dawley rats were given single doses of 0.05, 1, and 100 mg/kg po of ¹⁴C-vinyl chloride (VC), and the routes and rates of elimination of ¹⁴C activity were followed for 72 hr. Following 0.05 and 1 mg/kg, excretion in the urine as nonvolatile metabolites and as ¹⁴CO₂ in expired air accounted for 59%-68% and 9%-13%, respectively, of the administered dose. Only 1%-2% of the dose was expired by the lungs as VC. Conversely, after 100 mg/kg, 67% of the dose was eliminated by the lungs as VC, and urinary nonvolatile metabolites and ¹⁴CO₂ comprised 11% and 3%, respectively. Pulmonary elimination after 100 mg/kg showed an apparent biphasic clearance with half-times (t_{1/2}) of 14.4 and 40.8 min for the respective fast and slow phases. Following 0.05 and 1 mg/kg, the pulmonary clearance of VC was monophasic, with t_{1/2} of 53.3 and 57.8 min. The percentage of the dose remaining in the carcass after 72 hr was 10%, 11%, and 2% of the 0.05-, 1-, and 100-mg/kg doses, respectively. The urinary radioactivity was separated by high-pressure liquid chromatography into three major metabolites. Two of the three major urinary metabolites were identified as N-acetyl-S-(2-hydroxyethyl)cysteine and thiodiglycolic acid by gas chromatography-mass spectrometry. The proportions of the urinary metabolites were not influenced by dose. The fate of doses of 1-100 mg/kg VC was clearly dose-dependent. The results suggest that the metabolism of VC is a saturable process. (20 refs)

16. UPTAKE AND RATE OF METABOLISM OF VINYL CHLORIDE BY THE ISOLATED PERFUSED RAT LIVER PREPARATION.

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Int Arch Arbeitsmed; 40(2):101-110 1977

The metabolism of vinyl chloride (VC) under controlled, steady-state exposure conditions in varying concentrations was examined in the isolated perfused rat liver. The solubility of VC in the RBC perfusion medium at 37 C was constant from 50 to 25,000 ppm. The amount metabolized, (14.6%) as determined by the difference between VC concentrations before and after passage of the liver, was also constant throughout this concentration range. This indicates that there is no saturation of those enzymes that initiate metabolic conversion of VC. Ethanol (constant addition to 12 mM) and pyrazole (single addition to 200 uM) reduced VC metabolism by 12.7% and 31.6%, respectively. Bromobenzothiazole also inhibited metabolism (48.9%), SKF 525A was inactive, and phenobarbital pretreatment increased the conversion rate by 20.9%. Fasted animals showed a 31.2% increase in the metabolic conversion rate. Determination of SGOT, SGPT, and the lactate/pyruvate coefficient revealed no VC-induced

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changes, even at the highest concentration tested (24,000 ppm), but slight liver damage was detectable after increased metabolic VC transformation. This suggests the formation of a reactive intermediate, an epoxide, as a result of the first-step oxidation. The epoxide would be expected if the oxidation were catalyzed by cytochrome P-450. The involvement of other oxidases, however, cannot be ruled out. (19 Refs)

17. HEPATIC MACROMOLECULAR BINDING FOLLOWING EXPOSURE TO VINYL CHLORIDE.

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1803 Building, Dow Chemical Co., Midland, MI, 48640
Toxicol Appl Pharmacol; 44(3):571-579 1978

Male Sprague-Dawley rats were exposed by inhalation to 1, 25, 50, 250, 1,000, or 5,000 ppm ¹⁴C-labeled vinyl chloride (VC) for 6 hr, and covalent binding of VC to hepatic macromolecules and nucleic acids was studied to determine if VC-induced carcinogenesis might be related to electrophilic alkylation of macromolecules in vivo. The total amount of VC metabolized and hepatic glutathione (GSH) content were also measured. The total amount of radioactivity bound to hepatic macromolecules did not increase proportionately to the increase in the exposure concentration of VC, but it was related directly to the total amount of VC metabolized. At exposure concentrations greater than 50 ppm, the total metabolism of VC and covalent binding appeared to correlate with the induction of hepatic angiocarcinomas in the rats. Isolation of RNA and DNA by a nondigestive procedure from the liver of rats exposed to 1, 100, 250, and 1,000 ppm VC failed to reveal any detectable radioactivity. Hepatic GSH was depressed significantly only at greater than or equal to 100 ppm, suggesting that VC carcinogenicity is related to a decreased ability to detoxify the reactive metabolites of VC. The results do not associate the carcinogenic effect of VC with a disproportionate increase in binding of electrophilic metabolites of VC to hepatic macromolecules as the exposure concentration is increased. Moreover, the lack of preferential binding of the metabolites to the hepatocyte nucleic acids suggests that the carcinogenicity of VC may not be associated directly with this commonly accepted mechanism of carcinogenesis. (27 Refs)

18. COVALENT BINDING OF ¹⁴C-VINYL CHLORIDE TO PROTEINS AND NUCLEIC ACIDS IN VITRO AND IN VIVO (MEETING ABSTRACT).

Kappus H, Kaufmann R, Appel KE, Bolt HM
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Arch Pharmacol; 293(Suppl): R 64 1976

When rat liver microsomes were incubated in atmospheric air containing ¹⁴C-vinyl chloride (VC) gas, a max of 0.5 nanomoles of VC metabolites was covalently bound to microsomal protein. RNA and sulfhydryl-containing proteins bound VC metabolites when added to the incubation medium. All these microsome binding reactions could be inhibited by 1-naphthyl-4(5)-imidazole and CO. The addition of glutathione plus cytoplasmic fractions decreased the covalent binding of VC metabolites to microsomal proteins while the total metabolism of VC during incubation was enhanced. There was a two-fold increase in the covalent binding of VC metabolites to microsomal proteins when trichloropropene oxide was in the medium. The results support the concept that chloroethylene oxide formed by microsomal enzymes via an epoxidation step is involved in covalent binding of VC to proteins. After exposure of rats to ¹⁴C-VC gas, VC-derived

radioactivity incorporated into proteins was mostly detected in the liver, lung, kidney, and spleen. VC radioactivity was also incorporated into DNA and RNA isolated from rat liver. These results support the view that VC-induced carcinogenicity is caused by the alkylation of nucleic acids and/or proteins by a reactive metabolite of VC. (0 Refs)

19. LIVER MICROSOMAL UPTAKE OF ¹⁴C VINYL CHLORIDE AND TRANSFORMATION TO PROTEIN ALKYLATING METABOLITES IN VITRO.

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Inst. Toxicology, Univ. Tübingen, W. Germany
Toxicol Appl Pharmacol; 37(3):461-471 1976

Microsomal uptake and irreversible binding of vinyl chloride (VC) radioactivity were determined in Wistar rat liver microsomes incubated with 1,2-¹⁴C vinyl chloride, gas in an all-glass vacuum system. Both the uptake of VC by microsomes and the alkylation of proteins by VC were dependent on incubation time, enzymatically active microsomes, NADPH, oxygen, and the partial pressure of VC in the atmosphere, and could be inhibited by carbon monoxide. Incubation in the presence of NADPH resulted in a 10-x increase in the amount of VC taken up by microsomes. Uptake of VC by albumin solutions and liposomal suspensions was one-third to one-fourth of the microsomal uptake in the absence of NADPH. Addition of glutathione and cytoplasmic fractions to microsomal incubations with NADPH resulted in an increase in VC uptake and a decrease in protein alkylation by VC metabolites. Trichloropropene oxide had no effect on microsomal VC uptake but caused a 2-fold increase in the amount of protein bound by VC metabolites. The results are consistent with the involvement of chloroethylene oxide as the primary microsomal metabolite of VC capable of reacting with proteins. (31 Refs)

20. PHARMACODYNAMICS AND UPTAKE OF VINYL CHLORIDE MONOMER ADMINISTERED BY VARIOUS ROUTES TO RATS.

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J Toxicol Environ Health; 1(3):381-394 1976

To assess the hazard presented by the oral ingestion of vinyl chloride monomer, rats that had been surgically prepared with an indwelling jugular cannula were dosed by intragastric intubation with aqueous solutions containing up to 2.0 mg/ml vinyl chloride. Time-concentration curves were obtained from sequential samples of blood. The uptake of vinyl chloride by this route was found to be extremely rapid; peak concentrations were achieved less than 10 min after administration of the dose. Elimination from the blood compartment appeared to be biexponential. The distribution and elimination rates of vinyl chloride from the blood were also determined from the blood concentration data after the administration of an intravenous dose of aqueous or vegetable oil solution. Studies with the same animal model in a single restraint cage that allowed a "head only" exposure to concentrations of vinyl chloride up to 7,000 ppm in the gas phase have shown a similar rapid uptake followed by a plateau blood concentration during several hours of exposure. On removal from the vinyl chloride atmosphere, blood levels fell rapidly to barely detectable concentrations after 2 hr. Thus subsequent monitoring would not be a reliable indicator of exposure. Uptake profiles after oral dosage were extremely variable.

21. PHARMACOKINETICS OF HALOGENATED ETHYLENES (MEETING ABSTRACT).

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Naunyn-Schmiedeberg's Arch Pharmacol; 302(Suppl):R22 1978

The present discussion of toxic effects of vinyl chloride raises the question of interpretation of toxicological data. Evidently, biochemical and mechanistic concepts of action of halogenated ethylenes can only be correlated with toxicities observed in vivo, if differences in pharmacokinetics are taken into account. This consideration led to the present investigation. Rats were exposed in a closed system to atmospheric concentrations of fluoroethylene (vinyl fluoride), 1,1-difluoroethylene (vinylidene fluoride), chloroethylene (vinyl chloride), 1,1-dichloroethylene (vinylidene chloride), trans-1,2-dichloroethylene and cis-1,2-dichloroethylene, trichloroethylene, and bromoethylene (vinyl bromide). Pharmacokinetic analysis was done as previously described. The following principles could be derived. (1) 'Non-linear' (dose-dependent) pharmacokinetics may apply if the organism is exposed to higher concentrations of halogenated ethylenes. This is consistent with the concept of Watanabe, Young and Gehring. In the case of vinyl chloride, it refers to atmospheric concentrations higher than 250 ppm. (2) The equilibrium constant of distribution of the non-metabolized compound (concentration in the animal/concentration in the gas phase) increases from vinyl fluoride to vinyl bromide. (3) The rate of metabolism depends on the structural properties of the individual compound. Trans-1,2-dichloroethylene and vinylidene fluoride are extremely slowly metabolized, comparable to the rate of metabolism of 1,1,1-trichloroethane (methyl chloroform) which was used as a reference compound.

22. PHARMACOKINETICS OF VINYL CHLORIDE IN THE RAT.

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Inst. Toxicology, Univ. Tübingen, Tübingen, W. Germany

Toxicology; 7(2):179-188 1977

When rats were exposed to ¹⁴C-vinyl chloride (VC) in a closed system, the VC in the atmosphere equilibrated with that in the animals' tissues within 15 min. This course of equilibration was determined in male Wistar rats treated ip with 6-nitro-1,2,3-benzothiadiazole at a dose (50 mg/kg) sufficient to block the metabolism of 200-1,200 ppm VC for 4 hr. Saturation of the VC-metabolizing enzymes occurred at an atmospheric VC concentration of 250 ppm. Pharmacokinetic analysis showed no significant accumulation of VC or its major metabolites following repeated administration of the compound. The results support the theory that a reactive, short-lived metabolite, which occurs only in low concentrations, may be responsible for the toxic effects of VC. (25 Refs)

23. DOSE-DEPENDENT FATE OF VINYL CHLORIDE AND ITS POSSIBLE RELATIONSHIP TO ONCOGENICITY IN RATS.

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Environ Health Perspect; 17:145-152 1977

Studies were made of the disposition of radioactivity from different doses of po administered or inhaled ¹⁴C-vinyl chloride (VC) in excreta, expired air, and body tissues of treated rats and of nonprotein sulphydryl levels in the livers of treated rats. The disposition of VC was found to be a function of dose, particularly after administration po. The percentages of administered VC radioactivity in rats treated po with 0.05

mg/kg VC were 1.4%, 9.0%, 68.3%, 2.4%, and 10.1% in exhaled VC, exhaled carbon dioxide, urine, feces, and carcass, respectively; following 100 mg/kg VC, the corresponding values were 66.6%, 2.5%, 10.8%, 0.5%, and 1.8%; following inhalation of 10 ppm VC, the corresponding values were 1.6%, 12.1%, 68%, 4.5%, and 13.9%; following inhalation of 1,000 ppm VC, the corresponding values were 12.3%, 12.3%, 56.3%, 4.2%, and 14.5%. Exposure to 150, 250, 1,000 or 2,000 ppm VC caused a progressive depression of the hepatic nonprotein sulphydryl content; exposure to 50 ppm VC for 7 hr produced a small, inconsistent depression; no depression was observed in rats exposed to 10 ppm. These results indicate that statistical projections of data from rats exposed to high doses of VC are not valid for predicting effects of low-level exposure, because the metabolism of VC at different dose levels is not the same. (13 Refs)

24. METABOLIC APPROACH TO INDUSTRIAL POISONING: BLOOD KINETICS AND DISTRIBUTION OF ¹⁴C-VINYLCARBON MONOMER (V.C.M.) (MEETING ABSTRACT).

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Acta Pharmacol Toxicol Suppl (Kbh); 41(1):142-143 1977

Since the lungs (besides the skin) are one of the most important routes of occupational poisoning, we have developed acute inhalation tests with labeled substances. Rats were exposed (in total enclosure) for 5 min in a small glass pilot unit. This thermoregulated inhalation chamber received a dynamic air flow (200 or 400 liter/hr) into which vinylchloride monomer (VCM) was injected (1 liter/hr). At the exit, congealment methods recovered the waste VCM. For the blood kinetic studies (5 min inhalation with 10,000 ppm VCM), a permanent catheter had been implanted in the aortic artery and heparinized blood was regularly collected during the 5 min inhalation period and also during 90 min later. The data plotted on a diagram showed particular time variations, which were chosen for autoradiographic studies. New rats have been exposed (5 min inhalation with 20,000 ppm VCM), and 10, 20, 60, 120, 180 min later anesthetized and then frozen. Autoradiographs were then obtained. At 10 min the liver, bile duct, digestive lumen and kidneys contained radioactivity. Later the amount and the distribution of labeled substances (probably both VCM and its metabolites) increased. The urinary system, salivary and lacrimal glands, liver, skin and thymus contained a great deal of labeled molecules. These findings indicate that inhaled VCM is rapidly absorbed through the lungs and immediately accumulated in the liver. Observation of autoradiographs confirms an urinary excretion and probably indicates bile excretion. (no Refs)

25. THREE-STEP AUTORADIOGRAPHY OF ORGANIC SOLVENTS AND PLASTIC MONOMERS TO REGISTER TOTAL RADIOACTIVITY, NON-VOLATILE METABOLITES, AND NON-EXTRACTABLE METABOLITES (MEETING ABSTRACT).

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Acta Pharmacol Toxicol Suppl (Kbh); 14(1):22 1977

Whole-body autoradiography was used to study the distribution and fate of organic solvents and plastic monomers in the body. Following the administration of these substances, the animals were frozen in liquid nitrogen. Hemisections of the animals were taken with a saw and exposure was performed in a freeze-box at -80 C. Sections of the animals were then taken on tape, allowing the volatile material to evaporate, and autoradiography was performed at -20 C. The tape-fastened

sections were then extracted with water, trichloroacetic acid, and organic solvents and re-exposed at 20 C. This three-step autoradiographic procedure has been applied to distribution studies of organic solvents such as benzene, toluene, xylene, methylene chloride, chloroform, carbon tetrachloride and trichloroethylene and to plastic monomers such as vinylchloride and styrene. A common finding has been the presence of non-metabolized substances in the adipose tissues and the brain. Non-extractable metabolites of some organic solvents and plastic monomers have been found in different tissues, notably in the liver and the kidney. Several distinctive features in the distribution patterns have also been observed for these substances. (1 Refs)

26. PHARMACOKINETICS OF VINYLIDENE CHLORIDE IN THE RAT.

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Environ Health Perspect; 21:99-105 1977

The effects of inhaled vinylidene chloride (VDC; 1,1-dichloroethylene) were determined in rats and mice. In male Sprague-Dawley fasted and fed rats exposed to either 10 or 200 ppm VDC for 6 hr, fasting augmented the process whereby reactive intermediates formed from VDC induced tissue damage. Rats exposed to 200 ppm labeled VDC exhaled a greater percentage of their acquired body burden of radioactivity as unchanged VDC than did animals exposed to 10 ppm. However, rats exposed to the higher concentration showed a greater percentage of body burden remaining in the carcass at 72 hr after exposure. Retention of radioactivity in the carcass was greater in fasted rats exposed to 200 ppm VDC, despite a smaller fraction of the body burden biotransformed by fasted rats. The presence of mercapturic acid derivatives in the urine of exposed rats indicated a major role for glutathione in the detoxification of VDC. Apparently, VDC metabolism represents a balance between biotransformation pathways leading to detoxification by way of glutathione or to covalent binding to tissue nucleophiles and subsequent tissue damage. Enhanced susceptibility to VDC was noted in Ha(ICR) mice exposed to 10 ppm VDC for 6 hr, probably because of their more rapid metabolism of VDC and greater production of alkylating VDC metabolites over that in the rat. (9 Refs)

27. THE BIOLOGICAL FATE OF VINYLIDENE CHLORIDE IN RATS.

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Chem Biol Interact; 20(1):27-41 1978

The fate of vinylidene chloride (DCE) following intragastric (ig), iv, or ip administration to male Alderley Park rats was determined. In rats given 500-ug/kg or 350-mg/kg doses of labeled DCE by all three routes, almost all the radioactivity was recovered within 72 hr of dosing; with 500 ug/kg ig, however, small amounts of label were still being recovered 72-108 hr after dosing. With the higher ig dose, nearly 70% of the dose was excreted as unchanged DCE and 1% as DCE-related CO₂ by the lungs; with the lower dose, urinary excretion accounted for 80%, and less than 1% of the unchanged DCE plus 4%-6% of DCE-CO₂ were eliminated by the lungs. This change in excretion pattern appeared to be due to a saturable drug metabolism and an arterial-alveolar transfer of unchanged DCE from the blood. In comparison, 80% of the small iv dose was excreted unchanged from the blood within 1 hr (greater than 60% within 5 min). The excretion pattern after a small ip dose was intermediate between that resulting from iv and that from ig administration. For groups of rats administered various dose levels ig within a 1,300-fold

dose range, the plot of the pulmonary excretion of unchanged DCE against the log of the reciprocal doses was biphasic. Radiography following ig doses revealed the presence of large amounts of the ¹⁴C label in the kidneys and liver after 30 min and a more general distribution of ¹⁴C throughout the soft organs at 1 hr. The kidneys and liver retained the label for the longest times. Biotransformation resulted in thiodiglycolic acid and an N-acetyl-S-cysteinylacetyl derivative as the major urinary metabolites, together with substantial amounts of chloroacetic acid, dithioglycolic acid, and thioglycolic acid. (12 Refs)

28. DISPOSITION AND METABOLISM OF ¹⁴C 1,1-DICHLOROETHYLENE AFTER SINGLE ORAL ADMINISTRATION IN RATS (MEETING ABSTRACT).

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Naunyn Schmiedebergs Arch Pharmacol; 302(Suppl):R22 1978

1,1-Dichloroethylene (VDC, vinylidene chloride) is converted metabolically to mutagenic and carcinogenic intermediates. We have investigated the metabolic fate of ¹⁴C-VDC in rats after single oral doses of 0.5, 5 and 50 mg/kg by collecting and analyzing expired air, urine and feces for 72 hr following administration. The proportions of expired unchanged VDC/¹⁴CO₂/urinary activity were as follows: 0.5 mg/kg-0.9%/23%/52%; 5 mg/kg-20%/6%/36%. This change in the conversion rate and in the pattern of metabolites is indicative of a rapid saturation of VDC metabolism. This is consistent with previous studies on the uptake and metabolism of VDC by the isolated perfused rat liver. Nonvolatile radioactivity within the body after 72 hr comprised 2-4% of the administered dose and was highest in the liver, the other organs containing minimal amounts only. Thus, most of the VDC is rapidly excreted either unchanged or in the form of polar metabolites. Three major metabolites were separated by thin layer chromatography and gas chromatography, the main part of activity has been identified as thiodiglycolic acid by mass spectrometry.

29. THE USE OF INHALATION TECHNIQUES TO ASSESS THE KINETIC CONSTANTS OF 1,1-DICHLOROETHYLENE METABOLISM.

Andersen ME, Gargas ML, Jones RA, Jenkins LJ
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Patterson Air Force Base, OH, 45433
Toxicol Appl Pharmacol; 47(2):395-409 1979

Inhalation techniques were used to assess the kinetic constants of 1,1-dichloroethylene (1,1-DCE) metabolism. A closed chamber system was developed to study the rate of gas inhalation of rats. By analyzing the time course of uptake curves obtained at various concentrations, the K_m (as atmospheric ppm) of the reaction as well as the max velocity (V_{max}) of metabolism were determined. Two distinct phases could be traced in the gas phase uptake: whole body equilibrium was represented by a rapid phase with a concentration-independent rate constant of 2.2 hr⁻¹. The magnitude of the rapid phase was in proportion to the mass of rats in the chamber and the concentration of 1,1-DCE. Rapid phase uptake corresponded to a whole body/gas distribution coefficient of 4.04. The slow phase represented metabolism and was abolished by pretreatment with pyrazole or simultaneous exposure to CCl₄. The acute inhalation toxicity was shown to be a direct function of the amount of metabolite formed, and not of the concentration of 1,1-DCE. Mortality was produced by short-term exposures after formation of 25-30 mg of metabolite/kg. At concentrations between 200-1000 ppm, a direct correspondence was found between the time of

exposure required to kill the rats and the time calculated to produce a constant amount of metabolite(s). (34 Refs)

30. TISSUE DISTRIBUTION AND METABOLISM OF 1,2-DIBROMOETHANE (MEETING ABSTRACT).

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Proc Am Assoc Cancer Res; 17(1):56 1976

1,2-Dibromoethane (DBE), a compound carcinogenic to rats and mice, becomes widely distributed in tissues of treated rats and is a substrate for 2 different enzymes in rat tissues. At 1 and 3 hr following an intraperitoneal inj of an ethanol solution of (1,2-¹⁴C)-DBE, radioactivity is concentrated in the liver, kidney, and small intestine. After 24 hr, radioactivity remains in the liver and kidney. At this time, these organs have more radioactivity irreversibly bound to RNA, DNA, and protein than other tissues. In a process possibly related to the in vivo binding of DBE, an enzyme present in rat liver microsomes catalyzes a reaction leading to irreversible binding of radioactivity from DBE to protein in the reaction system. The reaction is dependent upon the presence of TPNH and is stimulated by MgCl₂ substrate for a glutathione-S-transferase present in liver, kidney, lung, testes, spleen, and heart of rats. For the liver transferase, the pH optimum is 8.2, and the Michaelis constant for DBE is 25 nM. This reaction presumably is involved in the detoxification of DBE. (Author Abstract)

31. DISTRIBUTION OF METABOLITES OF BENZO(A)PYRENE IN THE ISOLATED PERFUSED RABBIT LUNG PREPARATION (MEETING ABSTRACT).

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Toxicol Appl Pharmacol; 37(1):189-190 1976

The distribution of metabolites of benzo(a)pyrene in the isolated perfused rabbit lung was investigated. Trichloroethylene was added to the ventilating gas inhaled by the isolated lungs and was evident in the blood after 15 to 30 min of exposure. Chloral hydrate and trichloroethanol glucuronide were not observed. Trichloroethanol in lung tissue was estimated at about 30% of the total metabolites recovered in both rabbit and guinea pig preparations. Trichloroethanol production appeared to be independent of trichloroethylene concentrations; trichloroacetic acid was present in smaller amounts. Pretreatment of rats with phenobarbital significantly increased trichloroethanol formations in isolated lungs. Addition of ethanol to increase blood concentrations did not affect trichloroethanol formation. Although the lungs did show some deterioration with time, trichloroethanol appearance was linear over 3 hr. This system appears to be a valid one for the investigation of pulmonary metabolism of trichloroethanol. (no refs)

32. IRREVERSIBLE BINDING OF CHLORINATED ETHYLENES TO MACROMOLECULES.

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Environ Health Perspect; 21:107-112 1977

The binding of vinyl chloride (VC) and trichloroethylene (TCE) to male Wistar rat macromolecules was investigated and compared to that of carbon tetrachloride (CCl₄). Saturation of the rat metabolizing systems was achieved at 250 ppm VC, 150 ppm TCE, and 250 ppm CCl₄. Data on the uptake of the compounds, the urinary excretion of metabolites, and exhalation after exposure indicated that the chlorinated ethylenes were metabolized much faster than CCl₄. The metabolites of all three compounds bound

irreversibly to tissue proteins, mainly in the liver. Other sites of binding included the kidneys, small intestine, lung, and spleen. Irreversible binding of these compounds ranged within the same order of magnitude when related to the amount of the compound that had been absorbed. No differences in the relative portion of irreversibly bound metabolites were found after exposure of the rats to different atmospheric concentrations of the three compounds. In vitro studies indicated that TCE metabolism by rat liver microsomes in the presence of an NADPH-regenerating system leads to irreversible protein binding, mainly to albumin; similar findings have been reported for VC. Unlike VC, however, TCE metabolites also bind to non-SH proteins such as gamma-globulin and concanavalin A. Thus, TCE metabolites irreversibly bind not only to SH groups of a protein, but also to NH₂ groups. (28 Refs)

33. IRREVERSIBLE BINDING OF ¹⁴C-LABELLED TRICHLOROETHYLENE TO MICE LIVER CONSTITUENTS IN VIVO AND IN VITRO.

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Arch Toxicol (Berl); 37(4):289-294 1977

¹⁴C-labeled trichloroethylene (10 μmoles/g) administered to male NMRI mice resulted in irreversible binding to the protein of liver fractions. After oral or ip doses of undiluted trichloroethylene, peak liver concentrations were found between 60 and 90 min, with only slightly higher concentrations after ip injection. Covalent binding increased two-fold in microsomes of mice pretreated with phenobarbital. (20 Refs)

34. THE ENVIRONMENTAL FATE OF THREE CARCINOGENS: BENZO(ALPHA)PYRENE, BENZIDINE, AND VINYL CHLORIDE EVALUATED IN LABORATORY MODEL ECOSYSTEMS.

Lu PY, Metcalf RL, Plummer N, Mandel D

Dept. Entomology and Inst. Environmental Studies, Urbana, IL 61801

Arch Environ Contam Toxicol; 6(2-3):129-142 1977

The degradation, environmental fate, bioaccumulation, and food chain transfer of radiolabeled benzo(alpha)pyrene (BP), benzidine (BD), and vinyl chloride (VC) were evaluated in two laboratory model ecosystems. In a closed aquatic system, 0.002 ppm BP and 0.008 ppm BD were applied directly to the water and allowed to pass through an aquatic food chain. Their transfer and degradation were observed over a 3-day period. In a terrestrial-aquatic ecosystem, 0.2 mg of BP and BD, either alone or with 1.0 mg pipronyl butoxide, were topically applied in acetone solution to *Sorghum vulgare* seedlings, representing chemical fallout. They were then allowed to pass through a food chain. The resulting food chain by-products were then allowed to interact in the ecosystem over a 33-day period. It was shown that BP is highly lipophilic and it can bioaccumulate to potentially hazardous levels. This problem was intensified in snails and other organisms deficient in microsomal oxidase, or when there was a presence of mixed function oxidase inhibitors. BD was not bioaccumulated or transferred through food chains to high levels. BD levels were not affected appreciably by the presence of mixed function oxidase inhibitors. Vinyl chloride did not bioaccumulate or transfer appreciably through the food chains, at least at the ordinary temperatures studied due to its high volatility. There was an excellent correlation between bioaccumulation and octanol/water partition, illustrating that this property and water solubility can be of predictive value in environmental toxicological studies. (19 Refs)

2. Metabolism and Activated Intermediates of Vinyl Chloride and Related Compounds in Experimental Animals

The reader may also find the following abstracts of interest: 13, 14, 15, 19, 21, 27, 28, 32, 178, 196

35. THE CHEMISTRY AND BIOGENESIS OF THE S-CONTAINING METABOLITES OF VINYL CHLORIDE IN RATS.

Green T, Hathway DE

Imperial Chemical Industries Ltd., Central Toxicology Lab., Alderley Park, Cheshire SK10 4TJ, England
Chem Biol Interact; 17(2):137-150 1977

The biogenesis of the various urinary S-containing metabolites of vinyl chloride (VC) was investigated in adult male rats. Groups of rats were administered the following chemicals intragastrically: (1) ^{14}C -VC (100 mg/kg; 10 μCi), (2) chloroacetaldehyde (50 mg/kg), (3) S-(2-hydroxyethyl)-L-cysteine (500 mg/kg), or (4) S-(carboxymethyl)-L-cysteine (CMC: 250 mg/kg), and a 24-hr urine sample was taken. Two rats were given repeated daily ip injections of L-(U- ^{14}C) cysteine hydrochloride for 5 days and, 30 min after the final injection, a single dose of VC (100 mg/kg); a 24-hr urine sample was then taken. Two rats were given a single intragastric dose of ^{14}C -VC (450 mg/kg) and sacrificed after 45 min; they were dissected and their livers removed. N-Acetyl-S-(2-hydroxyethyl)cysteine (AHC) was a major VC metabolite, but, according to the method of protective esterification used, either N-acetyl-S-(2-chloroethyl)cysteine or AHC can be isolated from the body fluids. N-Acetyl-S-vinylcysteine was a second related metabolite. These S-containing VC metabolites were not mutagenic in *S. typhimurium*. Administration of the VC metabolites and related compounds to rats indicated that chloroacetaldehyde and CMC, but not chloroacetic acid, are on a pathway connecting VC with thiodiglycollic acid. The fact that chloroacetaldehyde produced both thiodiglycollic acid and AHC in the animal and that CMC was identified among the hydrolytic products from a hepatic extract of VC-treated animals is consistent (1) with the formation of chloroacetaldehyde and (2) with the reaction of chloroethylene oxide or chloroacetaldehyde with glutathione in the presence of a glutathione S-epoxide transferase to give the identified S-containing metabolites. (22 Refs)

36. INTERACTIONS OF VINYL CHLORIDE WITH RAT-LIVER DNA IN VIVO.

Green T, Hathway DE

Imperial Chemical Industries Ltd., Central Toxicology Lab., Alderley Park, Cheshire SK10 4TJ, England
Chem Biol Interact; 22(2/3):211-224 1978

The reaction of vinyl chloride (VC) with liver DNA in Wistar rats and the reaction of chloroacetaldehyde (CAA) and calf thymus DNA were investigated. 9beta-D-2'-Deoxyribofuranosylimidazo-(2,1-i)-purine (ethenodeoxyadenosine) and 1beta-D-2'-deoxyribofuranosyl-1,2-dihydro-2-oxoimidazo-(1,2-c)-pyrimidine (ethenodeoxycytidine) were identified in the enzyme hydrolysates obtained (1) from calf thymus DNA that had been modified by chemical reaction with CAA and (2) from liver DNA prepared from rats that had been exposed po to VC in their drinking water (250 ppm) for approx 2 yr. Thus, VC-derived chloroethylene oxide and/or CAA behaved as a bifunctional alkylating agent toward deoxyadenosine and deoxycytidine residues of DNA. It is concluded that modification of the DNA structure by VC, through imidazocyclization of deoxyadenosine and deoxycytidine residues and through depurination of the resulting ethenodeoxyadenosine residues, is related to the mutagenicity of VC. The carcinogenicity of VC in animals and in humans and its

mutagenic properties after biotransformation (by microsomal enzymes) into the active metabolites chloroethylene oxide and CAA, which show electrophilic reactivity toward DNA, would appear to conform with the idea of a relationship between carcinogenesis and mutagenesis. (41 Refs)

37. FORMATION OF ETHENO DERIVATIVES OF NUCLEIC ACID BASES IN VIVO BY METABOLITES OF VINYL CHLORIDE (MEETING ABSTRACT).

Laib RJ, Ottenwalder H, Bolt HM

Inst. Toxikologie, Univ. Tübingen, Wilhelmstr. 56, D-7400 Tübingen, W. Germany

Hoppe Seylers Z Physiol Chem; 359(3):293 1978

The detection of mutagenic and carcinogenic effects of vinyl chloride greatly stimulated research on the molecular mechanism of vinyl chloride disease. Rat liver microsomes were incubated with NADPH, 1,2- ^{14}C vinyl chloride and polyadenylic acid or polycytidylic acid. The latter were re-isolated from the incubation mixtures and hydrolyzed. The radioactivity originating from ^{14}C vinyl chloride, which was irreversibly bound to the polyadenylic or polycytidylic acid, was confined to 1,N⁴-ethenoadenosine or 3,N⁴-ethenocytidine. When rats were exposed to 1,2- ^{14}C vinyl chloride, part of the radioactivity was incorporated into the liver RNA. Analysis of hydrolysates of liver RNA showed that all natural nucleosides of RNA were labeled. Besides, small amounts of radioactivity could be detected which were confined to 1,N⁴-ethenoadenosine and 3,N⁴-ethenocytidine. DNA from livers of rats exposed to 1,2- ^{14}C vinyl chloride also contained significant amounts of radioactivity. When DNA was incubated with rat liver microsomes, NADPH and ^{14}C vinyl chloride, radioactivity was also incorporated into the DNA. Re-isolation of the DNA, hydrolysis and separation of the nucleosides showed that radioactive 1,N⁴-etheno-2'-deoxyadenosine and 3,N⁴-etheno-2'-deoxycytidine were formed. The experiments support the theory that vinyl chloride metabolites react with adenine or cytosine moieties of nucleic acids to form etheno analogues.

38. FORMATION OF 3,N⁴-ETHENOCYTIDINE MOIETIES IN RNA BY VINYL CHLORIDE METABOLITES IN VITRO AND IN VIVO.

Laib RJ, Bolt HM

Institut für Toxikologie, Universität Tübingen, Wilhelmstrasse 56, D-7400 Tübingen, W. Germany
Arch Toxicol (Berl); 39(3):235-240 1978

Rats were exposed to ^{14}C -vinyl chloride, and the in vivo liver metabolites were examined. In addition to RNA and 1,N⁴-ethenoadenosine, 3,N⁴-ethenocytidine was also radioactively labeled. In vitro experiments using vinyl chloride-exposed liver microsomes and NADPH produced the same results. These alkylation mechanisms are consistent with the mutagenic and carcinogenic properties of vinyl chloride. (22 Refs)

39. FORMATION OF IMIDAZOL DERIVATIVES OF NUCLEIC ACID BASES (DNA AND RNA) BY METABOLITES OF VINYL CHLORIDE IN VIVO AND IN VITRO (MEETING ABSTRACT). (PP. 84)

Laib RJ, Bolt HM

Inst. Toxicology, Tübingen, W. Germany

Fourth Meeting of the European Association for Cancer Research Held at Université de Lyon, September 13-15, 1977. European Association for Cancer Research, Lyon, France 1977.

Rat liver microsomes were incubated with NADPH, 1,2- ^{14}C vinyl chloride and polyadenylic acid or polycytidylic acid. The latter were re-isolated from the incubations and hydrolyzed. The radioactivity originating from ^{14}C vinyl chloride, which was irreversibly bound to the polyadenylic or

polycytidylic acid, was confined to 1,N⁴-ethenoadenosine or 3,N⁴-ethenocytidine. When rats were exposed to 1,2-C14-vinyl chloride, part of the radioactivity was incorporated into liver RNA. Analysis of hydrolysates of liver RNA showed that all natural nucleosides of RNA were labeled. Small amounts of radioactivity could be detected which were confined to 1,N⁴-ethenoadenosine and 3,N⁴-ethenocytidine. DNA of rat liver after exposure of the animals to 1,2-C14 vinyl chloride also contained significant amounts of radioactivity. When DNA was incubated with rat liver microsomes, NADPH and C14 vinyl chloride, radioactivity was also incorporated into the DNA. Re-isolation of the DNA, hydrolysis and separation of the nucleosides showed that radioactive 1,N⁴-etheno 2'-deoxyadenosine was formed. The experiments support the theory that vinyl chloride metabolites react with adenine or cytosine moieties of nucleic acids to form etheno analogs. These alkylation mechanisms are consistent with the mutagenic properties of vinyl chloride. (no Refs)

40. ALKYLATION OF RNA BY VINYL CHLORIDE METABOLITES IN VITRO AND IN VIVO: FORMATION OF 1-N⁴-ETHENO-ADENOSINE.

Laib RJ, Bolt HM

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Germany

Toxicology; 8(2):185-195 1977

The incorporation of 14C radioactivity from vinyl chloride into RNA of liver is described, and the possibility of formation of etheno-adenosine moieties in liver RNA on exposure of rats to 14C vinyl chloride is examined. Rat liver microsomes were incubated with NADPH, 1,2-14C vinyl chloride and poly-adenosine. Poly-adenosine was reisolated from the incubations and hydrolyzed. 14C vinyl chloride radioactivity was confined to 1-N⁴-etheno-adenosine. When rats were exposed to 1,2-14C vinyl chloride, part of the radioactivity was incorporated into RNA of liver and exhibited a first maximum, 14 hr, and a second maximum, 72 hr after ending the exposure. Analysis of hydrolysate of liver RNA showed that all natural nucleosides of RNA were labeled, and that small amounts of radioactivity were confined to 1-N⁴-etheno-adenosine. Thus, the experiments support the theory that vinyl chloride metabolites react with adenosine moieties of nucleic acid under formation of 1-N⁴-etheno-adenosine. The results show that measurement of incorporation of radioactivity into nucleic acids after exposure of animals to radioactive vinyl chloride is not applicable as a means of determining the alkylating potency of vinyl chloride metabolites towards nucleic acids in vivo. (29 Refs)

41. ALKYLATION OF DNA AND RNA BY METABOLITES OF VINYL CHLORIDE AND VINYL BROMIDE (MEETING ABSTRACT).

Laib RJ, Ottenwalder H

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Wilhelmstrasse 56, D-7400 Tübingen, W. Germany

Naunyn Schmiedeberg's Arch Pharmacol; 302(Suppl):R21 1978

If rats are exposed to 14C-vinyl chloride, radioactivity is incorporated into nucleic acids of the liver. In previous investigations we showed incorporation of radioactivity from 14C-vinyl chloride into the physiological bases of RNA. In addition, alkylation of adenosine and cytidine moieties occurred leading to formation of radioactive 1,N⁴-ethenoadenosine and 3,N⁴-ethenocytidine. The time courses of 1,N⁴-ethenoadenosine and 3,N⁴-ethenocytidine in rat liver RNA after vinyl chloride inhalation are dissimilar: 92 hr after ending exposure the ethenoadenosine is only 1/5 of its original value whereas the content of ethenocytidine persists. This ought to be indicative for the relative importance of cytidine alkylation. Formation of labeled etheno derivatives of adenosine and

cytidine was also observed if rats were exposed to 14C-vinyl bromide. To establish possible changes in DNA due to alkylation by vinyl chloride metabolites, DNA was incubated with rat liver microsomes, NADPH and 14C-vinyl chloride. Re-isolation of the DNA, hydrolysis and separation of the nucleosides on Aminex-A-6 showed that small amounts of radioactive 1,N⁴-etheno 2'-deoxyadenosine and 3,N⁴-etheno 2'-deoxycytidine were formed. In addition, a major alkylation product, presumably of 2'-deoxyguanosine was isolated which, on Aminex-A-6-columns, showed the same chromatographic behavior as a compound which was obtained from chemical reaction of 2'-deoxyguanosine with chloroacetaldehyde.

42. ALKYLATION OF DNA AND PROTEINS IN MICE EXPOSED TO VINYL CHLORIDE.

Osterman-Golkar S, Hultmark D, Segerback D, Calleman CJ, Gothe R, Ehrenberg L, Wachmester CA

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Biochem Biophys Res Commun; 76(2):259-266 1977

Male CBA, BALB, and ATL mice (2-3 mo old) were exposed to various doses (98-160 ppm/hr) of ¹⁴C-labeled vinyl chloride in glass inhalation chambers for 2-10 hr, and alkylation products recovered from their testes protein, and liver DNA were quantitatively measured. Chromatographic results indicated that vinyl chloride is metabolically activated to form an alkylating agent that introduces the 2-oxoethyl group onto nucleophilic sites; alkylation by chloroethanol was negligible. The alkylation of cysteine and histidine in Hb and of guanine-N-7 in liver DNA varied with the strain of mice used. Considering the sensitivity of the alkylating agents to changes in nucleophilic strength, chloroethylene oxide appeared to be the main reactive metabolite. Male gonads were exposed to the alkylating intermediate, and a risk of heritable damage as well as cancer can be expected. (18 Refs)

43. THE METABOLIC ACTIVATION OF VINYL CHLORIDE IN VITRO (MEETING ABSTRACT).

Ivanetich KM, Katz ID, Aronson I

Dept. Physiology and Medical Biochemistry, Univ. Cape Town Medical Sch., Cape Town, S. Africa

Mutat Res; 53(2):204 1978

In the presence of hepatic microsomes, vinyl chloride produces a 'Type I' difference spectrum and stimulates carbon monoxide inhibitable NADPH consumption. Vinyl chloride, therefore, appears to bind to and to be metabolized by hepatic microsomal cytochrome P-450 in vitro. The K_s value for the binding of vinyl chloride to cytochromes P-450 in uninduced microsomes (80 mM) is decreased to approx 10 mM following phenobarbital or 3-methylcholanthrene induction. The change in A_{max} and max velocity values are not altered by 3-methylcholanthrene induction, but are enhanced 2-to 3-fold by phenobarbital induction. These results indicate that more one type P-450 cytochrome binds and metabolizes vinyl chloride, but that the cytochrome P-450 induced by phenobarbital plays a major role in these processes. In the presence of NADPH and hepatic microsomes, vinyl chloride mediates the degradation of the heme moiety of cytochrome P-450. Under these conditions, the levels of other hepatic microsomal enzymes are not affected. The effect of vinyl chloride on the levels of cytochrome P-450 is slight in uninduced or 3-methylcholanthrene microsomes but is striking in phenobarbital microsomes. The effect is abolished in the absence of NADPH or vinyl chloride and is diminished by reduced glutathione. The activated metabolite of vinyl chloride produced by cytochrome P-450 may in part mediate the mutagenic and carcinogenic effects of vinyl chloride. (no Refs)

44. METABOLISM OF VINYL CHLORIDE: DESTRUCTION OF THE HEME OF HIGHLY PURIFIED LIVER MICROSOMAL CYTOCHROME P-450 BY A METABOLITE.

Guengerich FP, Strickland TW
Dept. Biochemistry, Vanderbilt Univ. Sch. Medicine,
Nashville, TN 37232
Mol Pharmacol; 13(6):993-1004 1977

The NADPH-dependent, vinyl chloride (VC)-mediated destruction of cytochrome P-450 (Cy P-450) was demonstrated in rat liver microsomes and in highly purified reconstituted enzyme systems containing NADPH cytochrome P-450 reductase and cytochrome Cy P-450. This loss of Cy P-450 could be attributed to heme destruction, but not to lipid peroxidation or binding of electrophiles to free sulfhydryl groups. The system required all the components necessary for mixed-function oxidation, including molecular oxygen, and it was inhibited by carbon monoxide, suggesting strongly that oxidative metabolism of VC by Cy P-450 is necessary for destruction. The NADPH Cy P-450 reductase-catalyzed destruction of free and Cy P-450-bound heme was also observed in reconstituted systems in the absence of VC. Inhibition experiments with carbon monoxide and catalase suggested that the VC-mediated destruction of Cy P-450 heme differs from these processes. Two proposed VC metabolites, VC epoxide and 2-chloroacetaldehyde, do not appear to be responsible for the heme destruction. Evidence for the involvement of free radicals could not be demonstrated when the reaction was examined by electron paramagnetic resonance spectroscopy or when attempts were made to inhibit Cy P-450 destruction with radical-trapping agents. (56 Refs)

45. THE INTERACTION OF VINYL CHLORIDE WITH RAT HEPATIC MICROSOMAL CYTOCHROME P-450 IN VITRO.

Ivanetich KM, Aronson I, Katz ID
Dept. Physiology Medical Biochemistry, Univ. Cape Town
Medical Sch., Cape Town, South Africa
Biochem Biophys Res Commun; 74(4):1411-1418 1977

The interaction of vinyl chloride (VC) in vitro with the cytochrome P-450 enzyme system of the hepatic endoplasmic reticulum of Long Evans male rats was investigated. The binding of VC to cytochrome P-450 in vitro was studied spectrally in microsomes from uninduced, 3-methylcholanthrene (3-MC)-induced, and phenobarbital (PB)-induced rats. VC bound to hepatic microsomal cytochrome P-450 in all types of microsomes, with production of a type I difference spectrum. Hanes plots of the spectral binding of VC to cytochrome P-450 were linear for all types of microsomes. VC increased CO-inhibitable NADPH consumption by hepatic microsomes from induced rats. Induction by 3-MC did not increase the apparent max velocity much above that obtained for uninduced microsomes. However, for PB-induced microsomes, max velocity was approx fivefold greater than the apparent max velocity obtained with uninduced microsomes. The effects of inhibitors on the interaction of VC with cytochrome P-450 were determined. SKF 525A fully inhibited the binding of VC to cytochrome P-450, but it did not decrease the enhancement of CO-sensitive NADPH consumption by VC. However, metyrapone did not significantly inhibit the binding of VC to cytochrome P-450 but did inhibit the enhancement of CO-sensitive NADPH consumption by VC. The influence of incubation of hepatic microsomes from induced rats with VC on microsomal enzyme levels was assessed. The levels of cytochrome P-450, cytochrome b5, and NADPH-cytochrome c reductase were not altered after incubation of hepatic microsomes with either VC, NADPH, or NADH. Cytochrome b5 and NADPH-cytochrome c reductase were not affected after incubation of

hepatic microsomes with VC plus NADPH, but cytochrome P-450 was decreased. The VC-mediated decrease in cytochrome P-450 was slight in control (8%) and 3-MC (7%) microsomes, but was significant in PB microsomes (31%). In PB-induced microsomes, microsomal heme was decreased by approx 30% of the decrease in cytochrome P-450. Reduced glutathione and CO inhibited the VC-mediated decrease in cytochrome P-450 in PB-induced microsomes by approx 30% and 80%, respectively. NADH supported the VC-mediated decrease in cytochrome P-450 by approx 30% in comparison to NADPH. The results may provide an explanation for the observation that prior exposure of laboratory animals to VC protects them against the toxic effects of VC. (17 Refs)

46. CYTOCHROME P-450 AND THE METABOLISM OF VINYL CHLORIDE.

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Cancer Lett (Amsterdam); 2(2):109-114 1976

The involvement of cytochrome P-450 in vinyl chloride metabolism was studied. Rat liver microsomes were obtained from male Alderley Park strain SPF albino rats (weighing 150-200 g), and U-¹⁴C vinyl chloride (1 mCi/millimole) was utilized. Enzymic oxidation of vinyl chloride was assayed by the formation of nonvolatile products. There was a time-dependent increase in the amount of label incorporated into nonvolatile water-soluble material. The reaction rate remained constant for 15 min but decreased later, possibly due to exhaustion of substrates and further metabolism of products. Label was not incorporated into either the soluble or solid fractions in the absence of microsomes or NADPH or in the presence of microsomes previously heated to 100°C for 5 min. Addition of 1 mM reduced glutathione to the reaction mixture increased the microsome-catalyzed formation of nonvolatile water-soluble products. In the absence of active enzymes, there was no reaction of vinyl chloride with glutathione. The concentration of cytochrome P-450 was found to be 0.6 nanoM/mg protein. Addition of 100 microM phenobarbital to a microsome suspension increased absorbance at 390 nanometers and decreased it at 420 nanometers (a typical type I difference spectrum). A similar difference spectrum was demonstrated after saturation of a microsomal suspension with vinyl chloride. The type I difference spectrum suggests an interaction with a cytochrome P-450 present in liver microsomes without induction. (12 refs)

47. METABOLISM OF ¹⁴C- AND ³⁶CL-LABELED VINYL CHLORIDE IN VIVO AND IN VITRO.

Guengerich FP, Watanabe PG
Dept. Biochemistry, Center Environmental Toxicology,
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Biochem Pharmacol; 28(5):589-596 1979

Studies were conducted to establish the roles of liver microsomal cytochrome P-450 and epoxide hydratase in the biotransformation of vinyl chloride (VC) to metabolites, particularly those bound to protein and nucleic acids. Label from ¹⁴CVC was covalently bound to protein and nucleic acids in vivo and in vitro in the presence of Sprague-Dawley rat liver microsomal fractions or highly purified cytochrome P-450 and NADPH-cytochrome P-450 reductase preparations. The ratio of bound to total nonvolatile metabolites increased in going from the in vivo to the microsomal to the purified system. ³⁶CVC was metabolized by microsomes and highly purified systems: no label was bound, and most of the metabolized chlorine could be accounted for as chloride ion. Phenobarbital pretreatment of rats did not induce total metabolism of VC in vivo at either the 10- or 250-ppm exposure levels; however, binding to protein and RNA was

enhanced at the 10-ppm but not the 250-ppm level. Phenobarbital pretreatment increased the in vitro microsomal conversion of VC to both total and bound metabolites. A sizeable fraction of the label of ¹⁴CVC metabolized in vivo was recovered in the microsomal fraction of the liver, but sodium dodecyl sulfate-polyacrylamide gel electrophoresis of in vitro incubations indicated that the metabolites were distributed among many microsomal proteins and not localized to cytochrome P-450. Evidence was obtained for the metabolism of the suspected VC metabolite chloroethylene oxide by microsomal epoxide hydratase. However, the epoxide hydratase inhibitor 3,3,3-trichloropropylene oxide, which blocks the microsomal degradation of chloroethylene oxide, did not enhance the level of VC bound to either protein or adenosine. (39 Refs)

48. VINYL CHLORIDE-MEDIATED CYTOCHROME P-450 DESTRUCTION (MEETING ABSTRACT).

Strickland TW, Guengerich FP
Vanderbilt Univ, Nashville, TN 37232
Fed Proc; 36(3):991 1977

The vinyl chloride (VC)-mediated destruction of cytochrome P-450 (P-450) and loss of mixed-function oxidase activity were demonstrated in rat liver microsomes. This P-450 destruction was also demonstrated in highly purified reconstituted systems consisting of P-450, NADPH-P-450 reductase (Fp), phosphatidylcholine, deoxycholate, VC, O₂, and NADPH; all components were required and destruction was inhibited 80% by the addition of 20% CO, suggesting that oxidative metabolism of VC by P-450 to a reactive metabolite is responsible for the destruction. Loss of heme paralleled P-450 destruction while the free sulfhydryl content was not lowered during incubation; several experiments indicate that lipid peroxidation does not play a role in the process. The destruction is not due to VC-epoxide or chloroacetaldehyde. Fp (in the presence of NADPH and O₂) also destroys both free heme (ferriprotoporphyrin IX) and P-450 heme in the absence of P-450 substrates. The latter two processes appear to be similar, but distinct from VC-mediated P-450 destruction, as judged by their sensitivity to catalase and insensitivity to CO. (Author Abstract)

49. RESOLUTION OF DOSE-RESPONSE TOXICITY DATA FOR CHEMICALS REQUIRING METABOLIC ACTIVATION: EXAMPLE - VINYL CHLORIDE.

Gehring PJ, Watanabe PG, Park CN
Health and Environmental Res., Dow Chemical USA,
Midland, MI, 48640
Toxicol Appl Pharmacol; 44(3):581-591 1978

The concept that the toxicity of many chemicals may not be a function of exposure to the chemical per se but rather to a biotransformation product is illustrated with vinyl chloride (VC). In such a case, it is necessary to determine the amount of the chemical undergoing biotransformation as a function of dose or exposure before a meaningful dose-response relationship can be established. Male Sprague-Dawley rats were exposed via inhalation to 1.4-4,600 ppm VC for 6 hr, and the total amount of VC metabolized was determined. Activation to the toxic form followed apparent Michaelis-Menten kinetics. A logarithmic probability plot of the incidence of hepatic angiosarcoma vs the amount of VC transformed, rather than the exposure concentration of VC, was linear. Assuming no threshold dose, extrapolation of the data below the range of doses causing experimentally observable responses predicted a 0.01% hepatic angiosarcoma incidence in rats exposed to 4.6 ppm VC. Theoretical extension of the extrapolation to humans exposed daily for 8 hr to 1 ppm led to a predicted incidence of 1.5/100,000,000. This incidence, although likely an overestimate in the light of evidence for at least a practical threshold in both rats and humans, is less than

that expected to occur spontaneously. Although this method of estimation is not without flaws, the rationale involved represents a new approach that utilizes more logic than current extrapolation methods. The concepts that evolved from this analysis reveal why pharmacokinetics must be considered in designing toxicology experiments as well as in interpreting the resulting data. (22 Refs)

50. COMPARATIVE MAMMALIAN METABOLISM OF VINYL CHLORIDE AND VINYLIDENE CHLORIDE IN RELATION TO ONCOGENIC POTENTIAL.

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Environ Health Perspect; 21:55-59 1977

Possible mechanisms for the mammalian metabolism of vinyl chloride (VC) and vinylidene chloride (VDC) are discussed in relation to the oncogenic potential of these agents. Studies in rats indicate that VC probably yields chloroethylene oxide (CEO), which is then transformed spontaneously into chloroacetaldehyde (CAA). Since CAA and CEO are mutagenic in the Ames test and in Chinese hamster V79 cells, they may be relevant to VC carcinogenicity. Observations in rats exposed to VC indicate that a degree of DNA depurination occurs. The alkylation that produces imidazo-derivative formation with DNA labilizes the N9-purine beta-glycoside linkage, which leads to depurination. The gap so produced might then be filled by various bases, resulting in mispairing during DNA replication. In general, there is excellent agreement between the severe damaging effect of DNA depurination and mutagenicity. Thus, VC would be considered mutagenic/carcinogenic. Experiments with rats exposed to VDC indicate that chloroacetic acid (CA), which is a VDC metabolite per se, lies on a major metabolic pathway for VDC. There is a strong supposition that CA is detoxified through a glutathione S-acyltransferase-catalyzed reaction process and ensuing degradative sequence for the resulting carboxymethylglutathione and that this represents the principal metabolic pathway for CA and a major one for VDC. Thiodiglycolic acid (TDC) is the ultimate detoxification product. Comparative studies of the processing of VDC in mice and rats show that in mice, the metabolic pathway from CA to TDC seems to be readily saturable, possibly on account of an inadequacy in the reaction catalyzed by glutathione S-acyltransferase. Under these circumstances, detoxification of 1,1-dichloroethylene oxide by glutathione S-epoxide transferase and the modification of DNA by 1,1-dichloroethylene oxide or chloroacetyl chloride would be expected to be more significant in mice than in rats. This diagnosis of species susceptibility agrees with the discovery of VDC oncogenicity in the kidneys of mice. Overall, VDC emerges as an agent of low oncogenic potential that is likely to be damaging only under special biological circumstances. (26 Refs)

51. STUDIES ON THE METABOLISM OF VINYL CHLORIDE.

Antweiler H
Universitat Dusseldorf, Dusseldorf, W. Germany
Environ Health Perspect; 17:217-219 1976

Current ideas concerning the metabolism of vinyl chloride (VC) in mice and in humans are discussed. It is believed that VC is first metabolized by oxidases to chloroethylene oxide, a strong mutagen. Spontaneous conversion to chloroacetaldehyde (CA) follows; CA may be mutagenic and carcinogenic. Dehydrogenation of CA leads to chloroacetic acid (CAA), a substance of known toxicity but unknown mutagenicity. Conjugation of CAA with glutathione leads to the formation of the principal urinary metabolites of VC; namely S-carboxymethylcysteine and thiodiacetic acid. CAA

may also be converted, via glycolic acid, to oxalic acid. (13 Refs)

52. PHARMACOKINETICS OF VINYL CHLORIDE.

Bolt HM

Inst. Toxicology, Univ. Tübingen, Wilhelmstrasse 56, D-7400 Tübingen 1, W. Germany
Gen Pharmacol; 9(2):91-95 1978

Data on the pharmacokinetic behavior of vinyl chloride (VC), all of which have been obtained from studies with rats, are reviewed. Consistent evidence shows that, above a saturation concentration, which on inhalation exposure is reached at 250 ppm VC, nonlinear (dose-dependent) pharmacokinetics apply. Two different models describing the pharmacokinetics of VC have been published. They show that VC can leave the body very rapidly via expiration by the lungs. However, special conditions apply if rats are exposed to atmospheric VC: the compound equilibrates with the organism within 15-30 min and is removed from this equilibrium metabolically, probably by formation of the reactive epoxide. The rapid elimination of VC and its major metabolites from the organism agrees with the current theory that a reactive, short-lived metabolite, which occurs in low concentrations only, may be responsible for the toxic effects of VC. (25 Refs)

53. DETERMINATION OF TWO VINYL CHLORIDE METABOLITES IN URINE (MEETING ABSTRACT).

Müller G, Norporth K

Institut für Staublungenforschung und Arbeitsmedizin,
Universität Münster, Münster, West Germany
Naturwissenschaften; 62(11):541 1975

A ninhydrin-positive compound was detected in the urine of female Wistar rats following the inhalation of vinyl chloride. The retention time of this compound corresponded to that of S-carboxymethylcysteine. Thiodiacetic acid was determined by capillary gas chromatography after its conversion to the dimethyl derivative. The findings indicate the value of determining the urinary thiodiacetic acid concentration in vinyl chloride-exposed subjects. (4 refs)

54. METABOLISM AND PHARMACOKINETIC PROFILE OF VINYLIDENE CHLORIDE IN RATS FOLLOWING ORAL ADMINISTRATION.

McKenna MJ, Zempel JA, Madrid EO, Braun WH, Gehring PJ

Toxicology Res. Lab., Dow Chemical Co., Midland, MI, 48640

Toxicol Appl Pharmacol; 45(3):821-835 1978

The pharmacokinetics and metabolism of po ingested vinylidene chloride (VDC) were investigated in Sprague-Dawley rats. After ingestion of ¹⁴C-VDC (1 or 50 mg/kg) in corn oil, the animals were housed in metabolism chambers for 72 hr before sacrificing. Rats given 1 mg VDC/kg metabolized and excreted in the urine and feces 78% of the dose, and exhaled 21% as CO₂ and 1-3% as unchanged VDC. After ingestion of 50 mg VDC/kg, 19% was expired as unchanged VDC. Fasting had no effect on the elimination of ¹⁴C activity in rats given a 1 mg/kg dose. In those given 50 mg VDC/kg, however, fasting increased the percentage of unchanged expired VDC to 29%, increased the amount of covalently bound ¹⁴C-VDC metabolites in the liver, and decreased urinary excretion of nonvolatile metabolites. Results of high-pressure liquid chromatography indicated that a major pathway for detoxification was via conjugation with glutathione. VDC metabolism in the rat appears to be a saturable process that is affected by the nutritional state of the animal. (11 Refs)

55. METABOLISM OF TRICHLOROETHYLENE BY THE ISOLATED PERFUSED LUNG.

Dalbey W, Bingham E

Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
Toxicol Appl Pharmacol; 43(2):267-277 1978

A method for the perfusion of isolated rat and guinea pig lung was developed and used to measure the metabolism of trichloroethylene (TRI). The main features of the perfusion technique included constant-pressure recirculating perfusion with heparinized, autologous, whole blood; cyclic subatmospheric pressure within a temperature-controlled ventilation chamber; and ventilating gas consisting of air containing approx 5% CO₂. The perfusions lasted up to 3 hr. Lungs were ventilated with 30-45 ppm TRI beginning 20 min after the start of perfusion; additional concentrations ranging from 24-129 ppm were given for guinea pig perfusions. Trichloroethanol (TCE) was noted in the perfusing blood within 15 min of initial exposure. The amount of TCE in the blood increased linearly with time; the rate of TCE appearance was much higher in the guinea pig preparations. Chloral hydrate and trichloroethanol glucuronide were not observed. Pretreatment of the rats with phenobarbital (75 mg/kg for 4 days) significantly increased TCE formation. Addition of ethanol to rat blood preparations did not affect TCE formation. The stability of the TCE appearance and of the physiological and biochemical parameters indicate that this perfusion system can serve as a useful model for investigations of pulmonary metabolism. (17 Refs)

56. MICROSOME-DEPENDENT COVALENT BINDING OF THE CARCINOGEN, TRICHLOROETHYLENE, TO CELLULAR MACROMOLECULES (MEETING ABSTRACT).

Banerjee S, Van Duuren BL, Goldschmidt BM

Lab of Organic Chemistry and Carcinogenesis, Inst of Environmental Medicine, N Y Univ Medical Center, N.Y., N.Y. 10016

Proc Am Assoc Cancer Res; 18:34 1977

Trichloroethylene (TCE) causes liver cancer in B6C3F₁ mice, but not in Osborne-Mendel rats (OM). There is higher incidence of tumors in male compared to female mice. In our continuing studies on the in vitro binding of TCE to microsomal protein (MP) (Cancer Res. 36, 2419-2422, 1976), MP from both these mice and rats were incubated with ¹⁴C-TCE. TCE binds 35-40% more to MP from mice compared to rats. TCE binds to a higher degree (35%) of MP of male compared to female mice. TCE binds to salmon sperm DNA in vitro only if MP from mice are present. TCE interacts 35% more with DNA in the presence of MP from male compared to female mice. TCE binding to DNA or protein in these animals was enhanced by phenobarbital and 3-methylcholanthrene, 3,3,3-Trichloropropane oxide augmented this binding. Thus a metabolite of TCE, eg an epoxide, binds covalently to the macromolecules and there is correlation between such binding and tumor induction. (Author Abstract)

57. COVALENT BINDING OF THE CARCINOGEN TRICHLOROETHYLENE TO HEPATIC MICROSOMAL PROTEINS AND TO EXOGENOUS DNA IN VITRO.

Banerjee S, Van Duuren BL

Lab. Organic Chemistry and Carcinogenesis, Inst. Environmental Medicine, New York Univ. Medical Center, New York, NY, 10016

Cancer Res; 38(3):776-780 1978

The metabolism of 1,2,2-trichloroethylene (TCE) in species that develop liver tumors following exposure to this carcinogen (B6C3F₁ hybrid mice) was compared with that in species resistant to TCE tumor induction (Osborne-Mendel rats). Hepatic microsomes from male B6C3F₁ mice covalently

bound 46% more TCE that did microsomes from Osborne-Mendel rats. Furthermore, 30% more TCE was bound to microsomes from mature male Sprague-Dawley rats than immature rats of the same strain. Binding to microsomal protein was 44% and 63% higher in 5-to 9-wk-old Sprague-Dawley rats than in Osborne-Mendel and Fischer rats of the same age. There was 29% more binding to proteins from male Osborne-Mendel rats than from females. In B6C3F1 mice TCE bound to stomach, lung, and kidney microsomes as efficiently as to liver microsomes; microsomes from female lung bound 18% more TCE than those from male lung. TCE also covalently bound to DNA, but only in the presence of microsomes. Thirty-seven percent more TCE bound to microsomal protein from male mice than that from female mice, and binding to DNA was 160% greater in the presence of the male microsomes. In vivo pretreatment of mice with 100 mg/kg sodium phenobarbital ip enhanced TCE binding to microsomal protein and DNA by 58% and 41%, respectively. Ip treatment with 30 mg/kg 3-methylcholanthrene increased binding to protein by 31%. At 1.2 mM, trichloropropene oxide increased TCE binding to protein and DNA by 15%; at concentrations greater than 1.2 mM, however, the amount of TCE bound to protein decreased, but there was a constant increase in the binding of TCE to DNA. (30 Refs)

58. INTERACTION BETWEEN TRICHLOROETHYLENE AND HEPATIC ENDOPLASMIC RETICULUM (MEETING ABSTRACT). (PP. 69-70)

Banerjee S, Van Duuren BL
Laboratory of Organic Chemistry and Carcinogenesis,
Institute of Environmental Medicine, New York
University Medical Center, New York, N.Y. U.S.A.
Third International Symposium On Detection And
Prevention Of Cancer. 1976.

Trichloroethylene (TCE) is a structural analog of vinyl chloride, which is known to induce angiosarcoma of the liver in rodents and is also a human carcinogen. TCE is a widely used organic solvent in industry and has also been used for many years as an anesthetic. We predicted recently that TCE is likely to be carcinogenic and that its epoxide probably is the activated carcinogenic intermediate. Subsequently, the National Cancer Institute reported that TCE induces hepatocellular carcinoma and other tumors in B6C3F1 hybrid mice. TCE epoxide is expected to be highly reactive toward cellular nucleophiles, eg proteins and nucleic acids. Hence, the microsomal metabolism of TCE and its covalent binding to microsomal protein was examined. Rat liver microsomes were incubated in vitro with ¹⁴C-TCE. The results showed that TCE binds covalently to microsomal protein since extensive organic extractions and pronase digestion do not dissociate the TCE-protein complex. The binding was decreased by 7,8-benzoflavone, blocked by SKF-525A and enhanced by intraperitoneal administration of phenobarbital. The possibility that TCE epoxide, once formed, could be converted to water-soluble products through enzymatic hydrolysis by epoxide hydase was also investigated. Addition of 3,3,3-trichloro propane oxide, a potent inhibitor of epoxide hydase to the incubation system markedly enhanced the binding of TCE. These observations support the view that TCE is metabolized to its epoxide, which is most likely involved in TCE carcinogenesis and toxicity. (Author Abstract)

59. COVALENT INTERACTION OF METABOLITES OF THE CARCINOGEN TRICHLOROETHYLENE IN RAT HEPATIC MICROSOMES.

Van Duuren BL, Banerjee S
New York Univ. Medical Center, New York, NY 10016
Cancer Res; 36(7):2419-2422 1976

Trichloroethylene (TCE), a structural analog of vinyl chloride, induces hepatocellular carcinoma and other tumors

in B6C3F1 hybrid mice. TCE epoxide, a possible metabolite, is expected to be highly reactive toward cellular nucleophiles; eg, proteins and nucleic acids. Hence, the microsomal metabolism of TCE and its covalent binding to microsomal protein were examined. Rat liver microsomes from male Sprague-Dawley rats were incubated in vitro with ¹⁴C-TCE. The results showed that TCE binds covalently to microsomal protein, since extensive organic extractions and Pronase digestion do not dissociate the TCE-protein complex. The binding was decreased by 7,8-benzoflavone, blocked by 2-diethylaminoethyl-2,2-diphenylvalerate;HCl (SKF-525A), and enhanced by ip administration of phenobarbital. The possibility that TCE epoxide, once formed, could be converted to water-soluble products through enzymatic hydrolysis by epoxide hydase was also investigated. Addition of 3,3,3-trichloropropene oxide, a potent inhibitor of epoxide hydase, to the incubation system markedly enhanced TCE binding. These observations support the view that, in order to bind to protein, it is necessary for TCE to be metabolized to its epoxide, a reactive intermediate that is most likely involved in TCE carcinogenesis and toxicity.

60. SPECTRAL EVIDENCE FOR 2,2,3-TRICHLORO-OXIRANE FORMATION DURING MICROSOMAL TRICHLOROETHYLENE OXIDATION (MEETING ABSTRACT).

Uehleke H, Poplawski S, Bonse G, Henschler D
Dept. Toxicology, German Health Office, D-1 Berlin 33,
Bundesgesundheitsamt, Postfach, W. Germany
Arch Pharmacol; 293(Suppl): R 64 1976

The biotransformation of 1,1,2-trichloroethylene (Tri) to 1,1,1-trichloroacetic acid was suggestive of an epoxide intermediate. Aerobic incubation of Tri with rabbit liver microsomes and NADPH resulted in a different absorption peak of 452 nanometers (nm). Addition of Tri-epoxide (2,2,3-trichlorooxirane) to reduced microsomes produced a high difference absorption at 452 nm. Dichloroacetyl chloride was the main thermal rearrangement product of Tri-epoxide and also produced 452 nm absorption in reduced microsomes. The difference absorption was only 20% that evoked by the intermediate formed during incubation of Tri in metabolizing microsomes. The absorption implied epoxide formation in microsomal Tri oxidation. Mice were injected ip with C14-labeled Tri. Maximal irreversible binding of 12 nanomole/mg protein and 20 nanomole/mg lipid was observed after 5 hr in the liver microsomal fraction. Irreversible binding of Tri was also followed in aerobic incubates of liver microsomes and NADPH. The oxirane intermediate might be responsible for the mutagenic effects in bacterial test systems and for tumors produced after po Tri administration. (0 Refs)

61. MECHANISM FOR TRICHLOROETHYLENE HEPATOTOXICITY (MEETING ABSTRACT).

Allemand H, Pessayre D, Descatoire V, Degott C,
Feldmann G, Benhamou JP
Unite de Recherches de Physiopathologie Hepatique
(INSERM), Hopital Beaujon, Clichy, France
Digestion; 16(4):331 1977

Trichloroethylene may produce hepatitis in man; the low incidence of liver lesions and their apparent unpredictability might be consistent with a metabolite-mediated toxicity; this hypothesis was tested in the rat. In vitro C14-trichloroethylene with hepatic microsomes and NADPH resulted in the irreversible binding of a C14-labeled material to microsomal proteins; there was no binding if NADPH was omitted and reduced binding if inhibitors of microsomal drug-metabolizing enzymes were added to the incubation mixture. Phenobarbital-pretreatment of the animals increased (a) cytochrome P-450, (b) in vitro covalent binding to microsomal proteins, (c) in vivo covalent binding to hepatic proteins, and (d) the extent of

liver cell necrosis after administration of trichloroethylene, whereas CoCl₂-pretreatment decreased (a) cytochrome P-450, (b) covalent binding, and (c) trichloroethylene hepatotoxicity. In vitro covalent binding to hepatic microsomes was decreased by glutathione. In vivo, trichloroethylene administration depleted hepatic glutathione in normal rats but not in rats whose metabolism was inhibited by piperonyl butoxide. It is concluded that (1) trichloroethylene is transformed into a reactive metabolite which covalently binds either to proteins or to glutathione, (2) binding to proteins produces liver necrosis, and (3) binding to glutathione decreases the amount of metabolite available for binding to proteins.

62. INTERACTION OF POTENTIAL ACTIVATED INTERMEDIATES OF THE CARCINOGEN ETHYLENE DIBROMIDE WITH PROTEIN AND DNA IN VITRO (MEETING ABSTRACT).

Kline SA, Banerjee S, Van Duuren BL
Lab. Organic Chemistry and Carcinogenesis, Inst.
Environmental Medicine, New York Univ. Medical
Center, New York, NY, 10016
Proc Am Assoc Cancer Res; 20:86 1979

This study was undertaken to evaluate bromoacetaldehyde (BA) and bromoethanol (BE) as activated metabolites in the microsome mediated covalent binding of the potent carcinogen ethylene dibromide (EDB) to microsomal protein and DNA. BA has been detected by others as a metabolite of EDB in vitro while BE is a likely metabolite. 14C-BA was synthesized from 14C-paraldehyde and 14C-BE was synthesized from 14C-ethylene oxide. In in vitro experiments, native microsomes from the livers of B6C3F1 mice (susceptible to EDB carcinogenesis) and salmon sperm DNA were incubated with either 14C-BA or 14C-BE in the absence of an NADPH regenerating system or with EDB in the presence of an NADPH regenerating system. Both BA and BE bound covalently to protein and DNA to a much greater extent than did EDB. The extent of binding of BA and BE was unaffected when denatured microsomes were used in place of native microsomes. The rate of binding increased with concentration of BA or BE. BA reacted much more rapidly than did BE. Thus BA and, to a lesser extent, BE bind to cellular macromolecules without prior metabolic activation and are to be considered potential activated intermediates in EDB tumorigenesis. (no Refs)

63. BINDING OF THE CARCINOGEN ETHYLENE DIBROMIDE TO CHROMOSOMAL CONSTITUENTS OF FORESTOMACH AND LIVER (MEETING ABSTRACT).

Banerjee S, Van Duuren BL
Lab. Organic Chemistry and Carcinogenesis, Inst.
Environmental Medicine, New York Univ. Medical
Center, New York, NY, 10016
Proc Am Assoc Cancer Res; 20:85 1979

Our earlier studies revealed that the covalent binding of the potent carcinogen ethylene dibromide (EDB), a widely used pesticide, to microsomal protein and salmon sperm DNA was dependent on microsomal metabolism. The present study was undertaken to determine whether EDB can interact with chromosomal constituents of forestomach and liver. Chromatin prepared and characterized from these organs of B6C3F1 mice (susceptible to EDB carcinogenesis) were incubated with 14C-EDB in the presence of microsomes and a NADPH regenerating system. After incubation EDB-bound chromatin was isolated and fractionated into DNA, histone and non-histone proteins. EDB was bound to a significantly greater extent to chromatin DNA compared to salmon sperm DNA and to chromatin protein compared to chromatin DNA. Binding to non-histone protein was greater than to histone protein. EDB was bound significantly more to chromatin

protein from forestomach, the target organ, than to chromatin protein from liver while the reverse was true for chromatin DNA. Such binding of EDB to chromatin structures probably produces alteration in the function of chromatin and this may be related to its carcinogenic action. (no Refs)

64. MACROMOLECULAR BINDING AND METABOLISM OF THE CARCINOGEN 1,2-DIBROMOETHANE.

Hill DL, Shih TW, Johnston TP, Struck RF
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Cancer Res; 38(8):2438-2442 1978

Biochemical mechanisms related to the activation and inactivation of the carcinogen 1,2-dibromoethane (1,2-DBE) were investigated. In rats inoculated ip with 1,2-¹⁴C-1,2-DBE 30.4 μCi; 4.2 micromoles (μmol); 0.2 ml ethanol, measurable amounts of radioactivity became bound to protein, RNA, and DNA of all major tissues. For each macromolecules class, the largest amounts of bound radioactivity were in the liver and kidneys. Optimum conditions for the rat liver glutathione S-transferase that uses 1,2-DBE as a substrate were established. The pH optimum was 8.2, the K_m for 1,2-DBE was 25 mM, and V_{max} was 2.1 μmol/min/g liver. Considerable enzyme activity was found in rat kidney; detectable activity was present in lung, testis, spleen, and heart. Enzymatic activity leading to the irreversible binding of radioactivity from ¹⁴C-1,2-DBE to proteins in the reaction system was present in rat liver microsomes. The activity was inducible by phenobarbital but not by benz-aanthracene. NADPH was required for activity of both the noninduced and the induced reactions; MgCl₂ stimulated both reactions. Bromoacetaldehyde, a reactive compound probably involved in the irreversible binding, was identified as a metabolite formed in the reaction system. Radioactivity from ¹⁴C-1,2-DBE also became bound to microsomal proteins by a nonenzymatic chemical reaction. The enzymatic reaction leading to binding to macromolecules and/or the chemical binding reaction may be involved in the biological activity of 1,2-DBE. (22 Refs)

65. INTERACTION OF ACTIVATED CARCINOGENIC INTERMEDIATES OF ETHYLENE DIHALIDES WITH PROTEIN AND DNA IN MICE AND RATS TISSUES IN VITRO (MEETING ABSTRACT).

Banerjee S, Van Duuren BL
Lab. Organic Chemistry and Carcinogenesis, Inst.
Environmental Medicine, New York Univ. Medical
Center, New York, NY, 10016
Proc Am Assoc Cancer Res; 19:67 1978

Ethylene dibromide (EDB) is known to cause cancer of the forestomach in B6C3F1 mice (BM) and Osborne-Mendel rats (OMR). Ethylene dichloride (EDC) is known to cause liver cancer in male B6C3F1 mice but not in female mice or OMR. In in vitro experiments microsomal preparations from liver and stomach of BM and OMR were incubated with C14-EDB and salmon sperm DNA. Covalent binding increases with increasing concentrations of microsomal proteins or EDB. There was no binding to DNA in the absence of microsomes. With denatured microsomes, binding to proteins was greater than 4% (p less than 0.01) compared to native microsomes; SKF-525A inhibited the binding to protein and DNA by 80% (p less than 0.02). Binding of C14-EDC was decreased by 90% (p less than 0.02) by addition of GSH or 1-methyl-2-mercaptoimidazole. C14-EDC binds 1-2 x more to liver microsomes from male BM compared to female BM or OMR of both sexes. The proposed activated carcinogenic intermediates are halohydrins, epoxides or other related electrophilic and transient species.

66. 1,1-DICHLOROETHYLENE HEPATOTOXICITY: PROPOSED MECHANISM OF ACTION AND DISTRIBUTION AND BINDING OF ¹⁴C RADIOACTIVITY FOLLOWING INHALATION EXPOSURE IN RATS.

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Environmental Health, Harvard Sch. Public Health, 665
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Environ Health Perspect; 21:113-119 1977

The mechanism of 1,1-dichloroethylene (1,1-DCE)-induced hepatotoxicity and its potentiation by fasting were determined in male Holtzman rats, and results on tissue distribution and binding of radioactivity (RA) were related to the proposed mechanism of action. Trichloropropane epoxide (TCPE: 0.1 ml/kg po), an epoxide hydrolase inhibitor, significantly increased the toxicity of 1,1-DCE (100-150 ppm by inhalation, x 4 hr) in 18-hr-fasted (FA) rats, as measured by serum sorbitol dehydrogenase (SDH) elevation. When FA rats were exposed to 250 ppm 1,1-DCE alone, hepatic citric acid levels were increased 416%, SDH activity 636.4-fold (vs increases of 122% and 100-fold in fed (FE) rats). It was hypothesized that mitochondrial injury was associated with inhibition of the tricarboxylic acid cycle and that monochloroacetic acid is the toxic metabolite of 1,1-DCE. When FE and FA rats were exposed for 2 hr to 2,000 ppm ¹⁴C-1,1-DCE in a recirculating exposure chamber, there was no difference in rate of uptake between the two groups. FA rats had more water- or trichloroacetic acid (TCA)-soluble 1,1-DCE metabolites in their tissues than FE rats. At 30 min postexposure, most of the total RA (mainly TCA-soluble) was detected in the kidneys of both groups. FA rats had more tissue-bound or TCA-insoluble RA in their mitochondrial and microsomal fractions than FE rats, but both groups had approx the same rate of disappearance of RA (half-time of 2-3 hr). At 26 hr, the urinary excretion of RA was similar in FE and FA rats (36.6%). The results suggest that although there are no significant metabolic differences between FE and FA rats, there does appear to be a significant difference in the in vivo pathway for the products of metabolism. The fact that mice develop renal tumors after long-term 1,1-DCE exposure but rats only show significant hepatocellular injury is explained.

67. DIFFERENCES IN METABOLISM OF VINYLIDENE CHLORIDE BETWEEN MICE AND RATS.

Jones BK, Hathway DE
Central Toxicology Lab., Imperial Chemical Industries,
Alderley Park, Cheshire SK10 4TJ, England
Br J Cancer; 37(3):411-417 1978

The metabolism of vinylidene chloride (1,1-dichloroethylene, DCE) was investigated in male Alderley Park rats and male Alderley Park mice. Following a single po dose of 50 mg/kg, pulmonary excretion of unchanged DCE accounted for 28% of the dose in rats, but for only 6% in mice. This suggested that the efficiency of DCE metabolism follows the known activity of cytochrome P-450 in the organs of mice, that the real exposure (expressed as amount of DCE metabolized) is relatively higher for orally dosed mice than rats, and that DCE is more likely to be carcinogenic in mice than rats. The mice metabolized DCE similarly to rats, but differences were noted. Qualitatively, mice, but not rats, excreted a small amount of N-acetyl-S-(2-carboxymethyl)cysteine. Quantitatively, (1) the relative proportions of the N-acetyl-S-cysteinylacetyl derivative that were formed in mice and rats paralleled the activity of liver glutathione-S-epoxide transferase, and (2) there were marked differences in the proportions of DCE metabolites belonging to the chloroacetic acid branch of the metabolic pathway. A

tracer study verified the beta-thionase hydrolysis of thiodiglycolic acid and the biogenesis of the N-acetyl-S-cysteinylacetyl derivative. It is suggested that the metabolites 1,1-dichloroethylene oxide and chloroacetyl chloride may be important in murine DCE carcinogenicity. (19 Refs)

68. DETECTION OF ELECTROPHILIC METABOLITES OF HALOGENATED OLEFINS WITH 4-(4-NITROBENZYL)PYRIDINE (NBP) OR WITH SALMONELLA TYPHIMURIUM (MEETING ABSTRACT).

Barbin A, Planche G, Croisy A, Malaveille C, Bartsch H
Unit Chemical Carcinogenesis, International Agency for
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France
Mutat Res; 53(2):150 1978

Metabolic conversion of volatile substances can be assayed by passing a gaseous mixture of the test compound and oxygen (air) through a mouse liver microsomal system and by trapping volatile alkylating metabolites by reaction with excess NBP. Using this system, epoxide formation from vinyl chloride or vinyl bromide was demonstrated; 2-chloro-1,3-butadiene (chloroprene) yielded an alkylating intermediate although, 1,1-difluoroethylene, 1,1-dichloroethylene and trichloroethylene did not. Chloroethylene oxide, perhaps the ultimate carcinogenic metabolite of vinyl chloride, showed potent biological activity in various short-term tests for the detection of potential carcinogens. In all the in vitro assays used, the color reaction with NBP showed the highest sensitivity for detecting chloroethylene oxide at a 2 uM concentration. S typhimurium TA100, in the presence of a 9000 x g supernatant of PB-treated mice, was exposed to gaseous mixtures of the following test compounds/air. Mutation rates (his+ revertant colonies/umol/hr/plate) taken from the linear region of time and dose-dependent assays either with or without NADP+, were as follows: vinyl acetate, 1,1-difluoroethylene and trichloroethylene 0 (0); vinyl chloride 6 (2); 1,1-dichloroethylene 15 (1); vinyl bromide 26 (9); 2-chloro-1,3-butadiene 51 (9); 1-chloro-1,3-butadiene 157 (81); 3,4-dichlorobutene-1, 490 (345). 1,4-Dichlorobutene-2 (77% trans-isomer), when incorporated in the soft agar layer, showed a mutagenic effect in TA100. Microsomal fractions from mouse and human liver enhanced the mutagenicity three-fold. The putative synthetic metabolite 1,4-dichloro-2,3-epoxy butane was, however, four times less mutagenic in TA100 than in the parent olefin. (no Refs)

69. METABOLISM OF HALOGENATED ETHYLENES.

Leibman KC, Ortiz E
Dept. Pharmacology and Therapeutics, Univ. Florida
Medical Sch., Gainesville, FL, 32610
Environ Health Perspect; 21:91-97 1977

Literature on the metabolic transformations of various chlorinated ethylenes is reviewed, and the results of studies on the products of metabolism of some of these compounds are presented. The metabolism of chlorinated ethylenes may be explained by the formation of chloroethylene epoxides as the first intermediate products. These epoxides appear to rearrange with the migration of chlorine to form chloroacetaldehydes and chloroacetyl chlorides. In experiments in which 1,1-dichloroethylene, trichloroethylene, and tetrachloroethylene were incubated with rat liver microsomal systems, monochloroacetic acid, chloral hydrate, and trichloroacetic acid, respectively, were found. Rearrangements of chloroethylene glycols formed from the epoxides by hydration may also occur, but they appear, at least in the case of 1,1-dichloroethylene, to be quantitatively less important. The unstable epoxide ring formed during the metabolism of chlorinated ethylenes may react with a variety of groups in compounds of biological interest. When these

R&S 111229

compounds are essential to cellular function the reaction may lead to alteration of cellular metabolism and subsequent cell necrosis or to carcinogenic or mutagenic events.

70. METABOLISM OF CHLORINATED ALKENES AND ALKANES AS RELATED TO TOXICITY.

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J Environ Pathol Toxicol; 1(2):125-133 1977

Chlorine substitution in aliphatic compounds results in a destabilization in alkanes and a stabilization in alkenes. With alkanes, therefore, the main pathways of metabolic transformation to reactive intermediates are radical formation by a C-C break and dechlorination or dehydrochlorination. In the chlorinated ethylenes, the first metabolic transformation step is oxidation to electrophilic oxiranes. These compounds may be hydrolyzed enzymatically or nonenzymatically, react with cellular nucleophiles, or rearrange to either chlorinated aldehydes or acyl chlorides. With tetrachloroethylene, 1,2-cis-dichloroethylene, trans-dichloroethylene, 1,1-dichloroethylene, and vinyl chloride, the metabolites identified in vivo experiments are identical to the thermal rearrangement products of the respective oxiranes. An exception is trichloroethylene, whose thermal rearrangement product is dichloroacetyl chloride; its metabolites in vivo, however, are entirely derived from trichloroacetaldehyde. Mutagenic and carcinogenic activities in the chlorinated ethylenes are determined by the stability of their chlorine substitution compounds: the relatively unstable and unsymmetric oxiranes of trichloroethylene, 1,1-dichloroethylene, and vinyl chloride are mutagenic in the Ames test, but the more stable asymmetric oxiranes of tetra-, 1,2-cis-, and trans-dichloroethylenes are inactive. (20 Refs)

B. Uptake, Distribution, and Metabolism of Vinyl Chloride and Related Compounds in Humans

The reader may also find the following abstracts of interest: 49, 53, 116

71. URINARY AND TISSUE GLYCOSAMINOGLYCAN PATTERNS IN ANGIOSARCOMA AND OTHER VINYL-CHLORIDE-EXPOSURE-ASSOCIATED LIVER INJURY (MEETING ABSTRACT). (PP. 170)

Kupchella CE, Tamburro CH

Univ Louisville, Louisville, KY 40208

Third International Symposium On Detection And Prevention Of Cancer. 1976.

Both the presence of certain cancers and disorders of connective tissue metabolism are accompanied by alterations in urinary glycosaminoglycan patterns. Because both fibrosis and angiosarcoma of the liver have been connected to vinyl chloride exposure, we evaluated glycosaminoglycan patterns associated with vinyl chloride injury to assess the usefulness of the patterns in early detection. Urines from fifty patients were analyzed for glycosaminoglycans. These included two angiosarcomas, ten cases of vinyl-chloride, work-related, liver injury other than angiosarcoma, and cases of hepatitis, cirrhosis, other cancers, metabolic disorders of the liver, and normal controls. Examined both histochemically and biochemically for glycosaminoglycans were liver tissue samples including two liver angiosarcomas - both tumor tissue and non-tumor tissue - five normal livers, and two cirrhotic livers. The urine of patients with vinyl chloride-associated liver injury other than angiosarcoma exhibited a characteristic shift

toward the chondroitin sulfates. Tissue analysis revealed up to four-fold greater concentrations of hyaluronic acid and heparin in tumor tissue than in adjacent non-tumor tissue. Angiosarcomatous livers exhibited greater concentrations of glycosaminoglycans than were found in normal livers. Biochemical results confirmed histochemical studies. One patient whose urinary glycosaminoglycan excretion patterns were followed for a two-week period prior to death from liver failure exhibited a pulse of glycosaminoglycan excretion peaking ten days prior to death. Several of these observations appear to have diagnostic significance. (Author Abstract)

72. DETERMINATION OF THIODIGLYCOLIC ACID IN URINE SPECIMENS OF VINYL CHLORIDE EXPOSED WORKERS.

Muller G, Norpoth K, Kusters E, Herweg K, Versin E

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Int Arch Occup Environ Health; 41(3):199-205 1978

Thiodiglycolic acid (TDGA) content was measured in the urine of workers exposed to varying amounts of vinyl chloride (VC), and an improved analytical method for these determinations was described. The analytical procedure used made it possible to distinguish between normal values (in 20 non-exposed men) and values obtained from 18 slightly exposed workers (0.14-7.0 ppm VCM measured by personal air samplers) at the 1% significance level. In all cases TDGA concentrations exceeding 2.1 microg/ml urine can be distinguished from normal concentrations with a 99% probability of confidence. Mean values obtained from the normal group and two exposed groups suggested a correlation between the extent of exposure and the amount of TDGA excreted. Increasing metabolite concentrations were found in the urine with increasing exposure. The correlation was tested by a distribution free statistical procedure and was confirmed at the level of p less than 0.01. The increase in metabolite excretion began shortly after the initiation of exposure each day and reached a peak in the first or second urine samples obtained after the highest possible VC-uptake. Significant increases in metabolite excretion were observed even at VC-concentrations below 5 ppm. The usefulness of using this analytical procedure for monitoring VC concentration in work places is discussed. (36 Refs)

73. METABOLISM OF TRICHLOROETHYLENE AND TETRACHLOROETHYLENE IN HUMAN SUBJECTS.

Ikeda M

Dept. Environmental Health, Tohoku Univ. Sch. Medicine, Sendai 980, Japan

Environ Health Perspect; 21:239-245 1977

The metabolism of trichloroethylene (3C-E) and tetrachloroethylene (4C-E) in humans and the urinary concentration of metabolites of these compounds in persons occupationally exposed to their vapors was determined. There was a linear correlation between 3C-E concentration in the work environments and the level of total trichloro compounds in the urine of workers. The trichloroethanol level was also linearly related to 3C-E concentration, but trichloroacetic acid levels deviated from linearity at 3C-E levels greater than 50 ppm. With 4C-E, the trichloroethanol, trichloroacetic acid, and total trichloro compound levels all plateaued at 4C-E levels less than 100 ppm. The respiratory and urinary half-lives of 3C-E were 25 and 42 hr, respectively, but those of 4C-E were 65 and 144 hr, respectively. Urinalysis of a 38-yr-old man addicted to 3C-E revealed a urinary half-life of greater than 70 hr. An automated system for the determination of total trichloro compounds in human urine is described. (35 Refs)

74. EVALUATION OF EXPOSURE TO TRICHLOROETHYLENE DURING THE DEGREASING OF SMALL COMPONENTS IN A MACHINERY PLANT.

Kalas D

Dept. Occupational Diseases, Dobrovskeho 597, 543 01

Vrchlabi, Czechoslovakia

Prac Lek; 29(8):299-304 1977

The urinary excretion of trichloroethylene (TRI) and its metabolites, trichloroacetic acid (TCA) and trichloroethanol (TCE), was studied in workers who inhaled TRI in a shop where TRI was used to degrease partially finished metal components. The TRI concentrations measured in the air at three work locations averaged 130-155 mg/cubic meter over the 5-day wk, slightly increasing from the first to the last weekday (from 135-141 to 153-162 mg/cubic meter). The TCE level in the urine rose sharply from less than 200 mg/liter to values around 300 mg/liter on day 1 of the exposure to drop to about 200 mg/liter on the day following the 5-day work wk, and the TCA level rose from under 100 mg/liter on day 1 to values around 150 mg/liter on the day following the 5-day work wk. The TRI, TCA and TCE levels were highest in the urine portion collected during the last 4 hr of the 7-hr workshifts, and they correlated best with the metabolite levels found in the 24-hr urine samples. (13 Refs)

75. TRICHLOROETHYLENE: RELATIONSHIP OF METABOLITE LEVELS TO ATMOSPHERIC CONCENTRATIONS: PRELIMINARY COMMUNICATION.

Smith GF

Occupational Health Service of the Post Office, South Western Region, Mercury House, Bond St., Bristol BS1 3TD, England

J R Soc Med; 71(8):591-595 1978

The amount of trichloroethylene (TRI) inhaled and the levels of its metabolite trichloroacetic acid (TCA) in urine were measured for two subjects continually exposed to TRI while operating a degreasing tank. The total air inspired by the subjects, the 24 hr retention (in mg) and concentration (as integral sample/day, parts/10⁶) of TRI, and av urine level (mg/liter) and daily output (in mg) of TCA were measured. The amount of TRI retained daily was compared with the amount of TCA excreted per day in the urine. The integrated TRI was compared with the av amount of TCA excreted. These values were calculated for the first three work days of the week (Monday, Tuesday, and Wednesday) and compared with each other. There appeared to be an individual rather than a general relationship between TRI and TCA. The ratio of TRI retention levels to TCA excretion values tended to increase during the week, with peak excretion 24-48 hr after exposure. The integrated TRI to av TCA excretion ratio varied between 1:1.32 and 1:2.63. Urinary levels of metabolites of TRI may be a reliable index of exposure of industrial workers to TRI. (28 Refs)

76. EVIDENCE FOR EXISTENCE IN HUMAN TISSUES OF MONOMERS FOR PLASTICS AND RUBBER MANUFACTURE.

Wolff MS

Environmental Sciences Lab., Dept Community Medicine, Mount Sinai Sch. Medicine, City Univ. New York, New York, NY 10029

Environ Health Perspect; 17:183-187 1976

Discussion is made of the storage in fat of lipophilic substances such as DDT, polychlorinated biphenyls, tetrachloroethylene, and trichloroethylene, which are chemically similar to many industrially-used monomers, plus styrene, acrylamide, and vinyl chloride. Data on the uptake, metabolism, storage, and excretion of these substances in

humans are provided when available. The storage and removal of lipophilic substances from fat tissues depend on fat solubility, volatility, and metabolism. Styrene is very soluble in blood and fat: following exposure at 100 ppm, blood levels of 0.2-15 ppm styrene have been determined. The urinary and breath half-lives of styrene metabolites and styrene, respectively, are about 8 hr and 1-3 hr, respectively. Detectable levels of styrene were present in the fat of styrene workers greater than 2 days following exposure, a much longer period than that over which styrene could be detected in the breath of people experimentally exposed to 100 ppm styrene for sustained periods. (28 Refs)

III. BIOLOGICAL EFFECTS IN BACTERIAL SYSTEMS, DROSOPHILA, AND EXPERIMENTAL ANIMALS

A. Acute and Subacute Toxicity of Vinyl Chloride and Related Compounds in Experimental Animals

77. EFFECTS OF POLYVINYL CHLORIDE INGESTION BY DOGS.

Johnson WS, Schmidt RE

Operating Location AA, US Air Force Occupational Environmental Health Lab., Kelly Air Force Base, TX
Am J Vet Res; 38(11):1891-1892 1977

Polyvinyl chloride (PVC) acrylic thermoplastic sheeting (0.125 g/kg bid for 5 days) was fed to 6 dogs to determine whether ingestion during periods of normal transit of military working dogs would be toxic and thus affect the safety of this material for construction of shipping containers. The test material passed through the digestive system of all animals unchanged and hematologic examination, blood chemical analyses, and urinalyses were within normal limits. Gross and microscopic lesions attributable to the test material were not seen in necropsied animals 10 days after the feeding was stopped. (9 Refs)

78. CHRONIC TOXICITY AND REPRODUCTION STUDIES OF HEXACHLOROBUTADIENE IN RATS.

Kociba RJ, Schwetz BA, Keyes DG, Jersey GC, Ballard JJ, Dittenber DA, Quast JF, Wade CE, Humiston CG
Toxicology Res. Lab., Health and Environmental Res., Dow Chemical Co., Midland, MI, 48640
Environ Health Perspect; 21:49-53 1977

The carcinogenic, reproductive, and toxic effects of po hexachlorobutadiene (HCB), an unwanted by-product of processes associated with the chlorination of hydrocarbons, were assessed in Sprague Dawley rats. The LD50 values following a single po dose ranged from 504 to 667 mg/kg in adult male rats and from 200 to 400 mg/kg in adult female rats. In 21-day-old male and female weanling rats, the LD50 values were 46-91 and 26-81 mg/kg, respectively. In a chronic toxicity study, the ingestion of 20 mg/kg/day HCB for up to 2 yr caused multiple toxicologic effects, primarily of the kidney. These included the development of renal tubular adenomas and adenocarcinomas. The ingestion of 2 mg/kg/day HCB caused lesser toxicity and no evidence of neoplasia. No toxic effects were observed in rats chronically exposed to a po dose of 0.2 mg/kg/day. Thus, a dose-response relationship was observed for HCB-induced toxicity, which affected primarily the kidney; HCB-induced neoplasms occurred only at a dose level higher than that causing discernible renal injury. In a reproduction study, 20 or 2.0 mg/kg/day HCB induced sl-

R&S 111231

ight maternal toxicity (primarily of the kidney), but caused no adverse effects on reproductive parameters (percent pregnancy and neonatal survival/development). A decreased neonatal body wt was noted at 20 mg/kg/day. No toxicologic effects were observed among adult rats at 0.2 mg/kg/day or among neonates at 0.2 or 2.0 mg/kg/day.

79. SHORT-TERM TOXICITY AND REPRODUCTION STUDIES IN RATS WITH HEXACHLORO-(1,3)-BUTADIENE.

Harleman JH, Seinen W

Dept. Pathology and Hygiene, Coll. Veterinary Medicine,
Univ. Illinois at Urbana-Champaign, Urbana, IL, 61801
Toxicol Appl Pharmacol; 47(1):1-14 1979

Wistar-derived rats were given 0.4-15.6 mg/kg/day hexachloro-(1,3)-butadiene (HCBd) by gavage for 13 wk, or 150 or 450 ppm in the diet for 2 wk. The main toxic action of HCBd was in the kidneys. Decreased urine-concentrating ability was found in females at low doses, and extensive tubular degeneration, degeneration and necrosis of individual epithelial cells, plus increased cellularity of the epithelial lining were noted in both sexes at high doses. There were no significant effects on fertility or progeny. (24 Refs)

80. SATURABLE METABOLISM AND THE ACUTE TOXICITY OF 1,1-DICHLOROETHYLENE.

Andersen ME, French JE, Gargas ML, Jones RA, Jenkins LJ

Naval Medical Res. Inst. Toxicology Detachment
(NMRI/TD), Wright-Patterson AFB, OH, 45433
Toxicol Appl Pharmacol; 47(2):385-393 1979

The saturable metabolism and the acute toxicity of 1,1-dichloroethylene (1,1-DCE) were studied. Concentration of and duration of exposure were examined as determinants of the inhalation toxicity of 1,1-DCE in fasted male rats of various ages. Phenobarbital sleep times (PBST) were significantly increased after exposures as brief as 0.5 hr in immature rats (100-150 g) exposed to 200 ppm 1,1-DCE for durations up to 2 hr; extensive dilation and vacuolization of the endoplasmic reticulum were also observed following 1,1-DCE exposure. Older rats (greater than 200 g) were less susceptible to 1,1-DCE than were younger rats. PBST was not increased during exposure of older rats. Groups of six older rats were exposed to various concentrations of 1,1-DCE for 4 hr and observed for mortality. The concentration-mortality curve increased rapidly between 100 and 200 ppm, but maintained a plateau as concentration was increased between 200 and 1,000 ppm. The dependence of LT50 (the time of exposure required to kill half an exposed group at a given concentration) on concentration was not very great. A 1-fold increase in concentration from 200 to 2,000 ppm decreased the LT50 by less than a factor of 3. It is apparent that, even in this narrow range of doses, a concentration x time relationship is not valid. This is further evidence that a saturable, enzymatic activation occurs in the expression of the toxicity of 1,1-DCE. (19 Refs)

81. ACUTE HEPATOTOXICITY OF ETHYLENE, VINYL FLUORIDE, VINYL CHLORIDE, AND VINYL BROMIDE AFTER AROCLOR 1254 PRETREATMENT.

Conolly RB, Jaeger RJ, Szabo S

Dept. Physiology, Harvard Sch. Public Health, Boston,
MA 02115

Exp Mol Pathol; 28(1):25-33 1978

The hepatotoxicity of ethane, vinyl ethylene, fluoride monomer (VFM), vinyl bromide monomer (VBM), and vinyl

chloride monomer (VCM) was determined in male Holtzman rats pretreated with Aroclor 1254. All compounds except ethane caused degeneration and necrosis of the liver. Ethylene, VFM, and VBM should be evaluated for chronic effects in view of their similarity of acute action to VCM, a known carcinogen. (20 Refs)

82. TOXICITY OF BETA-CHLOROPRENE(2-CHLOROBUTADIENE-1,3): ACUTE AND SUBACUTE TOXICITY.

Clary JJ, Feron VJ, Reuzel PG

Environmental and Health Affairs, Celanese Corporation,
1211, Avenue of the Americas, New York, NY, 10036
Toxicol Appl Pharmacol; 46(2):375-384 1978

The acute and subacute toxicity of beta-chloroprene (2-chlorobutadiene-1,3) was evaluated using acute inhalation toxicology, the Class B poison test, and a 4-wk range study. The approximate lethal concentration (ALC) was determined by exposing (inhalation) groups of six male albino rats to concentrations of beta-chloroprene ranging from 1.95 to 13.30 mg/liter for 4 hr; the rats were weighed daily for 14 days and then submitted for histological examination. A total of five rats died following inhalation of beta-chloroprene (1/6 at concentration of 8.42 mg/liter and 2/6 each at concentrations of 13.04 and 13.30 mg/liter; ALC = 8.42 mg/liter). Examination of the rats following exposure showed hemorrhagic infarction of the lungs and central and mid-central necrosis of the liver. Forty male and 40 female Specific Pathogen-Free rats were equally divided into four groups and exposed to beta-chloroprene concentrations of 0, 39, 161, and 625 ppm for 6 hr/day, 5 days/wk for 4 wk. Eye irritation, restlessness, lethargy, nasal discharge, and orange-colored urine were observed in animals exposed to the higher concentrations. Hair loss was observed in several female rats. The cumulative mortality was 5/10 males and 3/10 females at 625 ppm and 3/10 males and no females at 161 ppm. No rats at the lower exposure rates. In a similar experiment using hamsters, all the animals exposed to 630 ppm and 1/10 males and 3/10 females exposed to 162 ppm died during the first wk. Significant differences in relative organ wt between test and control animals were observed in all organs except the heart. The av body wt of both male and female rats tested decreased with increasing concentration of beta-chloroprene. It was concluded that beta-chloroprene is not a Class B poison. (19 Refs)

83. THE TOXICITY OF SOME HALOMETHANES IN MICE.

Bowman FJ, Borzelleca JF, Munson AE

Dept. Pharmacology, Medical Coll. Virginia, Richmond,
VA, 23298

Toxicol Appl Pharmacol; 44(1):213-215 1978

The toxicity of some halomethanes (trichloromethane, bromodichloromethane, dibromochloromethane, and tribromomethane) was tested in mice as part of an extensive toxicological evaluation designed to identify potential risk to humans. Trichloromethane and tribromomethane were the least toxic with LD50 doses above 1000 mg/kg in both sexes. Males were more sensitive than females to the lethal effects of the compounds. Necropsies performed on animals showed fatty liver infiltration; evidence of hemorrhaging was observed in the adrenals, lungs, and brain. Other tissues showed gross pathological changes. (6 Refs)

B. Morphologic and Biochemical Changes in Experimental Animals Exposed to Vinyl Chloride and Related Compounds

The reader may also find the following abstracts of interest: 124, 125, 244

84. EFFECTS OF VINYL CHLORIDE EXPOSURES TO RATS PRETREATED WITH PHENOBARBITAL.

Drew RT, Harper C, Gupta BN, Talley FA
Natl. Inst. Environmental Health Sciences, P.O. Box 12233,
Res. Triangle Park, N.C. 27709
Environ Health Perspect; 11:235-242 1975

Male Charles River CD-1 rats were exposed to ten consecutive days, 6 hours/day, to vinyl chloride vapors at an average concentration of 13,500 ppm. The exposed rats were divided into three groups of eight rats each: each group was pretreated with 3-methylcholanthrene (15 mg/kg, ip for two days prior to first exposure); one group was pretreated with phenobarbital (1 mg/ml in drinking water for three days prior to exposure and during exposure); and the third group received no treatment. Half the animals in each group were sacrificed 18 hr after the last exposure and half were sacrificed four days later. In a second experiment, four rats pretreated with phenobarbital were exposed to vinyl chloride vapors at a concentration of 17,300 ppm for two days and sacrificed on the third day. In both experiments control animals, also treated with phenobarbital or 3-methylcholanthrene, were exposed to air only. At the time of sacrifice, lungs, kidneys, spleen, heart, and a small piece of the liver from each animal were preserved for histological examination. The remainder of the liver was processed for assay of microsomal enzyme activity. The following parameters were investigated: growth rate, organ weights, morphological changes, and both benzphetamine-N-demethylase activity and cytochrome P-450 content of microsomes prepared from the livers. In both experiments the only marked difference noted in any group was a decrease in the growth rate of the animals exposed to vinyl chloride and treated with phenobarbital. This decreased growth rate was particularly apparent on the third day of the vinyl chloride exposures. Occasional morphological changes were also seen in the livers of the animals treated with phenobarbital and exposed to vinyl chloride. Although changes resulting from exposure to VC and phenobarbital have been demonstrated, these changes have not been shown to be preneoplastic.

85. ACUTE HEPATIC INJURY BY VINYL CHLORIDE IN RATS PRETREATED WITH PHENOBARBITAL.

Jaeger RJ, Reynolds ES, Conolly RB, Moslen MT, Szabo S, Murphy SD
Kresge Cent. Environ. Health, Harvard Sch. Public Health,
Boston, Mass.
Nature (Lond); 252(5485):724-726 1974

The potential of vinyl chloride monomer to enhance liver injury in male Holtzman rats pretreated with phenobarbital, an inducer of certain enzymes of the liver mixed-function oxidase system, was studied. Four experimental groups were defined: exposed to air and not pretreated; exposed to vinyl chloride monomer and not pretreated; exposed to air and pretreated with phenobarbital (0.1% in drinking water for 7 days); and exposed to vinyl chloride monomer and pretreated with phenobarbital. Nonpretreated and phenobarbital-pretreated rats exposed to air alone had no increase in serum alanine-alpha-ketoglutarate transaminase (AKT) and sorbitol dehydrogenase, enzymes that are highly specific for liver injury. In nonpretreated groups, exposure to 0.5% or 5% vinyl chloride monomer for a single six hour period did not cause a substantial rise in serum alanine-alpha-ketoglutarate

transaminase or sorbitol dehydrogenase, but after exposure to 10% vinyl chloride monomer there was a slight increase in these enzymes. Histologically, centrolobular hepatocellular vacuolization was noted only in the 10% exposure group. Phenobarbital pretreatment for seven days caused a marked enhancement of injury at the 5% level of exposure, with vacuolization of centrolobular parenchymal cells, focal necrosis of mid-zonal parenchyma, dilation of the rough endoplasmic reticulum, and formation of tubular snarls by smooth endoplasmic reticulum. Phenobarbital-pretreated rats killed after the last exposure to 5% vinyl chloride monomer following 5 consecutive days of exposure did not have increased activities of serum alanine-alpha-ketoglutarate transaminase or sorbitol dehydrogenase, suggesting that previous exposure to vinyl chloride monomer blocked the biochemical response which followed reexposure at short intervals.

86. BIOLOGICAL EFFECTS OF VINYL CHLORIDE: AN EXPERIMENTAL STUDY.

Winell M, Holmberg B, Kronevi T
Section Occupational Toxicology, Dept. Occupational
Medicine, Natl. Board Occupational Safety and Health,
S-100 26 Stockholm, Sweden
Environ Health Perspect; 17:211-216 1976

Liver damage caused by the exposure of albino NMRI mice to atmospheric vinyl chloride (VC) was assessed by estimating the plasma activities of alkaline phosphatase (AP), the transaminases, and lactate dehydrogenase (LDH). Three groups of 24 mice each were exposed by inhalation for 6 hr/day, 5 days/wk, to 50 ppm (52 wk) or 500 ppm VC (26 wk), or to air only (controls). The animals were also autopsied, and the tissue pathology was studied. Liver damage was indicated by a significant increase in total LDH levels after about 40 wk. After 46 wk, total LDH levels were increased about 2.5-fold following exposure to 500 ppm. A significant shift in the LDH isoenzyme profile to the M form also occurred. There was no corresponding elevation in transaminase activities, which might have served as an alternative indication of liver injury. AP activities also increased after about 40 wk: at this time levels were elevated 30%-40% and 50%-60% following exposure to 50 and 500 ppm VC, respectively. This elevation could indicate lesions in the hepatobiliary tract. Upon autopsy 12 mo after the start of exposure, no control mice had any lung adenomas or hemangiosarcomas, and 24 mice exposed to 24 ppm VC had lung adenomas and 8 had hemangiosarcomas. (30 Refs)

87. SOME ASPECTS ON DOSE-RESPONSE IN VINYL-CHLORIDE-INDUCED LIVER INJURY AND TUMORS IN MICE (MEETING ABSTRACT).

Holmberg B, Kronevi T, Winell M
Section Occupational Toxicology, Natl. Board
Occupational Safety and Health, Stockholm, Sweden
Scand J Clin Lab Invest; 37(Suppl147):74 1977

Vinyl chloride monomer (VCM) induces liver injury and liver hemangiosarcoma in PVC workmen and is also carcinogenic in rodents. Mice were exposed by inhalation to 50 and 500 ppm VCM during 12 and 6 mo respectively. Blood samples were taken every 6th wk for analysis of glutamic pyruvic transaminase (GPT), glutamic oxalacetic transaminase (GOT), acid phosphatase (AP), and total lactic dehydrogenase (LDH) as well as LDH isoenzymes. Some mice were sacrificed for histopathological examinations after 6 mo and the rest when dead or moribund. AP and total LDH activities were elevated in VCM exposed mice. The percentage of M form was also increased in exposed animals. The transaminases were not elevated. Enzyme activities were, however, increased after the appearance of tumors. A

tendency to a dose-dependency was observed in total LDH activities as well as in the frequency of tumor-bearing animals. The significance of the data will be discussed with reference to possible early detectability of VCM-induced tissue injury and with reference to current knowledge of dose-response relationships for chemically induced tumors.

88. INITIAL FEATURES OF VINYL CHLORIDE (VC) HEPATIC INJURY (MEETING ABSTRACT).

Schaffner F, Popper H, Selikoff IJ

Mount Sinai Sch. Medicine, City Univ. New York, New York, NY 10029

Gastroenterology; 71(5):A35/928 1976

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

89. ELEVATED GLUTATHIONE CONTENT, GLUTATHIONE-S-TRANSFERASE AND GLUTATHIONE REDUCTASE IN LIVER OF RATS EXPOSED TO VINYL CHLORIDE (MEETING ABSTRACT).

Du JT, Tamburro CH

Digestion, Disease and Nutrition Section, Dept. Medicine, Cancer Center, Univ. Louisville Medical Sch., Louisville, KY, 40232

Fed Proc; 37(6):1545 1978

Vinyl chloride (VC) is believed to be metabolized to chloroethylene oxide (CEO) and chloroacetaldehyde, and detoxified by way of glutathione. Rats were exposed to 28,000 ppm VC, 7 hr/day, 5 days/wk for 4 and 6 wk, the activity of glutathione epoxide-S-transferase (GEST) was elevated 30 to 54% over normal control and air control (9.71 $\pm$ 0.68 vs 7.52 $\pm$ 0.97 and 6.30 $\pm$ 0.68) respectively. However, the activity of glutathione aralkyl-S-transferase (GAST) was not significantly elevated until 6 wk of exposure to VC. The content of reduced glutathione was also elevated 45% in the VC treated group and the activity of the glutathione reductase, the enzyme to regenerate glutathione from the oxidized form was elevated 50%. These results demonstrate that VC exposed rats have the capacity to maintain glutathione reductase activity and

glutathione concentration for detoxification. Further, it suggests that the primary route of VC metabolism is initial oxidation to CEO and then detoxification by GEST directly. With longer exposure and probable saturation of the direct route, there is greater rearrangement of CEO to chloroacetaldehyde, and detoxification with glutathione as supported by the delayed induction of GAST.

90. THE EFFECT OF VINYL CHLORIDE MONOMER, CHLOROETHYLENE OXIDE AND CHLOROACETALDEHYDE ON DNA SYNTHESIS IN REGENERATING RAT LIVER.

Border EA, Webster L

Natl. Res. Inst. Occupational Diseases, S. African Medical Res. Council, P O Box 4788, Johannesburg, 2000 S. Africa

Chem Biol Interact; 17(2):239-247 1977

A study was made of the effects of vinyl chloride monomer (VCM) and two of its presumed metabolites, chloroacetaldehyde (CA) and chloroethylene oxide (CEO), on DNA synthesis in the regenerating livers of 100-g Wistar rats subjected to partial hepatectomy. VCM (0.5 ml of a 0.19% solution) injected iv 30 min after partial hepatectomy reduced the first ensuing wave of DNA synthesis (at 21 hr) by about 50%; no effect on the second wave of DNA synthesis (at 30 hr) was evident. Similar treatment with CEO and CA also depressed the first wave of DNA synthesis by about 50%. However, these substances had different effects on the second wave: CEO raised the rate of DNA synthesis by about 50%, but CA tended to desynchronize the normally well-defined second wave. It is concluded that VCM, CEO, and CA have similar effects as unrelated carcinogens in retarding DNA replication. (37 Refs)

91. VINYL CHLORIDE-INDUCED DEPRESSION OF HEPATIC NON-PROTEIN SULFHYDRYL CONTENT AND EFFECTS ON BROMOSULPHALEIN (BSP) CLEARANCE IN RATS.

Watanabe PG, Hefner RE, Gehring PJ

Toxicology Res. Lab., Health and Environmental Res.

1803 Building, Dow Chemical Company, Midland, MI 48640

Toxicology; 6(1):1-8 1976

The effects of acute inhalation exposure to vinyl chloride on the non-protein sulfhydryl content in male Sprague-Dawley rat liver were studied. The rats were exposed to 2,000, 1,000, 250, 150, 50, or 10 ppm. Exposure to 2,000 ppm resulted in a progressive depression of hepatic non-protein sulfhydryl content reaching 33% within 2 hr, 47% after 4 hr, and 62% after 7 hr. An apparent max depression was observed after 4 to 5 hr of exposure to vinyl chloride at 1,000, 250 or 50 ppm. Depression after 7 hr exposure to 50 ppm was inconsistent. Exposure to 1,000 ppm vinyl chloride did not alter the serum clearance of bromosulphalein. (25 Refs)

92. COMPARISON OF THE FATE OF VINYL CHLORIDE FOLLOWING SINGLE AND REPEATED EXPOSURE IN RATS.

Watanabe PG, Zempel JA, Gehring PJ

Toxicology Res. Lab., Health and Environmental Res.,

Dow Chemical USA, Midland, MI, 48640

Toxicol Appl Pharmacol; 44(2):391-399 1978

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

93. SOME BIOCHEMICAL AND HISTOPATHOLOGICAL CHANGES INDUCED BY POLYVINYL CHLORIDE DUST IN RAT LUNG.

Agarwal DK, Kaw JL, Srivastava SP, Seth PK
Industrial Toxicology Res. Centre, Mahatma Gandhi
Marg, Post Box No. 80, Lucknow-226001, India
Environ Res; 16(1/3):333-341 1978

Enzymatic and pathomorphologic alterations in rat lungs were studied at different time intervals up to 180 days after a single intratracheal administration of 25 mg of polyvinyl chloride dust. The activities of two energy-linked enzymes, succinic dehydrogenase (SDH) and adenosine triphosphatase (ATPase), and three lysosomal enzymes, acid phosphatase, beta-glucuronidase, and ribonuclease, were significantly increased in the early period and then started to decline. The activities of SDH and ATPase reached control values at 150 days, while those of the lysosomal enzymes remained significantly higher up to this period. Histopathologically, the pulmonary response was in the form of acute inflammatory changes during the early stages of dust burden, followed by the development of granulomatous lesions containing small amounts of stromal elements. (Author abstract) (32 Refs)

94. VINYLIDENE CHLORIDE-INDUCED ULTRASTRUCTURAL CHANGES IN RAT LIVER (MEETING ABSTRACT).

French JE, Andersen ME, Jenkins LJ
Experimental Pathology Dept., AFRR1-NNMC, Bethesda,
MS 20014
J Cell Biol; 70(2/Part2):361a 1976

Vinyl chloride and vinylidene chloride (1,1-dichloroethylene, DCE) are closely related chemicals and are known occupational and environmental contaminants. The pathobiological effects after oral administration of DCE (in corn oil) to fasted male Holtzman rats was determined by correlating the ultrastructural damage to the liver with changes in the serum levels of glutamic-pyruvic transaminase (SGPT) and glutamic-oxaloacetic transaminase (SGOT). In a completely randomized study, fasted rats received a single oral dose of 40 to 80 mg DCE/mg of body wt. After 0, 1, 2, 4, and 8 hr, SGPT and SGOT values were determined and liver tissue samples were immersion-fixed in 3% cacodylate buffered glutaraldehyde, post-fixed in osmium tetroxide and prepared by conventional EM methods. SGPT and SGOT values increased dramatically according to dosage and time of exposure in a linear manner, which indicated significant hepatic damage. The appearance of myelin-like bodies occurred at a similar frequency in both control and treated rats. Control rats were also characterized by slightly dilated rough endoplasmic reticulum (RER) and perinuclear cisternae. However, DCE-exposed rats showed significant dilation of the RER, loss of ribosomes, mitochondrial swelling, loss of cristae and chromatinolysis in a dose- and time-related manner. Margination of the chromatin along the nuclear envelope (chromatinorrhexis) did not occur within this time period of exposure and dosage of DCE. DCE is a very hepatotoxic xenobiotic and its pathobiology may be different according to the route of administration. (No refs)

95. TRICHLOROETHYLENE-INDUCED DEACTIVATION OF CYTOCHROME P-450 AND LOSS OF LIVER GLUTATHIONE IN VIVO.

Moslen MT, Reynolds ES, Boor PJ, Bailey K, Szabo S
Department of Pathology, The University of Texas Medical
Branch, Galveston, Texas 77550
Res Commun Chem Pathol Pharmacol; 16(1):109-120 1977

Liver microsomal enzyme activities and glutathione (GSH) contents of fasted male rats pretreated with phenobarbital (PBT) or vehicle controls were measured during

and after exposure to trichloroethylene (TRI) (1% x 2 hr). TRI caused morphologic liver injury only in the PBT animals. Cytochrome P-450 and b5 contents were diminished by the end of the first hr of TRI exposure and NADH-cytochrome c reduction increased three-fold by eight hr in the PBT animals. The only change in vehicle animals exposed to TRI was a decrease in NADPH-cytochrome c reductase activity by eight hr. Hepatic GSH contents of vehicle animals, constant during TRI exposure, rose with time. In contrast, in PBT animals, hepatic GSH contents decreased during TRI exposure and then rebounded. Decreases in GSH were most profound in the microsomal fraction. When fed animals with approximately equal to two-fold higher hepatic GSH levels than fasted animals were exposed to TRI, they had shorter anesthesia recovery times and less liver injury, although excreting similar or slightly more trichlorinated metabolite into their urine in 24 hr than their fasted counterparts. We suggest that the hepatotoxic effects of trichloroethylene are caused by inadequate detoxification of its reactive intermediates. (Author Abstract)

96. ACUTE TRICHLOROETHYLENE HEPATOTOXICITY AND INDUCTION OF MICROSOMAL ENZYMES (MEETING ABSTRACT).

Moslen MT, Reynolds ES, Szabo S
Peter Bent Brigham Hosp., Boston, MA
Am J Pathol; 82(2): 36a-37a 1976

To determine the effects of differential induction of mixed-function oxidase system components on the metabolism and hepatotoxicity of trichloroethylene, male rats were pretreated with isomolar doses (400 micromoles/kg/day) of phenobarbital (PBT), 3-methylcholanthrene (3-MC), hexachlorobenzene (HCB), pregnenolone-16alpha-carbonitrile (PCN) or spironolactone (SNL) or 150 micromoles/kg of Aroclor 1254 (A-1254) for 7 days by gavage. The animals were then exposed to trichloroethylene (1% in air for 2 hr) and sacrificed. Liver injury 24 hr after exposure was most severe in animals treated with PBT or A-1254. Hepatocellular injury was predominantly centrilobular in PBT-treated animals and periportal in A-1254-treated animals. SGOT elevations, morphologic injury and/or electrolyte change were of lesser extent 24 hr after exposure in 3-MC, HCB and PCN groups; changes were not apparent in the SNL group. Liver injury as quantitated by mean SGOT was related to the magnitude of induction of cytochrome P-450 and to a lesser extent to NADPH-cytochrome P-450 reductase. Enhanced urinary excretion of trichloroethylene metabolites was also correlated with P-450 content. (0 Refs)

97. TRICHLOROETHYLENE-INDUCED DEACTIVATION OF LIVER ENDOPLASMIC RETICULUM AND GLUTATHIONE DEPLETION (MEETING ABSTRACT).

Reynolds ES, Moslen MT, Boor PJ, Bailey K, Szabo S
Dept. Pathology, Univ. Texas Medical Branch, Galveston,
TX
Toxicol Appl Pharmacol; 41(1):217 1977

We have undertaken further studies to monitor mixed-function oxidase system activities and liver glutathione (GSH) contents during the development of trichloroethylene (TRI)-induced injury in phenobarbital (PBT)-pretreated animals. Male Charles River rats weighing 200 g were given PBT (400 micromole/kg) or vehicle po for 7 days. On the morning of day 8, after an overnight fast, animals were exposed to air or to 1% TRI for 2 hr. In the PBT-TRI group, contents of cytochrome P450 and cytochrome b5 diminished by the end of the 1st hr of TRI exposure and NADH-cytochrome c reduction increased three-fold by the 8th hr. In contrast, the only change in the vehicle-TRI group by 8 hr was decreased NADPH-cytochrome c reduction. Hepatic GSH contents of vehicle-TRI animals were constant during TRI exposure but

then rose almost twofold by 12 hr. Hepatic GSH contents of PBT-TRI animals decreased during exposure and then rebounded; decreases were most profound in the microsomal fraction. Because of this apparent involvement of GSH in TRI's biotransformation, we also exposed fed animals with approx 2 x higher hepatic GSH concentrations to TRI. While 24 hr urinary metabolite excretions were similar, the fed animals had shorter anesthesia recovery times and less liver injury. The hepatotoxicity of TRI appears to be caused by inadequate rates of detoxification of its reactive intermediates. (no Refs)

98. LIVER ENDOPLASMIC RETICULUM: TARGET SITE OF HALOCARBON METABOLITES.

Reynolds ES

Dept. Pathology, Peter Bent Brigham Hosp., Boston, MA 02115

Adv Exp Med Biol; 84:117-137 1977

The hepatotoxic effects of carbon tetrachloride, vinyl chloride, trichloroethylene, and halothane are reviewed. Initial injury produced by exposure to these chemicals involves the endoplasmic reticulum. There is dispersion of the ergastoplasm, then vacuolization and degranulation of the rough endoplasmic reticulum with concomitant retraction of the smooth endoplasmic reticulum into tightly clumped tubular aggregates. Membranes in these tubular aggregates seem to undergo supramolecular disassembly. This structural disorganization is accompanied by a diminished functional capacity in the organelle. Activation of these halocarbons to toxic species by the endoplasmic reticulum is indicated (1) by the enhancement of their toxicity upon pretreatment with chemicals, such as phenobarbital, or Aroclor 1254 that induce components of the mixed function oxidase system and (2) by the formation of certain metabolites and/or covalently bound products. It is not clear whether the halocarbons cause liver injury by the covalent binding of free-radical metabolites to tissue macromolecules or by initiating lipid peroxidation. (51 Refs)

99. BIOCHEMICAL AND TOXICOLOGICAL EFFECTS OF COMBINED EXPOSURE TO 1,1,1-TRICHLOROETHANE AND TRICHLOROETHYLENE ON RAT LIVER AND BRAIN.

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Occupational Health, Haartmaninkatu 1, SF-00290

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Xenobiotica; 8(3):191-196 1978

Male Wistar rats inhaled a mixture of 1,1,1-trichloroethane (1,1,1-TCE) (500 ppm) and trichloroethylene (200 ppm) 6 hr/day for 4 days. As a result, 1,1,1-TCE accumulated in the perirenal fat, the hepatic RNA content doubled, hepatic glutathione concentrations decreased slightly, and uridine diphosphate-glucuronosyl transferase activity doubled. A 5-day exposure increased the content of both solvents in various organs rapidly, depressed brain RNA, and decreased in styrene monooxygenase activity. Changes noted on day 5 had also occurred on days 1-4 but had reverted during each postexposure period. (22 Refs)

100. DAMAGE TO HEPATIC CELLULAR MEMBRANES BY CHLORINATED OLEFINS WITH EMPHASIS ON SYNERGISM AND ANTAGONISM.

Reynolds ES, Moslen MT

Dept. Pathology, Univ. Texas Medical Branch, Galveston, TX, 77550, 77550

Environ Health Perspect; 21:137-147 1978

The biochemical mechanisms responsible for the toxicity of vinyl chloride (VC), 1,1-dichloroethylene (1,1-DCE), trichloroethylene (TCE), and perchloroethylene (PCE) were

investigated in male Sprague-Dawley rats pretreated with phenobarbital, 3-methylcholanthrene, hexachlorobenzene, spironolactone, or pregnenolone-16alpha-carbonitrile. The most nonsymmetrically depolarized compound, 1,1-DCE, was the most hepatotoxic and caused a unique pattern of hepatocellular injury involving mitochondria, plasma membranes, and chromatin. The injury induced by the other chloroethylenes appeared to affect the structural integrity of the endoplasmic reticulum profoundly, with the toxic potential in the following order: TCE greater than VC greater than PCE. Pretreatments that increased the cytochrome P-450 content (increased metabolic activation) enhanced or were synergistic to the hepatotoxic potential of TCE, VC, and PCE, but they were protective or antagonistic to 1,1-DCE hepatotoxicity. This suggests that the biologic response to 1,1-DCE may be expressed by a different metabolic pathway. Glutathione appears to be involved in the biologic response to all nonsymmetric chloroethylenes and to act as an antagonist against injury. Marked differences in the patterns of injury and the biologic responses suggest that more than one mechanism is involved in the production of injury by chloroethylenes. (37 Refs)

101. AN EXPERIMENTAL APPROACH FOR EVALUATING GENETIC AND EPIGENETIC CONTRIBUTIONS TO CHEMICAL CARCINOGENESIS (MEETING ABSTRACT).

Reitz RH, Schumann AM, Watanabe PG, Quast JF,

Gehring PJ

Toxicology Res., Dow Chemical Co., Midland, MI, 48640

Proc Am Assoc Cancer Res; 20:266 1979

Many chemical carcinogens appear to cause cancer because of their ability to react irreversibly with cellular DNA, producing mutations which transform normal cells into malignant clones (genotoxicity). However, cancer has also been produced in animals by chemicals which do not appear to react with DNA, suggesting that epigenetic mechanisms can also be important. Because the safety precautions appropriate to each type of agent are quite different, we have attempted to evaluate the in vivo contribution from each type of mechanism with known animal carcinogens. Genetic effects are shown by dimethylnitrosamine (DMN). DNA isolated from the liver of treated rats (10 mg/kg) contains 0.3% alkylated bases and mice injected with 20 mg/kg DMN are carrying out 7.23 x as much DNA repair (hydroxyurea-resistant 3H-thymidine incorporation) as controls. In contrast, animals exposed to 500 mg/kg perchloroethylene (PERC) showed no evidence of DNA alkylation (less than 0.001%) but did show elevated DNA turnover (2 x controls) and histopathology in the liver. In studies with other animal carcinogens, DNA turnover and epigenetic carcinogenesis have been correlated with species sensitivity, tumor and nontumor sites, and tumorigenic and nontumorigenic doses. Consequently it appears that the relative importance of the two mechanisms of carcinogenesis can be estimated after in vivo measurements of DNA damage, DNA repair, and DNA turnover. (1 Ref)

102. REPAIR OF RAT LIVER DNA IN VIVO DAMAGED BY ETHYLENE DIBROMIDE.

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Fels. Res. Inst., Dept. Pathology, Temple Univ. Sch.

Medicine, Philadelphia, PA 19104

Biochem Pharmacol; 26(20):1941-1945 1977

Tube feeding of 14Cethylene dibromide (EDB) to non-fasted Wistar rats resulted in the incorporation of the radioactivity into liver DNA, RNA, and protein. The pesticide caused slower sedimentation of liver DNA in alkaline but not in neutral sucrose gradients. The slower sedimentation of liver DNA in alkaline sucrose gradients was apparent within 2 hr after the administration of a dose of 22 mg/100g body wt or 4

hr after a dose of 7.5mg/100g. The liver DNA damage induced by EDB at 7.5 mg/100 g was repaired significantly by 17.5 hr and almost completely by 96 hr. Administration of diethyldithiocarbamate, a free radical scavenger, did not inhibit liver DNA damage caused by EDB. The results indicate that EDB produces both chemical and physical lesions in liver DNA. (39 Refs)

C. Mutagenicity of Vinyl Chloride and Related Compounds in Bacterial Systems, Drosophila, and Experimental Animals

The reader may also find the following abstracts of interest: 39, 68, 166, 196, 199, 200, 201, 324

103. MUTAGENICITY OF INDUSTRIAL COMPOUND: VINYL CHLORIDE, STYRENE AND THEIR POSSIBLE METABOLITES (MEETING ABSTRACT). (PP. 175-176)

Loprieno N, Abbondandolo A, Barale R, Baroncelli S, Bonatti S, Bronzetti G, Cammellini A, Corsi C, Corti G, Frezza D, Leporini C, Mazzaccaro A, Nieri R, Rosellini D, Rossi AM

Laboratorio di Mutagenesi e Differenziamento, CNR e Istituto di Genetica della Università, Pisa, Italy
Third International Symposium On Detection And Prevention Of Cancer. 1976.

It has been proposed that mutagenicity tests are at the present the most appropriate for the prescreening of substances for possible carcinogenic activity. It is therefore interesting to develop biological analyses to assess the mutagenic activity of toxic industrial compounds already known as human carcinogens or those compounds under suspicion. In our analyses we have applied mutagenicity methodologies in the study of vinyl chloride (human carcinogen) and to styrene (under carcinogenic analysis at the present); the same analyses have been applied also to their possible metabolites (2-chloroethylene oxide, 2-chloroethanol, 2-chloroacetaldehyde, and styrene oxide) in order to correlate the mammalian metabolic fate of the compounds with their biological activity. The compounds have been studied by means of liver microsomal assay and host-mediated assay (mice), employing as a test organism the yeast *S pombe* and *S. cerevisiae* on which the induction of gene-mutations and of gene-conversions has been analyzed. Preliminary experiments have been done also with somatic mammalian cells (V79 chinese hamster), on which the induction of 8-azaguanine resistant clones has been assessed: From our analyses it has been found that vinyl chloride is mutagenic in the presence of liver microsomal preparations (in vitro) or in the host-mediated assay (in vivo). (Author Abstract)

104. MUTAGENICITY OF INDUSTRIAL COMPOUNDS: VINYL CHLORIDE, STYRENE AND THEIR POSSIBLE METABOLITES (MEETING ABSTRACT).

Loprieno N, Abbondandolo A, Barale R, Baroncelli S, Bonatti S, Bronzetti G, Cammellini A, Corsi C, Corti G, Frezza D, Leporini C, Mazzaccaro A, Nieri R, Rosellini D, Rossi A

Laboratorio di Mutagenesi e Differenziamento, CNR e Istituto di Genetica dell'Università, Pisa, Italy
Mutat Res; 38(2):114-115 1976

Mutagenicity methodologies were applied to the study of vinyl chloride, styrene, and their metabolites (2-chloroethylene oxide, 2-chloroethanol, 2-chloroacetaldehyde, and styrene oxide) to correlate the mammalian metabolic fate of the compounds with their biological activity. The compounds were studied by liver microsomal assay and host-mediated assay with the yeast *S pombe* and *S cerevisiae*. Preliminary

experiments were also done with somatic mammalian cells (V79 chinese hamster), on which the induction of 8-azaguanine resistant clones was assessed. Vinyl chloride was found to be mutagenic in the presence of liver microsomal preparations and in the host-mediated assay; moreover, the possible in vivo metabolite, 2-chloroethylene oxide, was responsible for mutagenic activity. Styrene was found to be inactive on yeast (+/- microsomes) or slightly active on hamster cells; styrene oxide was found to be active in different biological systems. (No refs)

105. A DOMINANT LETHAL STUDY IN MALE RATS AFTER REPEATED EXPOSURES TO VINYL CHLORIDE OR VINYLIDENE CHLORIDE.

Short RD, Minor JL, Winston JM, Lee CC
Pharmacology and Toxicology, Midwest Res. Inst., 425 Volker Blvd., Kansas City, MO, 64110
J Toxicol Environ Health; 3(5/6):965-968 1977

Germinal mutations, as manifested by a dominant lethal effect, in male rats exposed to 0, 50, 250, or 1000 ppm vinyl chloride or 55 ppm vinylidene chloride (6 hr/day for 5 days/wk) were studied. The males were mated with untreated females after 11 wk of exposure. No evidence of pre- or postimplantation loss in the pregnant females was observed. (9 Refs)

106. VINYL CHLORIDE: DOMINANT LETHAL STUDIES IN MALE CD-1 MICE.

Anderson D, Hodge MC, Purchase IF
Imperial Chemical Industries Ltd., Central Toxicology Lab., Alderley Park, North Macclesfield, Cheshire SK10 4TJ, England
Mutat Res ; 40(4):359-370 1976

The mutagenic activity of vinyl chloride (VC) was investigated in CD-1 mice by the dominant lethal test at inhalation exposure levels of 30,000, 10,000 and 3,000 ppm (6 hr/day for 5 days). The only significant mortality occurred in the groups exposed to the highest level of VC. Mice were also given ethyl methanesulfonate (200 mg/kg/day x 5, po) or cyclophosphamide (200 mg/kg on day 5, ip). Cyclophosphamide or methanesulfonate treatment increased the number of pregnancies with early deaths. The effect was significant in weeks 1 and 2 for the cyclophosphamide-treated group and week 2 for the methanesulfonate-treated group. No differences from controls were observed in the VC-treated group. As indicated by the total implants per pregnant female, VC caused no preimplantation egg losses. As demonstrated by the number of females with one or more early deaths, the number of early deaths/pregnancy, or the number of early deaths/total implants/pregnancy, VC caused no significant increase in the number of postimplantational early fetal deaths. It is concluded that, although mutagenic effects of VC have been reported, no such effects, as determined in the present study, occur in the germ cells of CD-1 mice. (14 refs)

107. HUMAN, RAT AND MOUSE-LIVER MEDIATED MUTAGENICITY OF VINYL CHLORIDE IN *S. TYPHIMURIUM* STRAINS.

Bartsch H, Malaveille C, Montesano R
Int. Agency Res. Cancer, Lyons, France
Int J Cancer; 15(3):429-437 1975

The mutagenicity of vinyl chloride monomer (VCM) and its presumed metabolites in *Salmonella typhimurium* strains as mediated by tissue fractions of mouse, rat, and human origin were studied. The male BD-IV rats (100-130 g) and male OF-1 mice (30-35 g) used were fed a Charles River CRF diet. After six hours of exposure to 20% VCM in air (vol/vol) strain TA 1530 was specifically reverted to His prototrophy. This mutagenic response was increased to 283% of the control value by mouse liver postmitochondrial fraction (9,000 x g

supernatant); to 345% of the control by rat liver postmitochondrial fraction; and from 270-700% of the control value by four samples of this fraction from four biopsies of human livers. Phenobarbitone sodium (PB) was added to the animals' drinking water (1 mg/ml) for seven days before tissue fractionation in some experiments. This treatment increased the above mutagenic response to 457% for mouse liver fractions and to 383% for rat liver fractions. No cytotoxic effects of VCM were seen. Chloroacetic acid (a urinary metabolite of VCM) and chloroacetaldehyde were toxic, while chloroethanol was weakly mutagenic for TA 1530. The effects of subcellular fractions from mouse liver on the mutagenic response after six hours of exposure to 20% VCM at 37 C were: postmitochondrial fraction, 323% of control; microsomal fraction, 182%; cytosol (supernatant after 100,000 x g) 144%; and microsomal fraction plus cytosol, 522% of control. The number of His⁺ revertants minus the number of spontaneous mutations found when no tissue fraction was added was used as the control value. A casual relationship between VCM exposure and angiosarcoma of the liver in man has been established.

108. MUTAGENICITY AND METABOLISM OF VINYL CHLORIDE.

Montesano R, Bartsch H
Unit Chemical Carcinogenesis, International Agency Res.
Cancer, Lyon, France
Adv Tumor Prev Detect Charact; 3:242-245 1976

Studies on the mutagenicity and metabolism of vinyl chloride are reviewed. The mutagenic and/or carcinogenic effect of vinyl chloride appears to be mediated through the formation of electrophilic metabolites by microsomal mixed-function oxidase. The pretreatment of rats with drugs that modify the activity of the enzyme results in changes in the in vitro mutagenicity of vinyl chloride. This supports the hypothesis that the carcinogen has to be converted into electrophilic and mutagenic metabolites. Pretreatment of rats with phenobarbitone increases the mutagenic response, whereas the administration of pregnenolone-16 α -carbonitrile and aminoacetonitrile reduces the liver-mediated mutagenicity of vinyl chloride. Experiments involving the trapping of chloroethylene oxide in vitro by 4-nitrobenzylpyridine, following activation of vinyl chloride in the presence of mouse liver microsomal enzymes, an NADPH-generating system, and oxygen, support the hypothesis that monochloroethylene oxide is a primary reactive and mutagenic metabolite of vinyl chloride.

109. COMMENT ON THE MUTAGENIC EFFECTIVENESS OF VINYL CHLORIDE METABOLITES.

Hussain S, Osterman-Golkar S
Wallenberg Lab., Univ. Stockholm, S-104 05 Stockholm,
Sweden
Chem Biol Interact; 12(3-4):265-267 1976

In the region of low doses on dose-response curves, the mutagenic effectiveness per unit dose, determined as the time integral of concentration, was found for several alkylating agents to be approximately proportional to the calculated rate of reaction at a certain low nucleophilic strength, *n* approximately equal to 2. This proportionality appears to be independent of the nature of the alkyl introduced, and for this reason the computed degree of alkylation at *n* equal to 2, and at a given tissue dose, may be used tentatively to estimate genetic risk. The mutagenic effectiveness of chloroethylene oxide was found to be higher than the values obtained for two

standard compounds, ethylene oxide and methyl methanesulfonate.

110. THE MUTAGENICITY OF THE CARCINOGEN VINYL CHLORIDE AND ITS COMPARISON WITH A KNOWN ALKYLATING MUTAGEN. (PP. 505-519)

Loprieno N, Barale R, Baroncelli S, Bronzetti G, Cammellini A, Corsi G, Leporini C, Nieri R, Rossi AM
Screening Tests In Chemical Carcinogenesis; International Agency for Res. on Cancer. (Brussels, Belgium, 9-12 June 1975, no. 12, 1976.

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

111. EVALUATION OF THE GENETIC EFFECTS INDUCED BY VINYL CHLORIDE MONOMER (VCM) UNDER MAMMALIAN METABOLIC ACTIVATION: STUDIES IN VITRO AND IN VIVO.

Loprieno N, Barale R, Baroncelli S, Bauer C, Bronzetti G, Cammellini A, Cercignani G, Corsi C, Gervasi G, Leporini C, Nieri R, Rossi AM, Stretti G, Turchi G
Istituto di Genetica, University, Pisa, Italy
Mutat Res; 40:85-95 1976

The mutagenic activity of vinyl chloride monomer (VCM) was observed on yeast in the presence of a pure preparation of mouse (Swiss albino) liver microsomes and in the "host-mediated assay"; the gene conversion inducible by *Saccharomyces cerevisiae* was also observed. VCM in the presence of purified microsomes (sedimented at 105,000 g) was converted into an active metabolite(s) that produced gene mutations in the yeast *S pombe* (forward mutation) and gene conversions in two loci of diploid *S cerevisiae*. No mutagenic activity was found when yeast cells were treated with VCM, a phosphate buffer, or microsomes alone; this demonstrates that the enzyme necessary to metabolize VCM into a biologically reactive compound is not present in the yeast. Moreover, the compound was active in the host-mediated assay, when mice were treated with an oral dose of 700 mg/kg of VCM. These results have demonstrated that VCM is mutagenic for eukaryotic organisms and that it produces other genetic changes; this activity is liver-microsome dependent and dose dependent. It is recommended that reliable methodologies, like this mammalian metabolic activation one, for assessing the toxicological values of many industrial compounds before they reach production, be made available.

112. VINYL CHLORIDE MUTAGENICITY VIA THE METABOLITES CHLOROOXIRANE AND CHLOROACETALDEHYDE MONOMER HYDRATE.

Elmore JD, Wong JL, Laumbach AD, Streips UN
Department of Chemistry, University of Louisville and
Department of Microbiology, University of Louisville,
Louisville, Ky. 40208 (U.S.A.)
Biochim Biophys Acta; 442(3):405-419 1976

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

113. MUTAGENICITY OF CHLOROACETALDEHYDE, A POSSIBLE METABOLIC PRODUCT OF 1,2-DICHLOROETHANE (ETHYLENE DICHLORIDE), CHLOROETHANOL (ETHYLENE CHLOROHYDRIN), VINYL CHLORIDE AND CYCLOPHOSPHAMIDE (MEETING ABSTRACT).

McCann J, Simmon V, Streitwieser D, Ames BN
Biochemistry Dept., Univ. California, Berkeley, Calif.
94720

Proc Natl Acad Sci USA; 72(8):3190-3193 1975

A rapid, sensitive bacterial test to detect chemical carcinogens as mutants utilizes a special set of histidine mutants of *Salmonella typhimurium* for reversion, and a rat (or human) microsomal system for metabolic conversion of carcinogens to their active forms. The mutagenicity of chloroacetaldehyde was tested in this system because the compound is a possible metabolite in mammals of the large-volume industrial chemicals 1,2-dichloroethane (ethylene dichloride; 3.5 billion kg/yr, U.S.) and vinyl chloride (2.5 billion kg/yr, U.S.), and of the antineoplastic agent, cyclophosphamide. Chloroacetaldehyde effectively reverted a new *Salmonella* bacterial tester strain (TA100) at all levels tested (1-5 mg). Chloroacetaldehyde was hundreds of times more effective in reverting TA100 than was chloroethanol (ethylene chlorohydrin), a known metabolic precursor of chloroacetaldehyde and a possible metabolite of dichloroethane and vinyl chloride; or vinyl chloride, which is itself mutagenic for TA100. Chloroethanol was activated by rat and human liver homogenates to a more highly mutagenic form with reversion properties similar to chloroacetaldehyde. Reversion properties of cyclophosphamide after in vitro metabolic activation suggests that chloroacetaldehyde is not the active mutagenic form of this antineoplastic drug. The likely involvement of chloroacetaldehyde in the metabolism of dichloroethane and chloroethanol indicates that the carcinogenicity of these industrial chemicals should be thoroughly examined.

114. MUTAGENICITY AND METABOLISM OF VINYL CHLORIDE AND RELATED COMPOUNDS.

Bartsch H, Malaveille C, Barbin A, Bresil H, Tomatis L, Montesano R
International Agency Res. Cancer, Unit Chemical
Carcinogenesis, 69008, Lyon, France
Environ Health Perspect; 17:193-198 1976

Experimental data concerning the metabolism and mutagenicity of vinyl chloride (VC) and related compounds are reviewed. The data suggest that the biological effects of VC are related to its conversion by microsomal enzymes into chemically reactive alkylating agents that can bind covalently to various cellular macromolecules. The mutagenicity of VC to *Salmonella typhimurium* strain TA1530, which is reverted to his⁺ by single base-pair substitutions, was increased 28-fold after exposure to an atmosphere of 20% VC (volume/volume) in air. Hepatic microsomal mixed-function oxidases from rats, mice, and humans were equally effective in transforming VC into alkylating agents in vitro. Two of the products of reaction with the microsomal enzyme system, chloroethylene oxide and 2-chloroacetaldehyde, demonstrated potent mutagenicity in microorganisms and Chinese hamster V79 cells. (31 Refs)

115. INDUCTION OF GENE MUTATIONS AND GENE CONVERSIONS BY VINYL CHLORIDE METABOLITES IN YEAST.

Loprieno N, Barale R, Baroncelli S, Bartsch H, Bronzetti G, Cammellini A, Corsi C, Frezza D, Nieri R, Leporini C, Rosellini D, Rossi AM
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Cisanello 147/B, 56100 Pisa, Italy
Cancer Res; 37(1):253-257 1977

Chloroethylene oxide and 2-chloroacetaldehyde, two metabolites of vinyl chloride, and 2-chloroethanol, a putative metabolic intermediate, were assayed for their genetic activity in the yeasts *Schizosaccharomyces pombe* and *Saccharomyces cerevisiae*. Chloroethylene oxide was found to be the most effective in inducing forward mutations in *Sch pombe* and gene conversions in *S cerevisiae*, increasing the mutation and conversion frequencies 340 and 50 times, respectively, over those of the controls. In either the presence or the absence of mouse liver microsomes, 2-chloroacetaldehyde showed only feeble genetic activity, and 2-chloroethanol was completely inactive in both yeast strains. In contrast to vinyl chloride, 2-chloroacetaldehyde did not induce forward mutations in *Sch pombe* in the host-mediated assay in mice. The results strongly support the hypothesis that chloroethylene oxide is one of the principal mutagenic agents formed from vinyl chloride in the presence of mouse liver enzymes. (Author Abstract)

116. VINYL CHLORIDE DEPENDENT MUTAGENESIS: EFFECTS OF LIVER EXTRACTS AND A FREE RADICAL GENERATING SYSTEM (MEETING ABSTRACT). (PP. 176)

Garro AJ, Gutterman JB, Milvy P
Mt. Sinai Sch Med, NY, NY 10029
Third International Symposium On Detection And
Prevention Of Cancer. 1976.

The relationship between vinyl chloride (VC) dependent mutagenesis and metabolic activation of VC by hepatic extracts was examined. VC itself was observed to be mutagenic for *Salmonella typhimurium* and mutagenesis was enhanced by the presence of mouse or rat liver extracts. The extracts prepared from mice pretreated either with VC or the microsomal enzyme inducer, Aroclor 1254, did not produce any greater stimulation of VC dependent mutagenesis than extracts from untreated animals. These same extracts, however, differed markedly in their capacity to stimulate the

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

117. STUDIES ON THE MUTAGENICITY OF VINYL CHLORIDE METABOLITES AND RELATED COMPOUNDS (MEETING ABSTRACT). (PP. 192-193)

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Dept Microbiol and Immunol, Sch Med, Dept Chem, Univ Louisville, Louisville, KY 40201

Third International Symposium On Detection And Prevention Of Cancer. 1976.

The mutagenic potential of several purified metabolites of vinyl chloride monomer (VCM) was determined by utilizing bacterial assay methods. First, a preliminary screen, the repair assay, using DNA repair deficient mutants of *Bacillus subtilis* was performed, then the compounds were tested quantitatively for mutagenicity with *Salmonella typhimurium* LT-2 strains obtained from B N Ames. From all the tested compounds the following were found to be mutagenic in the bacterial assays: chlorooxirane (chloroethyleneoxide), chloroacetaldehyde, chloroacetaldehyde hydrate, chloroacetaldehyde dimer hydrate, and chloroacetaldehyde trimer. In additional epichlorohydrin (1-chloro-2,3 epoxypropane), a related compound to chlorooxirane, was weakly mutagenic in our assays. All of the above compounds specifically reverted the *Salmonella* tester strain TA 100, indicating base pair substitution type of mutations. A recombination repair deficient strain of *B subtilis*, MC-1, was specifically inhibited in growth by the VCM metabolites. However, several excision repair deficient strains and the wild type (repair-positive) strain were relatively unaffected. These experiments suggest that VCM metabolites elicit recombination repair, an error prone process, for correction of damage. epichlorohydrin was not reactive in these experiments, indicating that either epichlorohydrin-induced lesions or the repair of these lesions differ from those caused by VCM metabolites. (Author Abstract)

118. THE MUTAGENICITY OF WASTE PRODUCTS FROM THE VINYL CHLORIDE INDUSTRIES (MEETING ABSTRACT).

Rannug U, Ramel C

Environmental Toxicology Unit, Wallenberg Lab., Stockholm, Sweden

Mutat Res; 38(2):113 1976

Vinyl chloride has been shown to possess carcinogenic and mutagenic properties. There is a risk that byproducts also possessing these properties may be formed in industrial processes involving this compound. The manufacture of vinyl chloride from acetylene and/or ethylene has given rise to a waste product, the EDC tar that contains ethylene dichloride as one of its main components. (This waste product has been

dumped into the sea in large quantities.) It was tested for mutagenicity with one of the strains in the *Salmonella* test system (TA1535), which responded to base-pair substitutions in DNA. Ethanol, dimethyl sulfoxide, and Tween 80 were used to dissolve or emulsify the tar. They produced a mutagenic effect which was approximately of the same magnitude. However, when a microsomal fraction from rat liver plus an NADPH-generating system was added, the EDC tar exhibited a considerably stronger mutagenic effect. These results suggest that there are direct as well as indirect mutagenic components in the EDC tar.

119. THE NON-MUTAGENICITY AND -RECOMBINOGENICITY OF VINYL CHLORIDE IN THE ABSENCE OF METABOLIC ACTIVATION.

Shahin MM

Dept. Genetics, Univ. Alberta, Edmonton, Alberta T6G 2E9, Canada

Mutat Res; 40(3):269-272 1976

The ability of vinyl chloride to induce reversion and mitotic recombination in the yeast *Saccharomyces cerevisiae* was investigated. Strain D5 was chosen for study of the induction of recombinational events and XV185-14C was chosen for reversion induction in mutants. Negative results were obtained for mutagenicity and recombinogenicity of vinyl chloride. Vinyl chloride had no effect on viability, even at a concentration as high as 0.55% and treatment up to 48 hr. The results demonstrate that vinyl chloride is not mutagenic or recombinogenic in yeast under these experimental conditions. (7 refs)

120. A COMPARISON OF THE MUTAGENIC PROPERTIES OF VINYL CHLORIDE AND METHYL CHLORIDE.

Andrews AW, Zawistowski ES, Valentine CR

Frederick Cancer Res. Center, Frederick, MD 21701

Mutat Res; 40(3):273-276 1976

The mutagenic properties of vinyl chloride and methyl chloride were compared in *Salmonella typhimurium* tester strain TA 1535. A level of 23% methyl chloride was toxic to the bacteria; an inhibitory level of vinyl chloride was not reached. With the exception of 0.5% methyl chloride, all concentrations of both chemicals (0.4-15.4% vinyl chloride and 0.5-23% methyl chloride) caused a significant number of revertants. Because of the similar properties of these gases and because vinyl chloride is a mutagen/carcinogen, methyl chloride should be considered and investigated as a possible carcinogen. (9 refs)

121. MUTAGENIC EFFECTS OF VINYL CHLORIDE IN *DROSOPHILA MELANOGASTER* (MEETING ABSTRACT).

Magnusson J, Ramel C

Wallenberg Lab., Univ. Stockholm, Stockholm, Sweden

Mutat Res; 38(2):115 1976

Genetic investigations on *Salmonella* have shown that vinyl chloride is converted to a mutagenic metabolite in liver microsomes. To study the effect of vinyl chloride in the gonads and the transmission of mutations to the next generation, tests with sex-linked recessive lethals in *Drosophila* were performed by the Muller 5 method. Males were treated with doses of vinyl chloride in the air for 3 hr and mated to Muller 5 females. A significant increase in recessive lethals was obtained both in the first and second generations; this indicated that the induction of recessive lethal mosaics took place. These results are in accordance with previous findings that *Drosophila* exhibits a metabolic conversion of indirect carcinogens, resembling the metabolic activation in mammals. (No refs)

122. MUTAGENIC EFFECTS OF VINYL CHLORIDE ON DROSOPHILA MELANOGASTER WITH AND WITHOUT PRETREATMENT WITH SODIUM PHENOBARBITURATE.

Magnusson J, Ramel C
Environmental Toxicology Unit, Wallenberg Lab., Univ.
Stockholm, Stockholm, Sweden
Mutat Res; 57(3):307-312 1978

Exposure of wild-type Karanas 60 *Drosophila* males (0-2 days old) to 10,000, 100,000 or 200,000 ppm vinyl chloride (VC) gas increased the number of complete and mosaic sex-linked recessive lethals. A threshold effect was observed that may be due to a limit of the mixed-function oxidase activity. In additional experiments, *Drosophila* were pretreated with a 1% soln of phenobarbital sodium (PB) dissolved in water containing 1% sucrose for 24 hr, followed immediately by exposure to 1,000 or 100,000 ppm VC gas (Group 1). Group 2 was treated with either concentration of VC alone, and Group 3 was not treated. PB pretreatment enhanced the number of recessive lethals over the numbers produced by Groups 2 and 3. Compared with Groups 2 (corresponding group) and 3, the total number of recessive lethals produced by PB + 10,000 ppm VC was significant, but not the number produced by PB + 100,000 ppm VC. In Groups 1 and 2, the higher VC dose did not produce a higher frequency of recessive lethals than the lower dose; again, there was a lack of a dose-response effect. The results indicate that the mixed-function oxidase system can be induced in *Drosophila* in the same way as in mammals. (12 Refs)

123. THE MUTAGENICITY OF CHLOROETHYLENE OXIDE, CHLOROACETALDEHYDE, 2-CHLOROETHANOL AND CHLOROACETIC ACID, CONCEIVABLE METABOLITES OF VINYL CHLORIDE.

Rannug U, Gothe R, Wachtmeister CA
Wallenberg Lab., Univ. Stockholm, S-104 05 Stockholm, Sweden
Chem Biol Interact; 12(3-4):251-263 1976

The ability of four conceivable metabolites of vinyl chloride - chloroethylene oxide, chloroacetaldehyde, 2-chloroethanol and chloroacetic acid - to cause base-pair substitution directly in *Salmonella typhimurium* TA1535 was compared. The main comparison was performed at initial concentrations from 0.1-1.5 mM. In this region, however, a mutagenic effect was observed only with chloroethylene oxide and chloroacetaldehyde, the former being approximately 20 times more effective than the aldehyde when compared on a molar basis. 2-Chloroethanol and chloroacetic acid were also studied at higher concentration (1 mM-1 M), and a weak mutagenic response was found with a 1 M 2-chloroethanol solution. With chloroacetic acid no enhancement of the mutation frequency could be detected. Chloroethylene oxide was found to be approximately 450 times more effective as a mutagen than chloroacetaldehyde when the comparison was based on exposure doses, defined as the time-dependent concentrations of the compounds in the treatment solutions, integrated between the times of onset and termination of treatment. Similarly, chloroethylene oxide was 10,000-15,000 times more effective as a mutagen than ethylene oxide, used as a positive control. Although chloroethylene oxide might play a part in the previously reported mutagenicity of vinyl chloride, it is more likely that it is the active metabolite of major importance, as this substance has the most pronounced property of producing a high number of mutants at low doses without causing a toxic effect.

124. ALKYLATING AND MUTAGENIC METABOLITES OF HALOGENATED OLEFINS PRODUCED BY HUMAN AND ANIMAL TISSUES.

Bartsch H, Malaveille C, Barbin A, Planche G, Montesano R
International Agency for Research on Cancer, 69008
Lyon, France
Proc Am Assoc Cancer Res; 17:17 1976

S typhimurium TA100 in the presence of a 9,000 x g sup of PB-pretreated mice was exposed to gaseous mixtures of 1-IX/air. Mutation rates (his⁺ rev colonies/umol/ hr/plate) taken from linear regions of dose and time dependent assays either with or without (figures bracketed) NADP⁺, were as follows: I: Vinyl acetate 0(0); II: 1,1-difluoroethylene 0(0); III: trichloroethylene 0(0); IV: vinyl chloride 6(2); V: 1,1-dichloroethylene 15(1); VI: vinyl bromide 26(9); VII: 2-chloro-1,3-butadiene 51(9); VIII: 1-chloro-1,3-butadiene 157(81); IX: 3,4-dichlorobutene-1 490(345). Liver fractions from 8 human biopsies converted compounds IV, VI, VII into mutagens with an activity comparable to those of untreated mouse liver. 1,4-Dichloro-butene-2 was mutagenic for TA100 and liver microsomal fractions from mouse or humans enhanced the mutagenic effect. Epoxide formation from vinyl chloride and vinyl bromide by mouse liver microsomes was demonstrated by trapping with 4-nitro (4-benzyl) pyridine. Using the same system, compound VII yielded an alkylating intermediate while compounds II, III and V did not. Thus, the conversion of these compounds to potential carcinogenic metabolites by human and animal tissues has been demonstrated. (Author Abstract)

125. MUTAGENICITY AND CHROMOSOMAL ABERRATIONS AS AN ANALYTICAL TOOL FOR IN VITRO DETECTION OF MAMMALIAN ENZYME-MEDIATED FORMATION OF REACTIVE METABOLITES.

Greim H, Bimboes D, Egert G, Goggelmann W, Kramer M
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D-8042 Neuherberg, W. Germany
Arch Toxicol (Berl); 39(1/2):159-169 1977

The mutagenic activity of various chemicals was tested in bacterial and mammalian assay systems. Trichloroethylene, 1,1-dichloroethylene, vinyl chloride, tetrachlorocyclopentadiene, and the nitroso derivatives of the pesticides Carbaryl, Prometryn, and Dodin were mutagenic to *Escherichia coli* K12 and/or *Salmonella typhimurium* in the presence of metabolically active mouse liver microsomes. Under the same conditions, tetrachloroethylene, 1,2-cis- and trans-dichloroethylene, hexachlorocyclopentadiene, carbon tetrachloride, chloroform, halothane, trichlorofluoromethane, and styrene were not activated to mutagenic species. Incubation of human lymphocytes with dimethylnitrosamine in the presence of mouse liver microsomes induced chromosomal aberrations: there was a significantly increased number of gaps, but crossovers or translocations and breaks were less frequent. It is concluded that human lymphocytes can be successfully used in metabolizing test systems in combination with mouse liver microsomes to activate potential mutagens.

126. GENETIC ACTIVITY OF ALLYL CHLORIDE.

McCoy EC, Burrows L, Rosenkranz HS
Dept. Microbiology, New York Medical Coll., Valhalla,
NY, 10595
Mutat Res; 57(1):11-15 1978

The mutagenic activity of allyl chloride (3-chloroprene) for *Salmonella typhimurium* TA100 and TA1535, but not

TA1538, was demonstrated using an assay procedure that protected against evaporation of the volatile test substance. Allyl chloride also induced gene conversions in *Saccharomyces cerevisiae* and displayed DNA-modifying activity for *Escherichia coli*. These results are in contrast to a recent study that reported that allyl chloride was devoid of genetic activity for *S. typhimurium*, and they indicate that the volatility of the test agent is an important factor that must be taken into consideration. (30 Refs)

127. THE MUTAGENIC EFFECT OF 1,2-DICHLOROETHANE ON *SALMONELLA TYPHIMURIUM* I. ACTIVATION THROUGH CONJUGATION WITH GLUTATHION IN VITRO.

Rannug U, Sundvall A, Ramel C

Environmental Toxicology Unit, Univ. Stockholm, S-106 91 Stockholm, Sweden

Chem Biol Interact; 20(1):1-16 1978

The weak mutagenicity of 1,2-dichloroethane (1,2-DE) for *Salmonella typhimurium* TA1535 was increased by the addition of a metabolizing system, ie, the S-9 postmitochondrial rat liver fraction. This activation was further increased by the addition of reduced glutathione (GSH). No activation occurred when GSH was added in the presence of a totally denatured S-9 fraction or in the absence of this fraction. Glutathione S-transferases A and C significantly increased the mutagenicity of 1,2-DE in the presence of GSH. A synthetic conjugate, S-(2-chloroethyl)-L-cysteine, gave a strong direct mutagenic effect at 0.2-5.0 $\mu\text{mol}/\text{plate}$, concentrations at which no effects were seen with 1,2-DE. Thus, it is concluded that 1,2-DE is activated by conjugation to GSH. (24 Refs)

128. MUTAGENIC EFFECTS OF PETROL IN *DROSOPHILA MELANOGASTER*. I. EFFECTS OF BENZENE AND 1,2-DICHLOROETHANE.

Nylander PO, Olofsson H, Rasmuson B, Svahlin H

Dept. Genetics, Univ. Umea, S-901 87 Umea, Sweden

Mutat Res; 57(2):163-167 1978

The mutagenic effects of petrol, and two of its components, benzene and 1,2-dichloroethane were investigated in *Drosophila melanogaster*. A sex-linked genetically unstable system in *D. melanogaster* of genotype $sc\ z\ w^{++}$ was used and results were compared with the genetically stable system, $zDpw^{++}+69elq$. Survival of flies (the total number of hatching males from 800 untreated larvae) and the frequency of mutations (the frequency of flies with red sectors) were measured. Petrol was added to the medium at 1 and 2.5%. Benzene (1 and 2%) and 1,2-dichloroethane (0.1 and 0.5%) were in the medium to which newly hatched larvae were transferred. A significant increase in mutation frequency occurred at both concentrations of petrol in the unstable genotype. The stable genotype showed small and insignificant increases in mutation frequency. The differences between the stable and unstable genotypes were significant at 2.5% petrol, but not at 1% petrol. Benzene, in either concentration tested, did not significantly affect the mutation frequency. High mutagenetic activity was observed in both genotypes exposed to 1,2-dichloroethane, and the unstable genotype exhibited a significantly higher mutation frequency than the stable genotype. Toxicity was also very high. It is suggested that at least part of the observed mutagenic activity of petrol is due to its content of 1,2-dichloroethane. The existence of a metabolic activating system in *Drosophila* is discussed. (17 Refs)

129. THE MUTAGENICITY AND METABOLISM OF 1,2-DICHLOROETHANE (MEETING ABSTRACT).

Rannug U, Ramel C

Environmental Toxicology Unit, Wallenberg Lab., Univ. Stockholm, Stockholm, Sweden

Mutat Res; 53(2):251-252 1978

The tar-like waste product from the vinyl chloride production has shown mutagenic properties in the *Salmonella* microsome test using strain TA1535. Ethylenedichloride (1,2-dichloroethane), one of the main components in the tar, was also mutagenic in the test but cannot be responsible for the mutagenicity of the total tar. In both cases an increase in the number of mutants is seen when the metabolizing system is present, but the activation of the tar is NADPH-dependent and the activation of 1,2-dichloroethane is NADPH-independent. The metabolism and mutagenicity of the latter was therefore studied in more detail with *Salmonella* and different metabolizing systems. From the results it can be concluded that the activation to a more potent mutagen is carried out by enzymes in the soluble fraction. This activation is further stimulated by addition of glutathione to the system, indicating a formation of a conjugate between 1,2-dichloroethane and glutathione. 1,2-Dichloroethane has also been tested on the same *Salmonella* strain (TA-1353) with perfused rat-liver as metabolizing system. In this test the bile produced, within half an hour after the addition of 1,2-dichloroethane, is strongly mutagenic, while no effect can be seen in the perfusate. A corresponding enhancement in the mutagenicity of 1,2-dichloroethane was seen if the bacteria were incubated in the presence of enzyme preparations of glutathione S-transferases, glutathione and 1,2-dichloroethane. It can therefore be concluded that one metabolic pathway of 1,2-dichloroethane involves direct conjugation with glutathione. This conjugate is excreted in the bile, where the mutagenicity is found. Normally the conjugation with glutathione is regarded as a detoxication, but in this case the effect is quite the contrary. The substance is activated by the conjugation. The results also illustrate the usefulness of the mutagenicity test based on *Salmonella* and in vitro metabolism in tracing metabolic pathways which could be more difficult to detect in vivo. (no Refs)

130. THE MUTAGENIC EFFECT OF 1,2-DICHLOROETHANE ON *SALMONELLA TYPHIMURIUM*. II. ACTIVATION BY THE ISOLATED PERFUSED RAT LIVER.

Rannug U, Beije B

Division Toxicology Genetics, Wallenburg Lab., Univ. Stockholm, Stockholm, Sweden

Chem Biol Interact; 24(3):265-285 1979

Isolated Wistar rat liver was perfused with a solution containing 1,2-dichloroethane (DCE), 1,2-dibromoethane (DBE), or 2-chloroethanol (CE), and the mutagenicities of the perfusates for *Salmonella typhimurium* strains TA1530 and TA1535 were tested. Bile samples (diluted 10-fold) produced by DCE-treated livers were strongly mutagenic for TA1535, the greatest values (800 and 600 mutants/plate) being observed 15 or 30 min after addition of DCE 360 micromoles (μmol) at 0 and 90 min, respectively. Bile from DBE-treated livers (1 dose of 12 μmol DBE) was also mutagenic for TA1535, producing 50 and 60 mutants/plate at 15 and 30 min, respectively. Bile from DCE-treated Sprague-Dawley rats was significantly less mutagenic than that of Wistar rat bile (p less than 0.001), and the former was clearly more mutagenic after 30 min than after 15 min. CE was not mutagenic in this system. The results with DCE and DBE indicated an activation through conjugation to glutathione with a subsequent excretion through the bile. Bile produced by mice treated ip with DCE

(80 mg/kg) was also mutagenic for TA1535, the mutagenicity being greater 30 min after injection than 60 min after injection. S-(2-chloroethyl)-L-cysteine and N-acetyl-S-(2-chloroethyl)-L-cysteine were equally mutagenic for TA1535 in the concentration range 0.2-0.6 μ mol/plate, whereas S-(2-hydroxyethyl)-L-cysteine was not directly mutagenic. Differences and similarities in the metabolism of DCE and vinyl chloride are discussed on the basis of these results. (49 Refs)

131. TISSUE-MEDIATED MUTAGENICITY OF VINYLIDENE CHLORIDE IN SALMONELLA TYPHIMURIUM TA1535.

Jones BK, Hathway DE
Central Toxicology Lab., Imperial Chemical Industries Ltd., Alderley Park, Cheshire, SK10 4TJ, England
Cancer Lett; 5(1):1-6 1978

The Ames' mutagenicity assay, modified to assess the mutagenicity of gases and vapors, was used to assess the mutagenic potential of vinylidene chloride (VDC) when incubated with a fortified mammalian kidney or liver tissue postmitochondrial supernatant (S-9 mix) from various species. Seeded dishes of *Salmonella typhimurium* strain TA100 or TA1535 were exposed to an atmosphere of 5% VDC in air for 72 hr. TA100 and TA1535 gave similar results. VDC was strongly mutagenic when mediated by mouse kidney (23-fold increase in mutation frequency) and liver (18-fold increase) S-9 mix from Aroclor 1254 induced animals. VDC was weakly mutagenic when mediated by S-9 mix from uninduced mouse kidney (2.3-fold increase) and liver (1.6-fold increase). VDC was weakly positive (5-fold) when mediated by liver S-9 mix from similarly induced rats, but it was not mutagenic (less than or equal to 1.2-fold) when mediated by kidney or liver S-9 mix from noninduced rats. VDC showed weak mutagenicity (3-fold) when tested in a system mediated by liver S-9 mix from a human who had received long-term phenobarbital medication, but it was not mutagenic when mediated liver S-9 mix from noninduced marmosets or a noninduced human. Thus, the mutagenic potential of VDC depends considerably on the degree of activation of relevant drug-metabolizing enzymes. The results agree with the greater availability in treated mice than in rats of the reactive VDC metabolites 1,1-dichloroethylene oxide and chloroacetyl chloride and with the VDC carcinogenicity found in mice but not in rats. The data suggest that the limited number of primates examined respond more like rats than mice with regard to generation of alkylating metabolites and their reaction with bacterial DNA. (10 Refs)

132. MUTAGENICITY OF VOLATILE ANESTHETICS (MEETING ABSTRACT).

Baden J, Wharton R, Hitt B, Brinkenhoff M, Simmon V, Mazze R
Stanford University and Va Hospital, Palo Alto, Ca 94304
and Stanford Research Institute, Menlo Park, Ca 94025
Fed Proc; 35(3):410 1976

Surveys of operating room personnel suggest that inhalational anesthetic agents may be carcinogenic. Therefore, an in vitro microbial system was used to test the mutagenicity of these compounds. Halothane was tested first because it is the most commonly used volatile anesthetic and because its metabolism proceeds through highly reactive intermediates. Two histidines requiring mutants of *S typhimurium* (developed by B Ames) TA 98 and TA 100, were used. Halothane in concentrations ranging from 0.1% to 30%, was incubated with bacteria in the presence or absence of NADP, glucose-6-phosphate, and hepatic post mitochondrial supernatant prepared from rats treated with Aroclor 1254.

After incubation for 1 hour at 37 degrees C, the reaction mixtures were overlayed onto glucose minimal media. The plates were incubated for 48 hours at 37 degrees C and revertant colonies counted. Vinylidene chloride and 4-aminobiphenyl were positive controls for TA 100 and TA 98, respectively. Trifluoroacetic acid, the major metabolite of halothane, and urine from patients anesthetized with halothane were also tested in this system. Halothane, trifluoroacetic acid, and patients' urine were not mutagenic. However, preliminary studies suggest that trichloroethylene, an industrial solvent and anesthetic agent, is mutagenic. (Author Abstract)

133. ACTIVATION MECHANISMS IN CHLORINATED ALIPHATIC COMPOUNDS. EXPERIMENTAL POSSIBILITIES AND CLINICAL SIGNIFICANCE.

Henschler D
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Arzneim Forsch; 27(9b):1827-1832 1977

Asymmetric chlorinated ethylene (tri-1,1-dichloroethylene and vinyl chloride) are mutagenic in a modified Ames test system whereas symmetrically substituted molecules are inactive. These differences are attributed to the electron withdrawal effect of chlorine in the asymmetric molecules. The in vivo and in vitro rearrangement mechanisms in the biotransformation of these compounds are outlined. (20 Refs)

134. MUTAGENICITY OF INDUSTRIAL COMPOUNDS EVALUATED BY MEANS OF YEAST GENETIC SYSTEMS (MEETING ABSTRACT).

Fumero S, Mondino A
Istituto di Ricerche Biomediche 'A Marxer', Ivrea, Italy
Mutat Res; 53(2):189 1978

There are many chemical compounds of wide use in the chemical industry (solvents, halogenated hydrocarbons, aromatic polycyclic hydrocarbons, monomers employed in the resin and plastic industry) which have been shown to produce different genetic effects (reverse and forward mutations, gene-conversions and mitotic recombinations) on yeasts (*Saccaromyces cervisiae* and *S pombe*). The use of yeasts, moreover, in the mutagenic analyses of such a class of compounds has resulted in the study of the 'in vitro' and 'in vivo' metabolic conversion of the original compounds tested. We will present data related to the mutagenic analyses of some other chemicals (trichloroethylene and its epoxidic metabolite, epichlorohydrine) in comparison with known chemical carcinogen: 'in vivo' studies with host-mediated assay have provided data of extreme interest in the evaluation of the mutagenic activity of these compounds for a prediction of their possible cancerogenic activity. (no Refs)

135. MUTAGENIC ACTIVITY OF CHEMICALS IDENTIFIED IN DRINKING WATER (MEETING ABSTRACT).

Simmon VF, Kauhanen K, Mortelmans K, Tardiff R
Stanford Res. Inst., Menlo Park, CA
Mutat Res; 53(2):262 1978

Approx 300 chemicals have been identified in finished drinking water in the US. Some of these chemicals are known to be carcinogens in rodents (eg, aldrin, carbon tetrachloride) and/or humans (benzopyrene). We have begun to analyze these chemicals for their mutagenic activity in micro-organisms. Of 128 chemicals that we have tested, 21 were mutagenic in preliminary spot tests on *Salmonella typhimurium* TA100 (without metabolic activation). We have obtained dose-dependent mutagenic responses with 19 of these compounds (benzopyrene, bromochloromethane,

bromodichloromethane, bromoform, bromomethane, n-butyl bromide, sec-butyl bromide, tert-butyl bromide, technical grade chlordane, chlorodibromomethane, bis(2-chloroethyl) ether, dibromomethane, 1,2-dichloroethane, 1,1-dichloroethylene, hexachloro-1,3-butadiene, iodomethane, methyl chloride, methylene chloride and vinyl chloride) in strains of *S. typhimurium*. Additional mutagenicity assays using *Escherichia coli* WP2 and *Saccharomyces cerevisiae* D3 are underway. (no Refs)

136. THE MUTAGENIC ACTIVITY OF HALOGENATED COMPOUNDS FOUND IN CHLORINATED DRINKING WATER.

Simmon VF, Tardiff RG
Microbial Genetics Program, Stanford Res. Inst.
International, Menlo Park, CA, 94025
Water Chlorination; 2:417-431 1978

The mutagenic activities of 22 halogenated compounds found in chlorinated drinking water were determined using the Ames Salmonella/microsome procedure with *S. typhimurium* strains TA1535 and TA100. Two known carcinogens, carbon tetrachloride and chloroform, were not mutagenic in this system, probably because mutagenic metabolites were formed in insufficient amounts or they were so unstable that they did not survive long enough to penetrate the bacteria and interact with the DNA. Known carcinogens that were mutagenic were vinyl chloride, vinylidene chloride, 1,2-dichloroethane, 1,1,2-trichloroethylene, bis-(2-chloroethyl) ether, methyl iodide, and bromoform. Mutagenic activity was also observed with bromodichloromethane, chlorodibromomethane, methylene bromide, bromochloromethane, methylene chloride, methyl bromide, methyl chloride, 2-chloropropane, 1-chloropropene, bis(2-chloroisopropyl) ether, n-butyl bromide, t-butyl bromide, and s-butyl bromide. The results indicate that the number and amount of alkyl halides in potable water should be reduced to lessen possible health hazards. (20 Refs)

137. THE MUTAGENICITY AND DNA-MODIFYING EFFECT OF HALOALKANES.

Brem H, Stein AB, Rosenkranz HS
Coll. Phys. Surg., Columbia U., New York, N. Y.
Cancer Res; 34:2576-2579 1974

A series of haloalkanes were tested for their ability to inhibit the growth of normal (pol A+) and DNA polymerase I-deficient (pol A1-) *Escherichia coli*. These compounds were also tested for the mutagenic effects on *Salmonella typhimurium*. All of the haloalkanes examined preferentially inhibited the growth of the pol A1- strain of *E. coli*. The bromoalkanes appeared to be more active than their chloro analogs (e.g. 1,2-dibromoethane (1,2-DBE) was more active than 1,2-dichloroethane (1,2-DCE) and tetrabromoethane was more active than tetrachloroethane). The mixed haloethane 1-bromo-2-chloroethane had an activity intermediate to those of 1,2-DBE and 1,2-DCE. When the bromine was on the same carbon, the biological activity was enhanced (1,1-DBE was more active than 1,2-DBE), although when the halogens were on different carbon atoms, the distance between them had no effect on the activity. All of the haloalkanes tested, with the exception of 1,1,2,2-tetrabromoethane, were mutagenic for *S. typhimurium* TA 1530 and TA 1535. The number of mutations was related to the amount of reagent added, the rate of

diffusion, and the size of the zone of growth inhibition. None of the substances tested induced mutations in *S. typhimurium* TA 1538. Since many of the compounds tested are widely used in industry and in the home, further determination of their potential hazard to health is indicated.

138. TISSUE MEDIATED MUTAGENICITY AND CARCINOGENESIS (MEETING ABSTRACT). (PP. 73)

Bartsch H
International Agency for Research on Cancer, Unit of
Chemical Carcinogenesis, 150 cours Albert Thomas,
69008 Lyon, France.
Third International Symposium On Detection And
Prevention Of Cancer. 1976.

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

139. THE PREDICTIVE VALUE OF TISSUE-MEDIATED MUTAGENICITY ASSAYS TO ASSESS THE CARCINOGENIC RISK OF CHEMICALS. (PP. 467-491)

Bartsch H, Malaveille C, Montesano R

Screening Tests in Chemical Carcinogenesis Proceedings of a workshop organized by IARC and the Commission of the European Communities and held in Brussels, Belgium, 9-12 June 1975. Montesano R, Bartsch H, Tomatis L, Davis W, ed., International Agency for Research on Cancer. (Lyon, France); IARC Scientific Publications No. 12, 1975.

The Salmonella microsome system was used to assess the in vitro Salmonella mutagenicity assay for predicting possible carcinogenic effects of chemicals, to compare the capacity of different tissues and different species to convert chemical substances into mutagens, and, in particular, to investigate the metabolic activation of nitrosamines and chlorinated olefinic hydrocarbons. The mutagenicity of a series of cyclic nitrosamines in *S. typhimurium* strain TA 1530 was similar in liquid suspension and in soft agar, but discrepancies arose when a series of dialkyl nitrosamines of the form $(C_nH_{2n+1})_2N-NO$ with different chain lengths were considered. The dialkyl nitrosamines with $n = 3$ did not show an enzyme-mediated response in the liquid incubation system, and in the soft agar metabolically activated dimethylnitrosamine and diethylnitrosamine exhibited negligible mutagenic activity. These findings reflect false negatives from both systems, perhaps brought about by the deterioration of microsomal enzymes by lipid peroxidation in the liquid system and by the trapping of short-lived alkylating molecular species by nucleophilic components of the agar. When the mutagenicity of a series of propylated nitrosamine derivatives was studied with microsomes from hamster and rat tissues, there was not a good correlation between tissue-specific activation to mutagenic intermediates and the known susceptibility of different tissues to carcinogenesis. A better correlation was seen when the activation to mutagenic metabolites of vinyl chloride by microsomes derived from rat and mouse liver, kidney, and lung tissues was studied. The major enzymic activities were located in both liver and kidney, sites where angiosarcoma and nephroblastoma are induced in animals exposed to vinyl chloride. No tissues studied exhibited a higher enzymic capacity than the liver to bring about the production of mutagenic metabolites. Microsomes from human livers were capable of generating mutagenic metabolites from *N*-nitrosomorpholine and vinyl chloride. Some aspects of the metabolism of chlorinated olefinic hydrocarbons are discussed further. (56 refs)

140. METABOLIC ACTIVATION OF CHLORINATED ETHYLENES: DEPENDENCE OF MUTAGENIC EFFECT ON ELECTROPHILIC REACTIVITY OF THE METABOLICALLY FORMED EPOXIDES.

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Arch Toxicol (Berl); 39(1/2):7-12 1977

Investigations of the chemical reactivity, biotransformation, and toxicity of the chloroethylenes are reviewed. In chlorinated ethylenes, the chlorine substitution exerts, by its electron-withdrawal effect, a stabilization of the molecule that increases with the number of chlorine residues. Epoxides are short-lived metabolic intermediates that rearrange to give two possible products: acylchlorides (as with tetra-, tri-, and 1,1-dichloroethylenes) or aldehydes (1,2-cis- and 1,2-trans-dichloroethylenes and vinyl chloride). The aldehydes subsequently undergo reduction and oxidation to alcohols and acids, respectively. The chlorinated ethylenes

were tested for mutagenic potential in a modified Ames system, and three members of the group were active: vinyl chloride, vinylidene chloride, and trichloroethylene. The molecular feature common to the active molecules is an asymmetric chlorine substitution, but in the inactive compounds there is a symmetric distribution of the chlorine residues. It is hypothesized that the increased electrophilicity caused by the asymmetrical chlorine substitution offers an enhanced chance for alkylating reactions of the epoxides, which overpower the deactivation mechanisms of conjugation, rearrangement, and hydrolysis. The three mutagenic chloroethylenes have also produced carcinogenic effects in animals.

141. MUTAGENICITY OF HALOGENATED ALKANES AND THEIR DERIVATIVES.

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NY, 10595

Environ Health Perspect; 21:79-84 1977

The DNA-modifying activity and mutagenicity of some haloalkanes, haloethanols, and 2-haloacetaldehydes were investigated. DNA-modifying activity was determined by comparing ratios of the areas of zones of inhibition around platings of DNA-polymerase-deficient (*polA*-) and non-deficient (*polA*+) *Escherichia coli* strains. Mutagenicity was assayed by counting revertants of *Salmonella typhimurium* strains from histidine-dependent to histidine-independent growth. Most active haloalkanes in the *E. coli* assay were tetrabromoethane and 1,1-dibromoethane; least active was 1,2-dichloroethane. All the haloalkanes were mutagenic (base substitutions) for *S. typhimurium* strains TA 1530 and TA 1535, but none for TA 1538. The greatest mutagenic activity was achieved with 1,2-dibromoethane and 1,5-dibromopentane. The order of reactivities of the haloalkanes differed in the two tests. Of the haloethanols tested, 2-iodoethanol had the most DNA-modifying activity, 2-bromoethanol was the most mutagenic, and ethanol and 2-fluoroethanol were without either activity. 2-Chloroacetaldehyde was somewhat mutagenic for strain TA 1535, but 2-bromoacetaldehyde was not mutagenic at all. Both compounds had some DNA-modifying activity. The chemical basis of the mutagenic action of these compounds is discussed. (37 Refs)

142. GENETIC AND TOXICOLOGICAL EFFECTS OF ALPHA-BENZENE HEXACHLORIDE, DIBUTYL PHTHALATE AND TRICHLOROETHYLENE ON SACCHAROMYCES CEREVISIAE STRAIN XV185-14C FOR REVERSION STUDIES (MEETING ABSTRACT).

Shahin MM, Von Borstel RC

Dept. Genetics, Univ. Alberta, Edmonton, Alberta,
Canada T6G 2E9

Mutat Res; 53(1):84-85 1978

Saccharomyces cerevisiae strain XV185-14C for reversion studies was used to investigate the genetic activity of alpha-benzene hexachloride, dibutyl phthalate and trichloroethylene. The data indicate that none of the three compounds tested was genetically active when yeast cells were tested in phosphate buffer (pH 7.0) in the absence of a metabolic conversion system. This was observed at different concentrations of the compounds used, and at various survival levels. On the other hand, AF-2 (furylfuramide) and EMS (ethyl methanesulfonate) which were used as positive controls exhibited mutagenic activity as expected. The results of the experiments with XV185-14C and mice liver microsomal fraction and all needed components for metabolic conversion did not alter the non-mutagenic response of alpha-benzene hexachloride or dibutyl phthalate. However, there is a mutagenic effect after treatment with trichloroethylene. Trichloroethylene appears to induce frameshift as well as base

substitution mutations. Trichloroethylene is far more lethal to yeast cells than alpha-benzene hexachloride or dibutyl phthalate.

143. CHARACTERIZATION OF S-9 ACTIVATION OF DBCP IN THE SALMONELLA TEST SYSTEM (MEETING ABSTRACT).

Biles R, Connor T, Trieff N, Legator M
Univ. Texas Medical Branch, Galveston, TX, 77550
Pharmacologist; 20(3):155 1978

1,2-Dibromo-3-chloropropane (DBCP) has little direct mutagenicity in the Salmonella test system. However, pure DBCP is quite mutagenic when activated to the ultimate mutagen using S-9 preparations from Aroclor pre-treated rats. We utilized such S-9 and S typhimurium TA1535 to characterize the responsible mutagenic activation components. S-9 was purified by centrifugation (10,000 and 105,000 x gravity) to obtain the pure microsomal preparation. The concentrations of DBCP tested ranged 10-500 ug/plate and produced dose-response mutagenicity. Standard S-9 preparations were found to be heat labile and require NADPH generating systems for mutagenicity. With fractionated S-9, the microsomal fraction alone was responsible for mutagenic activity while the supernatant did not activate DBCP. The microsomes produced greater mutagenic activity at lower doses than the parent S-9. When microsomes and supernatant were recombined, mutagenicity was identical to the parent S-9. The mutagenic activity was reduced as glutathione was added in increasing amounts to both the parent S-9 and pure microsomes. Thus, glutathione inactivates rather than activates DBCP, which is contrary to recent findings for activation of ethylene dibromide and 1,2-dichloroethane. (no Refs)

144. THE INFLUENCE OF CONTAMINANTS ON THE MUTAGENIC ACTIVITY OF DIBROMOCHLOROPROPANE (DBCP).

Biles RW, Connor TH, Trieff NM, Legator MS
Div. Environmental Toxicology, Dept. Preventive Medicine
and Community Health, Univ. Texas Medical Branch,
Galveston, TX, 77550
J Environ Pathol Toxicol; 2(2):301-312 1978

The causative agent(s) and mechanism of mutagenic activity of technical grade (TG) 1,2-dibromo-3-chloropropane (DBCP) were investigated in the Ames mutagenesis test using Salmonella typhimurium TA1535. Without metabolite activation, TG DBCP was weakly mutagenic in the concentration range 50-1,000 ug/plate, whereas pure DBPC showed little or no mutagenicity in the same concentration range. Purification of the TG compound by distillation resulted in a first distillate with more than two-fold greater mutagenicity than the TG compound and a second distillate with mutagenicity similar to that of the TG compound. The first distillate was found to contain epichlorohydrin (ECH), which was present in the TG compound in an amount close to 1.5% by wt, as well as an unidentified compound. The second distillate contained smaller amounts of both compounds. The amount of ECH in the TG sample was calculated for each dose level tested, and the number of revertants obtained in tests of this sample could be attributed solely to the calculated amount of ECH in each test dose. Both TG and pure DBCP were strongly mutagenic in the concentration range 20-200 ug/plate after S-9 metabolic activation. Results similar to those of the Ames test were obtained using a desiccator technique. The data indicate that in the direct in vitro evaluation, the mutagenicity of DBCP can be attributed almost entirely to the addition of the stabilizer ECH. (22 Refs)

145. MUTAGENICITY OF PESTICIDES CONTAINING 1,3-DICHLOROPROPENE.

De Lorenzo F, Degl'Innocenti S, Ruocco A, Silengo L, Cortese R
I and II Cattedra di Chimica Biologica, Univ. Naples, Via Sergio Pansini 5, 80131 Naples, Italy
Cancer Res; 37(6):1915-1917 1977

The widely used pesticides Telone and D.D. soil fumigant were tested for mutagenicity in Salmonella typhimurium strains TA1978, TA1535, TA100, TA1537, and TA98. D.D. soil fumigant is composed of 40% 1,3-dichloropropene, 40% 1,2-dichloropropane, and 20% other unknown chemicals. Telone is composed of 30% cis-1,3-dichloropropene, 30% trans-1,3-dichloropropene, 20% 1,2-dichloropropane, 5% 2,3-dichloro-1-propene, 2% allyl chloride, and about 15% unknown chemicals. Both pesticides were mutagenic in strains TA100 and TA1535 in the presence and absence of a rat liver activating system; both pesticides were mutagenic in strain TA1978 only in the presence of such a system. The cis and trans isomers of 1,3-dichloropropene were strongly mutagenic in strains TA1535 and TA100, which are sensitive to base-pair substitutions, and only weakly mutagenic in strain TA1978. 2,3-Dichloro-1-propene showed similar behavior. 1,2-Dichloropropane was mutagenic in strains TA1535 and TA100 but only at concentrations 500 times higher than those of dichloropropene. The mutagenic properties of the purified components do not fully account for the mutagenicity of the commercial preparations; the difference might be due to the presence of unknown components. (12 Refs)

D. Teratogenicity of Vinyl Chloride and Related Compounds in Experimental Animals

The reader may also find the following abstract of interest: 79

146. STUDY OF THE TERATOGENIC AND EMBRYOTOXIC EFFECT OF VINYL CHLORIDE IN CFY RATS.

Ungvary GY, Hudak A, Tatrai E, Lorincz M, Folly G
Orszagos Munka- es Uzemegeszsegstan Intezet, Budapest, Hungary
Egeszsegstudomany; 21(4):363-369 1977

Inhalation of vinyl chloride (4,000 mg/m³) between the 8th and 14th days of pregnancy increased the absolute and relative wt of the liver of pregnant CFY rats significantly, but there was no significant increase in resorption, embryonal mortality, and developmental anomalies. In addition, vinyl chloride was found in the maternal and fetal blood and amniotic fluid following exposure of the mothers to 5,500-33,000 mg/m³ vinyl chloride for 2.5 hr on the 18th day of pregnancy. (31 Refs)

147. A TERATOLOGIC EVALUATION OF PLASMA-SOLUBLE EXTRACTS OF POLYVINYL CHLORIDE PLASTICS IN RATS (MEETING ABSTRACT).

Chen TS, Fernandes J, Lewandowski M
Travenol Laboratories, Inc., Morton Grove, IL, 60053
Fed Proc; 38(3,part1):438 1979

Plasma extracts of two polyvinyl chloride plastics (designated PL-130 and PL-146) containing diethylhexyl phthalate (DEHP) as a plasticizer and used in the manufacture of parenteral fluid storage bags were administered iv to pregnant rats daily from the 6th through 15th day of gestation. Two groups of rats received PL-130 extracts in doses equivalent to 1.3 and 4.7 mg DEHP/kg per day, and two

groups received PL-146 extracts in doses equivalent to 1.4 and 5.3 mg DEHP/kg per day. The higher doses are similar to that predicted for a 60-kg man receiving an exchange transfusion of 21-day-old blood. A control group of rats received the plasma vehicle only. No differences were seen in growth rates or behavior between control and treated groups. There were no significant effects of fetal wt, crown-rump, and transumbilical distances. The numbers of live and resorbed fetuses were not significantly different in control and treated groups. The incidence of gross external, skeletal, and visceral defects was similar in all groups and was not statistically different between control and treated groups. It is concluded that plasma extracts of PL-130 and PL-146 were not teratogenic when administered iv to pregnant rats during the critical period of organogenesis. (no Refs)

148. EFFECTS OF VINYL CHLORIDE EXPOSURE ALONE AND IN COMBINATION WITH TRYPAN BLUE - APPLIED SYSTEMATICALLY DURING ALL THIRDS OF PREGNANCY - ON THE FETUSES OF CFY RATS.

Ungvary G, Hudak A, Tatrai E, Lorincz M, Folly G
Dept. Experimental Pathology, State Inst. Occupational Health Budapest, H-1450 Budapest P.O.B. 22, Hungary
Toxicol Appl Pharmacol; 11(1):45-54 1978

The teratogenic and embryotoxic effects of vinyl chloride and/or trypan blue were investigated in CFY rats. VC was found in the fetal and maternal blood as well as in the amniotic fluid of pregnant CFY rats exposed to an atmospheric concentration of 5,500, 18,000, or 33,000 mg/m³ VC for 2.5 hr on gestation day 18, indicating the permeability of the placenta to the agent. Investigation of the offspring of pregnant rats exposed continuously to 4,000 mg/m³ VC during the first, second, or last trimester showed that VC has no teratological or embryotoxic effects when applied during the second or last trimester. However, exposure to VC during the first trimester resulted in an increased fetal mortality and in the manifestation of embryotoxic effects. Fetal losses and the induction of CNS malformations due to trypan blue (50 mg/kg sc on gestation days 7 and 8) were not potentiated by 4,000 mg/m³ VC. Occupational exposure of women of childbearing age may be hazardous. (34 Refs)

149. INHALATION STUDIES TO EVALUATE THE TERATOGENIC AND EMBRYOTOXIC POTENTIAL OF BETA-CHLOROPRENE (2-CHLOROBUTADIENE-1,3).

Culik R, Kelly DP, Clary JJ
Haskell Lab. Toxicology and Industrial Medicine, E.I. du Pont de Nemours and Co., Inc., Wilmington, DE, 19898
Toxicol Appl Pharmacol; 44(1):81-88 1978

Inhalation studies were performed to evaluate the teratogenic and embryotoxic potential of beta-chloroprene (2-chlorobutadiene-1,3) (BC). Soviet Union researchers recently reported that BC, used in large quantities to manufacture neoprene rubber, was embryotoxic, teratogenic, and mutagenic at atmospheric concentrations below the existing Soviet maximum allowable concentration of 1 ppm. Two studies were carried out on pregnant rats. Both experimental groups were exposed by inhalation to 0, 1, 10, and 25 ppm of beta-chloroprene for 4 hr daily. Fifty rats per group (in the first study) were exposed on days 1 through 12 and sacrificed on day 17. The purpose of this study was to evaluate the embryotoxic potential of BC. In the second teratology study, 25 rats per group were exposed on days 3 through 20 and sacrificed on day 21 of gestation. In a reproduction study, male rats were exposed to 25 ppm of BC (4 hr daily for 22 days) and bred with untreated virgin females. In the female groups, no maternal, embryonal, or fetal toxicity was observed and the reproductive capability of males was not impaired.

These results indicate that 25 ppm of BC, the present threshold limit value, is not embryotoxic or teratogenic and does not impair reproductive capability of male rats. These results are at variance with previous findings of studies conducted in the Soviet Union. (16 Refs)

150. INHALATION OF ETHYLENE DIBROMIDE DURING GESTATION BY RATS AND MICE.

Short RD, Minor JL, Winston JM, Seifter J, Lee CC
Dept. Pharmacology and Toxicology, Midwest Res. Inst., Kansas City, MO, 64110
Toxicol Appl Pharmacol; 46(1):173-181 1978

The teratogenic potential of ethylene dibromide (EDB) was evaluated in rats and mice. Charles River CD rats and CD-1 mice were housed in chambers containing 20, 38, or 80 ppm EDB for 10 days, beginning on day 6 of gestation. Animals were sacrificed on day 18 or 20 of gestation, and fetuses were examined for anomalies. Rats exposed to 38 and 80 ppm EDB suffered wt loss, but deaths, reduced number of implants, and evidence of embryotoxicity were seen only in those exposed to 80 ppm. The incidence of fetal soft-tissue anomalies found in treated rats did not differ significantly from that of controls; however, the percentage of fetuses with normally ossified centra was significantly lower in the group exposed to 20 ppm EDB than in controls. Deaths occurred in mice exposed to 38 and 80 ppm, and in those exposed to 20 ppm, there was an increase in the percentage of late resorptions and a decrease in fetal body wt. Exencephaly was seen in fetuses of mice exposed to 20 ppm, and the incidence of some skeletal anomalies was significantly greater in fetuses of EDB-exposed mice. These fetal morphological changes, however, occurred at concentrations that also affected maternal welfare. Consequently, EDB was judged to have little primary effect on development. (10 Refs)

E. Transforming Activity of Vinyl Chloride and Related Compounds in Animal Cell Cultures

151. VINYL CHLORIDE EXPOSURE INDUCED LYMPHOCYTE TRANSFORMATION IN SPLENIC CULTURES (MEETING ABSTRACT).

Sharma RP, Gehring PJ
Utah State Univ., Logan, UT, 84322
Fed Proc; 37(3):502 1978

Vinyl chloride (VC) disease has been suggested as an immune complex disorder. The influence of VC exposure on selected immunologic parameters of mice and rabbits was studied. In male mice, inhalation of VC (10,000 and 1,000 ppm for 6 hr/day, 5 days/wk) for up to 8 wk caused no toxic effects, as indicated by body wt gain, clinical hematology, or organ wt, with the exception of an increase in spleen wt at the highest exposure level. After 2 wk of exposure to 1,000 ppm and after 4 and 8 wk to all levels, cultured splenic lymphocytes showed an increase in DNA synthesis (as measured by H³-thymidine uptake by cells in culture). The response of splenic lymphocytes to phytohemagglutinin (phytohemagglutinin and pokeweed mitogen) at the above levels of VC exposure was increased severalfold. In rabbits, exposure to 1,000 ppm VC caused a slight but inconsistent rise in serum immunoglobulin levels. Rabbits immunized with tetanus toxoid and Freund's adjuvant revealed no VC-related changes in serum antitetanus titers, skin reactivity to tuberculin, or the number of plasma cells in popliteal lymph nodes. There was no increase in immunization induced lymphocyte transformation in either mice or rabbits. The results indicated an increase of lymphocyte

transformation in splenic cultures that may be related to the immune complexes observed in VC syndrome.

152. MALIGNANT TRANSFORMATION OF A BABY HAMSTER LUNG CELL LINE BY 2-CHLOROBUTADIENE (MEETING ABSTRACT). (PP. 78)

Papadopoulos D, Markovits P, Beesau O, Hubert-Habart M

Fondation Curie-Institut du Radium, 26 rue d'Ulm, 75005-Paris, France

Fourth Meeting of the European Association for Cancer Research Held at Université de Lyon, September 13-15, 1977. European Association for Cancer Research, Lyon, France 1977.

From trypsin-dispersed baby hamster lung tissue, a control hamster lung cell line was established, which remained very stable and non-transplantable during a long period of time in vitro. Semiconfluent cell cultures of this line were exposed to either 1, 10, or 100 microg/ml for 6 consecutive wk, or, to either 500 or 1000 microg/ml for two days, of 2-chlorobutadiene (CB). Three and one-half mo after the start of the treatment, morphologically altered spindle-shaped cells appeared in all the treated cultures. While these cells were dominant in the CB 1 microg/ml treated cultures, only infrequent groups of them were observed in the cultures treated previously with higher concentrations of CB. Cultures treated with 1 microg/ml of CB caused tumors in all hamsters grafted 3.5 mo after starting treatment. Cells treated with higher concentrations of CB provoked tumors only 8 mo after the starting of treatment. Histologically, the tumors were fibrosarcomas and the ones caused by cells treated with 1 and 10 microg/ml were highly malignant. It seems that 1 microg/ml of CB is an optimal concentration for malignant transformation. This work is the first experimental demonstration of the malignant transforming capacity of 2-chlorobutadiene, which was shown previously to be mutagenic. Experiments are underway to confirm these preliminary results. (no Refs)

153. IN VITRO MALIGNANT TRANSFORMATION OF CELLS OF WHOLE EMBRYOS, FETAL BRAIN, AND NEWBORN LUNG OF HAMSTER (MEETING ABSTRACT).

Levy S, Markovits P, Beesau O, Benda P

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J Microsc (Paris); 27(1): 17a 1976

Chemical carcinogens were used to transform cultured cells from the whole embryo, fetal brain, and newborn lung of hamsters. Cells from the whole embryo were exposed to polycyclic hydrocarbons and heterocyclic mitogen-containing compounds for 24-48 hr. After 2 mo growth, the cells lost contact inhibition and their growth rate increased. The ability to produce sarcomas after an sc graft in syngeneic hamsters did not appear until 5 mo after treatment. Lung cells exposed to 7,12-benzo(a)anthracene under the same culture conditions underwent malignant transformation more slowly. Intraocular grafts proved more likely to produce tumors than sc grafts. When lung cells were exposed to repeated doses of chlorobutadiene (3 doses every 14 days) over a 16-mo culture period, transformation took place in 3.5 mo. Fetal brain cells exposed to nitrosomethylurea underwent transformation in 4 mo. Glial cell tumors occurred after intraocular or intracerebral grafts of the transformed cells. It is believed that malignant transformation of lung and nerve cells by chemical carcinogens occurred for the first time in these experiments. (0 Refs)

154. TRANSFORMING ACTIVITIES OF TRICHLOROETHYLENE AND PROPOSED INDUSTRIAL ALTERNATIVES.

Price PJ, Hassett CM, Mansfield JI

Microbiological Associates, Torrey Pines Res. Center, 2945 Science Park Road, La Jolla, CA, 92037

In Vitro; 14(3):290-293 1978

The carcinogenicity of trichloroethylene (TCE) and three industrial substitutes, 1,1,1-trichloroethane, tetrachloroethylene, and methylene chloride, was tested in vitro using the F1706 Fischer rat embryo cell system. All compounds induced transformation in the rat cells. Toxicity studies indicated that TCE was the least toxic of the four compounds by a factor of at least 100. Sc injection of transformed cells into newborn Fischer rats resulted in undifferentiated fibrosarcomas at the injection site in 100% of the animals in 27-68 days. (4 Refs)

155. HAMSTER CELLS, UNTREATED AND TREATED WITH CHEMICAL CARCINOGENS, MAINTAINED IN VITRO FOR 2 1/2 YEARS.

Papadopoulos D, Levy S, Chamaillard L, Beesau O,

Hubert-Habart M, Markovits P

Fondation Curie-Institut du Radium, Section de Biologie, 26 rue d'Ulm, 75005 Paris, France

Br J Cancer; 36(1):65-71 1977

The properties of untreated hamster whole embryo, fetal brain, and neonate lung cells maintained in culture for 1-2.5 yr were compared with those of cells transformed by the following chemical carcinogens: 7,10-dimethylbenzo(c)acridine, benzo(a)pyrene, 7,12-dimethylbenzo(a)anthracene, 7-methylbenzo(a)anthracene, 3-methylcholanthrene, and 2-chlorobutadiene. Among the seven untreated lines studied, only one spontaneous transformation was observed during the first year of culture. The cells of the six other lines remained normal and diploid and were not transplantable during the first 9 to 12 mo of culture. After 12 mo, changes appeared in their in vitro behavior and their transplantability: grafts of 0.5×10^5 cells induced tumors in the hamster; fewer cells did not. In vitro chemically transformed hamster cells were fundamentally different from untreated cells of the same origin, not only in morphological and growth characteristics but also in transplantability. Of the nine lines obtained, seven induced tumors after injection of 10^4 - 10^5 cells and two after injection of 10^5 cells per animal. (15 Refs)

156. MICROSOME-MEDIATED MUTAGENESIS OF A CHINESE HAMSTER CELL LINE BY VARIOUS CHEMICALS (MEETING ABSTRACT).

Drevon C, Kuroki T, Montesano R

International Agency for Res. on Cancer, 150 cours Albert Thomas, 69008, Lyon, France

Mutat Res; 53(2):181-182 1978

A microsome-mediated mutagenesis system for mammalian cells has been established using V79 cells, a Chinese hamster cell line. The cells, grown in monolayer, were treated with the chemicals to be tested in the presence of a post-mitochondrial fraction (S15) and cofactors for 1 hr or more (depending on the chemicals), washed and incubated for 2-3 hr on fresh culture medium, and then the cells were plated for toxicity and mutagenicity assays. Mutation was determined by resistance to 20 ug/ml 8-azaguanine or 1 milliM ouabain. In our assay system, S15 and cofactors were not found to be toxic to the cells. The chemicals tested included 12 nitrosamines, 3 chlorinated hydrocarbons, several polycyclic hydrocarbons and aflatoxin B1. Dose-related mutation and cytotoxicity were induced after incubation with dimethylnitrosamine (DMN) only in the presence of both the S15 fraction of the livers of

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

F. Carcinogenicity of Vinyl Chloride and Related Compounds in Experimental Animals

The reader may also find the following abstracts of interest: 153, 326

157. ONCOGENIC RESPONSE OF RAT SKIN, LUNGS, AND BONES TO VINYL CHLORIDE.

Viola PL, Bigotti A, Caputo A
Regina Elena Inst. Cancer Res., Rome, Italy
Cancer Res; 31(5):516-522 1971

Male rats were exposed to vinyl chloride vapors for 4 hr per day, 5 days per wk for 12 months; the vinyl chloride was diffused into the air of the containers which held the rats in amounts of 3% vinyl chloride v/v (30,000 ppm). Almost all the rats developed tumors of the skin and lungs. Among 17 rats surviving the 12 month course, all had skin tumors and 6 had lung tumors; 5 of the 17 had bone tumors. Most skin tumors were epidermoid carcinomas; there were 2 mucoepidermoid carcinomas and 2 epidermoid carcinomas of the keratinizing type. Among lung tumors, there were 3 adenocarcinomas, a squamous cell carcinoma and an adenocanthoma. Bone tumors were localized in the metacarpal and metatarsal bones of all 4 extremities; all were osteochondromas. Skin tumors were localized in the area of the submaxillary and parotid glands.

158. VINYL CHLORIDE CARCINOGENICITY: AN EXPERIMENTAL MODEL FOR CARCINOGENESIS STUDIES. (PP. 119-146)

Maltoni C
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Incidence of Cancer in Humans, Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation. Vol. 4, Hiatt HH, Watson JD, Winsten JA, ed. Cold Spring Harbor, Cold Spring Harbor Laboratory, Origins of Human Cancer., 602 pp., 1977.

The carcinogenicity of vinyl chloride (VC) was evaluated in Sprague-Dawley rats, Wistar rats, Swiss mice, and golden hamsters. In inhalation studies, 50-30,000 ppm VC produced Zymbal gland carcinomas, nephroblastomas, hepatic angiosarcomas (HAS) and angiosarcomas of other sites, sc

angiomas, skin carcinomas, hepatomas, brain neuroblastomas, and mammary carcinomas in adult Sprague-Dawley rats after 52-wk of exposure. Rats exposed to only 25 ppm VC for 87 wk developed HAS. Reducing the length of treatment sharply reduced the onset of several tumor types, particularly HAS: when rats were treated for 5 wk at 10,000 and 6,000 ppm, no HAS were observed. VC also had a transplacental effect: exposure of pregnant rats to 10,000 or 6,000 ppm VC on days 12-18 of pregnancy produced VC-dependent tumors in the offspring. Newborn rats were also more susceptible to VC carcinogenesis than older ones. Exposure of Wistar rats to varying VC concentrations for 52 wk resulted in basically the same tumors as those produced in Sprague-Dawley rats. Exposure of Swiss mice to 50-10,000 ppm VC for 30 wk resulted in lung tumors, mammary carcinomas, HAS, vascular tumors of other types and/or sites, and epithelial tumors of the skin. In golden hamsters, the same VC concentrations resulted in HAS, skin trichoepitheliomas, melanomas, and forestomach epithelial tumors. In addition, the latency time of lymphomas was decreased from 82 wk (in controls) to 48 wk. Ingestion of 50, 16.65 or 3.33 mg/kg/day VC by Sprague-Dawley rats, 4-5 days/wk for 52 wk produced essentially the same spectrum of tumors as the inhalation studies. One nephroblastoma and one sc angiosarcoma were found among 240 Sprague-Dawley rats that had received one to four ip injections of 4.25 mg VC, and one nephroblastoma was found among 75 animals that had received the same dose sc. It is concluded that the neoplastic response to VC depends largely on the species and strain of animal and that age is also important with respect to tumor incidence and distribution. (5 Refs)

159. PULMONARY TUMORS INDUCED IN MICE BY VINYL CHLORIDE MONOMER.

Suzuki Y
Environmental Science Lab., Mount Sinai Sch. Medicine,
Fifth Ave. and 100th St., New York, NY, 10029
Environ Res; 16(1/3):285-301 1978

The incidence of lung tumors due to vinyl chloride (VC) inhalation was studied in 27 CD1 Charles River male mice and precancerous changes and the resulting tumor were characterized ultrastructurally. The mice were exposed to 2,500 or 6,000 ppm VC 5 hr/day, 5 days/wk, for 5 or 6 mo and then sacrificed 2, 6, or 37 days later. Pulmonary tumors were found in 26/27 mice but in none of the 16 controls. The tumors were round, whitish, multiple, and variable in size from 1 to 5 mm in diameter. The tumors were arranged in tubulopapillary or adenomatous formations. There were no metastases to regional lymph nodes or other organs, parenchymal fibrosis, or fibrotic adhesions of the pleura, although occasional mitotic divisions and invaginations into the bronchiolar lumen were noted. Under the electron microscope, the characteristic features of the neoplastic cells were short microvilli, tight junctions between two adjacent cells, osmiophilic lamellar bodies, large irregularly shaped mitochondria, well-developed Golgi complexes, continuous or discontinuous basement membranes, occasional appearance of sequestration and of crystalloids, and a lack of cilia and mucous secretory granules. Some of the cells were poorly differentiated and were equipped with poorly developed organoids, without the formation of osmiophilic lamellar bodies. The gross anatomical and histological aspects of the tumors indicated that they were alveologenic tumors. The neoplastic cells were assumed to have been transformed from type II alveolar epithelium via its hyperplastic form, because of the ultrastructural similarities between normal type II cells and the neoplastic cells. It is concluded that the mouse lung is a sensitive indicator of the oncogenicity of VC. (40 Refs)

160. INHALATION TOXICITY OF VINYL CHLORIDE AND VINYLIDENE CHLORIDE.

Lee CC, Bhandari JC, Winston JM, House WB, Peters PJ, Dixon RL, Woods JS
Pharmacology and Toxicology, Midwest Res. Inst., 425 Volker Blvd., Kansas City, MO, 64110
Environ Health Perspect; 21:25-32 1977

Experiments on the inhalation toxicity and carcinogenicity of vinyl chloride (VC) and vinylidene chloride (VDC) in mice and rats are reported. The exposure of mice to 1,000 ppm VC for 6 hr/day, 5 days/wk caused some acute deaths with toxic hepatitis and marked tubular necrosis of the renal cortex. During the sixth month, mice exposed to 1,000, 250, or 50 ppm VC became lethargic, lost weight quickly, and died; only a few mice exposed to 50 ppm survived for 12 mo. In mice exposed to 50, 250, or 1,000 ppm VC, there was a high incidence of bronchioloalveolar adenoma, mammary gland tumors (including ductular adenocarcinoma), squamous and anaplastic cell carcinomas with metastasis to the lung, and hemangiosarcoma (HS) in the liver and, to a lesser extent, in other organs. The incidence and severity of these tumors were proportional to the levels and duration of exposure. Malignant lymphoma involving various organs was observed in a few mice. Rats were more resistant to the toxic effects of VC, and exposure to 1,000 ppm slightly depressed the body wt of females. Exposures of 250 and 1,000 ppm VC caused a number of deaths and hepatic HS during the 9th mo. Most rats with hepatic HS also developed HS in the lung. HS occasionally occurred in other tissues, including omentum, mesentery, or sc tissue, of rats exposed to 50, 250, or 1,000 ppm VC. The exposure of mice to 55 ppm VDC also caused a few acute deaths and a few hepatic HS. Inflammatory, degenerative, and mitotic changes occurred in the liver. No mouse exposed to VDC developed any mammary gland tumors. Several mice had a bronchioloalveolar adenoma. The exposure of rats to 55 ppm VDC slightly depressed body wt; HS occurred in the mesenteric lymph node or sc tissue of two rats.

161. CARCINOGENICITY OF VINYL CHLORIDE AND VINYLIDENE CHLORIDE.

Lee CC, Bhandari JC, Winston JM, House WB, Dixon RL, Woods JS
Midwest Res. Inst., 425 Volker Blvd., Kansas City, MO, 64110
J Toxicol Environ Health; 4(1):15-30 1978

The effects of exposure to 50, 250, or 1,000 ppm vinyl chloride (VC) or 55 ppm vinylidene chloride (VDC) for 6 hr/day, 5 days/wk, were studied in albino CD-1 mice and CD rats. The animals were killed after 1, 2, 3, 6, 9, or 12 mo. Bronchioloalveolar adenomas developed in 12/63, 22/63, and 48/69 mice exposed to 50, 250, and 1,000 ppm VC, respectively. Bronchioloalveolar adenomas developed in 6/35 animals exposed to VDC. Three of 29, 23/63, and 31/69 mice exposed to 50, 250, and 1,000 ppm VC, respectively, developed hemangiosarcomas (HS) in the liver. In the mice exposed to VDC, HS developed in the livers of two males and one female. Mammary gland tumors occurred in 9/34, 3/34, and 13/36 female mice exposed to 50, 250, 1,000 ppm VC respectively, and they included ductular adenocarcinomas and squamous and anaplastic cell carcinomas with metastasis to the lung. Malignant lymphomas were found in various organs of mice exposed to VC but not in any of the mice exposed to VDC. Twelve of 70 and 21/70 rats exposed to 250 and 1,000 ppm VC, respectively, developed HS in the liver; 3/34 female rats exposed to 250 ppm VC and 13/70 rats exposed to 1,000 VC also developed HS in the lung. Two of 36 male rats exposed to VDC developed HS in the mesenteric lymph node or sc tissue.

It is concluded that VC is highly carcinogenic in mice; the incidence and severity of the tumors increased with dose and length of exposure. Rats were more resistant to the carcinogenic effects of VC and VDC. (26 Refs)

162. CARCINOGENICITY STUDIES ON HALOGENATED HYDROCARBONS.

Weisburger EK
Carcinogen Metabolism and Toxicology Branch, NCI, NIH, Bethesda, MD, 20014
Environ Health Perspect; 21:7-16 1977

The acute and chronic carcinogenicities of a series of halogenated hydrocarbons were studied in Osborne-Mendel rats and B6C3F1 mice. The test chemical was given by gavage 5 days/wk for 6 wk (acute studies) or 78 wk (chronic studies). Trichloroethylene had little effect on rats but caused hepatocellular carcinomas (HC) in mice. Chloroform caused HC in mice, kidney tumors in male rats, and thyroid tumors in female rats. 1,1,1-Trichloroethane had no effect on either species, whereas iodoform produced a slight increase in thyroid tumors in male rats. 1,2-Dibromoethane and 1,2-dibromo-3-chloropropane (DBCP) caused squamous cell carcinomas of the stomach with metastases in both species: DBCP also caused mammary tumors in female rats. 1,2-Dichloroethane produced some stomach tumors in male rats, HC in male mice, and lung tumors in males and females of both species. 1,1-Dichloroethane had little effect on rats, but caused a slight increase in HC in male mice. 1,1,2-Trichloroethane and hexachloroethane also had little effect on rats but increased the number of HC in mice, whereas 3-chloropropene decreased the hepatomagenic effect in mice. Tetrachloroethylene increased the number of HC in mice but had no effect in rats. Carbon tetrachloride, used as a positive control, produced HC in rats and mice as well as thyroid tumors in mice. The results suggest that po administration of many halogenated aliphatics might pose a carcinogenic hazard to humans on continued exposure.

163. EXPERIMENTAL STUDY OF THE CARCINOGENICITY OF CHLOROPRENE.

Zil'fian VN, Fichidzhian BS, Garibian DKh, Pogossova AM
Lab. Carcinogenesis, Scientific Res. Inst. Roentgenology and Oncology, Armenian SSR Ministry Public Health, Erevan, USSR
Vopr Onkol; 23(4):61-65 1977

The carcinogenicity of chloroprene (CP) was studied in male and female albino mice and rats. A rapid skin test, based on the disappearance of sebaceous glands and hair follicles upon topical application, revealed no carcinogenic activity for CP. Long-term tests of CP included topical application to mice (50% solution in benzene, 50 times), sc administration to rats (10 x 400 mg/kg or 50 x 200 mg/kg), intragastric administration to rats (50 x 200 mg/kg), and intratracheal administration to rats (5 x 200 mg/kg at 20-day intervals). None of these animals developed tumors. No tumors were found after topical application of CP (50% solution, 50 times) plus dimethylbenzanthracene (DMBA: 0.01% solution, 5 times) but DMBA alone (0.1% solution, 50 times) induced tumors in 92% of the mice. When CP was administered sc (50 x 200 mg/kg) with DMBA (1 x 0.5 mg), the tumor induction rate was 57.1%, but the same dose of DMBA alone induced tumors in 64% of the rats. The findings indicate that CP is not carcinogenic. (24 Refs)

164. DETERMINATION OF THE BLASTOMOGENIC ACTIVITY OF SOME CHEMICAL SUBSTANCES BY A RAPID TEST METHOD.

Garibian DKh, Papoian SA
Inst. Roentgenology and Oncology, Ministry Public
Health Armenian SSR, Erevan, USSR
Gig Sanit; (8):74-76 1977

The possible blastomogenic effects of tobacco smoke tar, sodium dichromate, chloroprene, and vinyl acetate were studied in 870 random-bred mice aged 2-3 mo. The substances were applied to the skin in single doses or three times per week in a 30-day experiment. The blastomogenic effects were evaluated by a rapid method based on the disappearance of the sebaceous glands. Cigarette tar caused the sebaceous glands to disappear after 5-11 days, but the glands reappeared after 15 days. Thickening of the skin, crust formation, progressive hyperplasia, and dystrophy of the epidermis were seen. Sodium dichromate, chloroprene, and vinyl acetate did not cause the sebaceous glands to disappear. The findings, in keeping with the results of other studies, suggest that cigarette tar is blastomogenic but that the other substances tested are not. (3 Refs)

165. CARCINOGENICITY OF TRICHLOROETHYLENE: FACT OR ARTIFACT?

Henschler D, Eder E, Neudecker T, Metzler M
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Versbacher Landstrasse 9, D-8700 Würzburg, W.
Germany
Arch Toxicol (Berl); 37(3):233-236 1977

Because trichloroethylene (TCE) was previously reported to produce a high incidence of hepatocellular carcinomas in mice (but not rats) after high daily doses po, this compound was studied further. Analysis of a sample of technical grade TCE (same as that used in the bioassay experiment for carcinogenicity) by gas chromatography/mass spectrometry showed the presence of two major contaminants, epichlorohydrin and 1,2-epoxybutane, both of which were found to be highly mutagenic in the Ames test using *Salmonella typhimurium* TA100. A low activity was found for trichloroethylene itself, and no activity was found for the other contaminants (diisobutylene, carbon tetrachloride, chloroform, and 1,1,1-trichloroethane). The carcinogenic effect of TCE is concluded to be due to epichlorohydrin and epoxybutane. (10 Refs)

166. TETRACHLOROETHYLENE (PERCHLOROETHYLENE).

Parker JC, Bahlman LJ, Leidel NA, Stein HP, Thomas AW, Wolf BS, Baier EJ
Natl. Inst. Occupational Safety and Health, 5600 Fishers Lane, Rockville, MD, 20857
Am Ind Hyg Assoc J; 39(3):A-23-A-29 1978

Animal and human data on the toxicity of tetrachloroethylene (perchloroethylene) are reviewed. Force feeding of the compound to B6C3F1 mice at doses of 536 or 1,072 mg/kg/day for males and 386 or 772 mg/kg/day for females for 78 wk resulted in hepatocellular carcinoma in greater than 50% of the males and 40% of the females. Studies in which the compound was inhaled did not provide sufficient data for evaluation of carcinogenicity. Tetrachloroethylene has been shown to cause liver and kidney damage, CNS depression, skin irritation, and cardiac depression in animals; it is also teratogenic in rats and mice. Human data indicate that it is toxic to the liver and kidneys, it is an eye irritant, and it can cause burns, blistering, and erythema of the skin; CNS depression has also been observed. This compound is usually absorbed through the lungs, but it can be absorbed from the

intestines if ingested. It is deposited in the body fat and has an estimated biological half-life of 6 days in humans. It is suggested that this compound be handled in the workplace as if it were a human carcinogen. (14 Refs)

167. OCCURRENCE OF HEPATOCELLULAR TUMORS AND HEMANGIOSARCOMA IN RATS INHALED 1,2-DIBROMOETHANE UNDER THE INFLUENCE OF DISULFIRAM TREATMENT (MEETING ABSTRACT).

Wong LC, Winston JM, Hong CB, Lee CC, Bhandari JC
Pharmacology and Toxicology, Midwest Res. Inst., Kansas City, MO, 64110
Pharmacologist; 20(3):174 1978

An 18-mo carcinogenicity study has been conducted in Sprague-Dawley rats inhaled 20 ppm of 1,2-dibromoethane (EDB) with and without 0.5% dietary disulfiram (DS) treatment. Groups of 48 males and 48 females each are treated with: (1) Air/control diet; (2) air/0.05% DS diet; (3) EDB/control; (4) EDB/0.05% DS diet. Animals are exposed to either air or 20 ppm EDB 7 hrs a day and 5 days a wk. Treatment with DS alone and the combination of EDB and DS have depressed body wt gain and food consumption of these rats. High mortality was noted during the 1st 12 mo in EDB/DS rats. The major organs affected were liver, kidney, spleen, mesentery, testes and mammary glands. Tumors developed in EDB/DS rats as early as 6 mo. Among the tumors that occurred were hepatocellular tumors and hemangiosarcoma of the liver, spleen, mesentery, and kidneys. These results indicate that a combined EDB and DS treatment was lethal and caused high incidences of hepatocellular tumors and hemangiosarcoma. A further evaluation of the tumor incidence will be reported following the completion of the study. (no Refs)

168. REPORT ON CARCINOGENESIS BIOASSAY OF 1,2-DICHLOROETHANE (EDC).

National Cancer Institute
U.S. Dept. Health, Education, and Welfare, NIH, NCI,
Bethesda, MD, 20014
Am Ind Hyg Assoc J; 39(11):A26-A30 1978

The halogenated solvent 1,2-dichloroethane (ethylene dichloride, or EDC) was administered to rats and mice for 78 weeks at time-weighted av dosages of 95 mg/kg/day (high dose) and 47 mg/kg/day (low dose) in a carcinogenesis bioassay. In male rats, EDC caused forestomach cancers, multiple hemangiosarcomas, and subcutaneous fibromas. In female rats, EDC induced mammary cancers, appearing in some high-dose animals as early as the 20th week. EDC also caused breast and uterine cancers in female mice and respiratory tract cancers in both male and female mice. (no Refs)

169. REPORT ON BIOASSAY OF 1,1-DICHLOROETHANE FOR POSSIBLE CARCINOGENICITY.

Fredrickson DS
NIH, Bethesda, MD, 20014
Fed Regist; 43(143):32190-32191 1978

1,1-Dichloroethane was administered by gavage to male and female Osborne-Mendel rats (382-950 mg/kg/day) and B6C3F1 mice (1,442-3,331 mg/kg/day) 5 days/wk for 78 wk. Rats were sacrificed 33 wk later, mice 13 wk later. Survival rates were poor in all rats and in several mouse groups. There were dose-related marginal increases in adenocarcinomas and in hemangiosarcomas among female rats and there was a statistically significant increase in the incidence of endometrial stromal polyps among female mice. (no Refs)

170. BIOASSAY OF 1,1,2,2-TETRACHLOROETHANE FOR POSSIBLE CARCINOGENICITY.

Carcinogenesis Program National Cancer Institute
National Cancer Inst., Bethesda, MD

Bioassay of 1,1,2,2-Tetrachloroethane for Possible Carcinogenicity. Available Through National Technical Information Service, Springfield, Va, as PB-277 453/7GA, DHEW/PUB/NIH-78-827, 90 pp., 1978.

A bioassay for the possible carcinogenicity of technical grade 1,1,2,2-tetrachloroethane was conducted using Osborne-Mendel rats and B6C3F1 mice. The compound was administered in corn oil by gavage at two dose levels to groups of 50 animals of each species and sex for 78 wk. The time weighted av doses were 108 and 62 mg/kg/day for male rats, 76 and 43 mg/kg/day for female rats, and 282 and 142 mg/kg/day for all mice. Twenty animals of each species and sex were placed on test as vehicle controls and another 20 were used as untreated controls. There was a highly significant positive dose related trend in the incidence of hepatocellular carcinoma in mice of both sexes. No statistically significant incidence of neoplastic lesions was observed in male or female rats. However, two hepatocellular carcinomas and one neoplastic nodule, which are rare tumors in the male Osborne-Mendel rat, were observed in the high dose males. Under the conditions of this bioassay, orally administered 1,1,2,2-tetrachloroethane is a liver carcinogen in B6C3F1 mice of both sexes. The results do not provide conclusive evidence for the carcinogenicity of 1,1,2,2-tetrachloroethane in Osborne-Mendel rats. (Author abstract)

171. INTERIM RESULTS OF TWO-YEAR TOXICOLOGICAL STUDIES IN RATS OF VINYLIDENE CHLORIDE INCORPORATED IN THE DRINKING WATER OR ADMINISTERED BY REPEATED INHALATION.

Rampy LW, Quast JF, Humiston CG, Balmer MF, Schwetz BA

Toxicology Res. Lab., Health and Environmental Res.,
Dow Chemical, U.S.A., Midland, MI, 48640
Environ Health Perspect; 21:33-43 1977

Interim results of a 2-yr toxicological study of male and female Sprague-Dawley rats exposed to vinylidene chloride (VDC) po or by inhalation are reported. Groups of 48 rats of each sex were given VDC in drinking water at mean concentrations of 0, 68, 106, and 220 ppm, corresponding to dosage levels of 0, 5.9, 10.0, and 19.3 mg/kg for male rats and 0, 7.5, 12.6, and 25.6 mg/kg for female rats. In the inhalation study, 86 rats of each sex were exposed to 0, 10, or 40 ppm VDC vapor for 6 hr/day, 5 days/wk, for 5 wk, after which the exposure levels were changed to 0, 25, and 75 ppm VDC. Exposure continued for a total of 18 mo, and the rats were held an additional 6 mo for observation. A separate 90-day study was made of 20 rats of each sex who were exposed to 0, 25, and 75 ppm VDC vapor. Based on gross tumor count, tumor incidence in VDC-exposed rats was not significantly greater than that in controls. Increased cytoplasmic vacuolation of hepatocytes was seen in the livers of rats given 200 ppm VDC in drinking water or 25 or 75 ppm VDC vapor by inhalation.

172. CARCINOGENICITY BIOASSAYS OF VINYLIDENE CHLORIDE: RESEARCH PLAN AND EARLY RESULTS.

Maltoni C, Cotti G, Morisi L, Chieco P
Inst. Oncology and Tumour Centre, Bologna, Italy
Med Lav; 68(4):241-262 1977

Early results (82-93 wk) of long-term carcinogenicity bioassays of vinylidene chloride (VDC) are presented. VDC was administered by inhalation to Sprague-Dawley rats (200-150, 100, 50, 25, and 10 ppm), Swiss mice (200, 100, 50, 25, and 10 ppm), and Chinese hamsters (25 ppm) and by ingestion to

rats (20, 10, 5, and 0.5 mg/kg body wt in olive oil by stomach tube). The treatment was given four to five times per week for 1 yr. In the mice, inhalation at 200, 100 and 50 ppm was discontinued after a few days because of excessive acute toxicity. In rats exposed to VDC by inhalation, the incidence of mammary tumors was higher among treated animals than in controls. No increase in mammary tumors was seen in rats given VDC by intubation. The most important result was the onset of kidney adenocarcinomas in mice exposed to 25 ppm. Male mice appeared to be more responsive than females. This tumor was not observed in mice exposed to 10 ppm or in the other treated species. No tumors were found in the hamsters. In vivo and in vitro studies indicate that VDC is probably metabolized by epoxidation into a more reactive compound that is responsible for its toxic mutagenic and carcinogenic effects. The rate at which active metabolites are formed and metabolized seems to depend on the dose of VDC as well as on the metabolic pathways of the test animals. These pathways appear to be influenced by species and sex. (15 Refs)

173. CARCINOGENICITY STUDIES ON VINYLIDENE CHLORIDE.

Viola PL, Caputo A

Regina Elena Inst. Cancer Res., Rome, Italy
Environ Health Perspect; 21:45-47 1978

The possible carcinogenicity of vinylidene chloride (VDC) was determined in two experiments, one using Wistar rats, one using Sprague-Dawley rats. The Wistar rats inhaled VDC for 4 hr/day, 5 days/wk, for 12 mo at a concentration of 200 ppm for 5 mo, 100 ppm thereafter. The animals were allowed to die spontaneously (life-span was 22-24 mo). Tumors, all occurring in the abdominal cavity except for one in the liver and one in the lung, were found in 8/51 males and 9/23 females. The diagnosis was reticulum cell sarcomas of a nonsyncytial type. However, many abdominal tumors were also found in control rats (5/30 males, 10/30 females). This prompted the second experiment, in which Sprague-Dawley rats were exposed to 75 or 100 ppm. Tumor incidence in the controls was practically identical to that found in the 100 ppm group and higher than that in the 75 ppm group. Microscopic examination of the tissues and organs from all animals is incomplete. Nevertheless, it seems clear that there is no grossly observable correlation between tumor formation and VDC inhalation. (7 Refs)

174. BIOASSAY OF 1,1,1-TRICHLOROETHANE FOR POSSIBLE CARCINOGENICITY (MEETING ABSTRACT).

Author not identified

NCI, Bethesda, MD

Gov Rep Announce Index; 77(13):111 1977

A bioassay for the possible carcinogenicity of technical grade 1,1,1-trichloroethane was conducted using Osborne-Mendel rats and B6C3F1 mice. The 1,1,1-trichloroethane was administered po by gavage in corn oil to 50 animals of each sex and species at two dose levels 5 days/wk for 78 wk. The rats received two doses of 1500 and 750 mg/kg, which produced a moderate depression of body wt in the 1st yr of the study. A yellow discoloration of lower abdominal fur, eye and nasal discharge and dyspnea were observed during the 2nd yr. Both male and female test animals were killed at 117 wk of age. In mice, the doses were increased twice and the time-weighted av doses were 5,616 and 2,807 mg/kg. There was a moderate depression of body wt throughout the study in both sexes, and survival was significantly decreased. Neoplasms encountered in both the treated and control animals had been seen previously in untreated animals. The neoplasms were not believed to be attributable to 1,1,1-trichloroethane since no relationship was established between the dosage group species, sex, type of neoplasm or site of occurrence.

175. CARCINOGENIC ACTIVITY OF DI- AND TRIFUNCTIONAL ALPHA-CHLORO ETHERS AND OF 1,4-DICHLOROBUTENE-2 IN ICR/HA SWISS MICE.

Van DUUREN BL, Goldschmidt BM, Seidman I
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Institute of Environmental Medicine, New York
University Medical Center, New York, New York 10016
Cancer Res; 35(9):2553-2557 1975

Four bifunctional and one trifunctional alpha-chloro ethers were tested for carcinogenicity. These compounds were bis-1,2-(chloromethoxy)ethane (Compound I), bis-1,4-(chloromethoxy)butane (Compound II), bis-1,6-(chloromethoxy)hexane (Compound III), bis-1,4-(chloromethoxy)-p-xylene (Compound IV), and tris-1,2,3-(chloromethoxy)propane (Compound V). Trans-1,4-Dichlorobutene-2 (Compound VI) was tested along with the five alpha-chloro ethers. All six compounds were tested in female ICR/Ha Swiss mice for 502 to 569 days, depending on survival, by skin application or sc and ip injection. There were 30 or 50 mice/group. The ip and sc injections were given once weekly at 0.1 or 0.3 mg of compound dissolved in 0.05 ml tricapylin for Compounds I to V and 0.05 mg/0.05 ml tricapylin for Compound VI for the duration of the tests. The skin applications, three times weekly, were at doses of 0.3 or 1.0 mg/0.1 ml cyclohexane for the alpha-chloro ethers and 1.0 mg/0.1 ml acetone for Compound VI. Vehicle and no treatment controls were carried out together with the test compounds. Significance values (p) were calculated for all the compounds tested. Three compounds, I, IV and V, gave notable tumor incidences by all three routes of administration. Compounds II, III, and VI were either inactive by one or more routes of administration or gave low tumor yields. (Author Abstract)

176. TRANS-1,4-DICHLOROBUTENE. (PP. 149-154)

IARC Working Group

IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man: Some Fumigants, the Herbicides 2,4-D and 2,4,5-T, Chlorinated Dibenzodioxins and Miscellaneous Industrial Chemicals. Lyon, International Agency for Research on Cancer, Vol 15, 1977.

The carcinogenicity of trans-1,4-dichlorobutene has been tested in ICR/Ha Swiss mice given the compound po, sc and ip. Low incidences of local sarcomas were noted in the sc and ip studies, but these results do not permit conclusive evaluation of carcinogenicity. No human epidemiological data were available for review. (11 Refs)

177. CARCINOGENICITY AND CHEMICAL REACTION WITH GUANINE OF 1-CHLOROPROPENE AND TWO OF ITS POTENTIAL METABOLITES (MEETING ABSTRACT).

Goldschmidt BM, Van Duuren BL, Goldstein RC, Smith AC

Lab. Organic Chemistry, Inst. Environmental Medicine,
New York Univ. Medical Center, New York, NY, 10016
Proc Am Assoc Cancer Res; 20:90 1979

1-Chloropropene, the simplest homologue of the human carcinogen vinyl chloride, along with two of its potential metabolites, 1-chloro-1,2-epoxypropane and 2-chloropropanal, were tested for carcinogenicity in female ICR/Ha Swiss mice (30/group). Repeated skin application of the alkene or aldehyde, and single dose initiation of the three compounds followed by promotion with phorbol myristate acetate failed to yield skin tumors. However, weekly sc injection of the aldehyde (1.0 mg) yielded 4 local sarcomas (P less than 0.005). Weekly intragastric feeding of the alkene (1.0 mg) led to 10 forestomach papillomas and 3 carcinomas (P less than 0.0005) while the aldehyde (1.0 mg) led to 6 forestomach

papillomas (P less than 0.05). Upon being allowed to react with guanine in dimethylsulfoxide the alkene failed to react, while the epoxide and aldehyde yielded the identical new compound, C₈H₈C₁N₅O. Based on UV and nuclear magnetic resonance spectra and other data the structure of the compound was established. It is an enamine formed by reaction at the 2-amino group of guanine. It should be noted that the potent carcinogenic metabolites of benzo(a)pyrene react predominantly with the 2-amino group of guanine in polynucleotides, just as the potential metabolites of 1-chloropropene did in our study. (no Refs)

178. MOUSE SKIN CARCINOGENICITY TESTS OF THE FLAME RETARDANTS TRIS(2,3-DIBROMOPROPYL)PHOSPHATE, TETRAKIS(HYDROXYMETHYL)PHOSPHONIUM CHLORIDE, AND POLYVINYL BROMIDE.

Van Duuren BL, Loewengart G, Seidman I, Smith AC, Melchionne S

Lab. Organic Chemistry and Carcinogenesis, Inst.
Environmental Medicine, New York, NY, 10016
Cancer Res; 38(10):3236-3240 1978

The flame retardants tris(2,3-dibromopropyl)phosphate (tris), tetrakis(hydroxymethyl)phosphonium chloride (THPC), and polyvinyl bromide (PVB) were tested for carcinogenic activity by thrice weekly skin application in female Icr/Ha Swiss mice for 420-496 days. Tris, at doses of 30 or 10 mg/application (30 mice/group), induced benign and malignant tumors of the skin, forestomach, and oral cavity (tongue and gingiva) in a statistically significant number of mice (p less than 0.0005). A statistically significant incidence of papillary tumors of the lung was observed at both doses (p less than 0.0005). One carcinoma of the liver was observed at both doses, and the higher dose also resulted in a tubular adenocarcinoma of the kidney in one mouse. THPC (2 mg/application, 60 mice) and PVB (0.1 ml latex suspension/application, 30 mice) were inactive. PVB was also injected sc (approx 23 mg) into the mice once weekly for 48 wk; the mice were observed for an additional 12 wk. Liposarcomas were induced in 19/30 mice; the tumors were ascribed to physical carcinogenesis because the aqueous suspension contained 90% solids. The internal tumors observed in the PVB-treated animals were not significantly different from those observed in controls. (28 Refs)

179. INDUCTION OF STOMACH CANCER IN RATS AND MICE BY HALOGENATED ALIPHATIC FUMIGANTS.

Olson WA, Habermann RT, Weisburger EK, Ward JM, Weisburger JH

Hazleton Labs., Inc., Vienna, Va.

J Natl Cancer Inst; 51(6):1993-1995 1973

Ethylene dibromide (EDB) and 1,2-dibromo-3-chloropropane (DBCP) were administered to Osborne-Mendel rats and (C57BL X C3H)F₁ mice via chronic oral intubation five times per wk at experimentally predetermined maximally tolerated doses and at half those doses. Fifty animals of each sex were used for each dose level-a total of 200 rats and 200 mice for each compound. As early as 10 wk after initiation of treatment, both compounds induced a high incidence of squamous cell carcinomas of the stomach in both species. In addition, DBCP induced mammary adenocarcinomas in the female rats. These results are most pertinent to agricultural and food storage workers who disperse these volatile materials through soil or food. Although the hazard to any such workers would probably be largely through inhalation and not through oral exposure as was done in this study, anyone exposed to DBCP or EDB should take protective measures.

180. BIOASSAY OF DIBROMOCHLOROPROPANE FOR POSSIBLE CARCINOGENICITY. CAS NO. 1836-75-5.

National Cancer Institute Carcinogenesis Program
Carcinogenesis Program, NCI, Bethesda, MD
Bioassay of Dibromochloropropane for Possible
Carcinogenicity. CAS No. 1836-75-5. Available Through
National Technical Information Service, Springfield, Va.,
as PB-277 472/7GA.; NCI-CG-TR-28,
DHEW/PUB/NIH-78-828, 93 pp., 1977.

A bioassay for the possible carcinogenicity of technical grade dibromochloropropane (DBCP) was conducted using Osborne-Mendel rats and B6C3F1 mice. The compound was administered in corn oil by gavage at two doses for varying lengths of time ranging from 47-78 wk. Time weighted av doses of DBCP were 29 mg/kg/day for high-dose rats; and 15 mg/kg/day for low-dose rats. The time-weighted av concentrations for the high-dose male and female mice were 219 and 209 mg/kg/day, respectively. For low-dose male and female mice the concentrations were 114 and 110 mg/kg/day, respectively. Fifty animals of each species and sex served as vehicle (corn oil) controls. Twenty animals of each species and sex also served as untreated controls. In rats and mice of both sexes, there was a statistically significant incidence of forestomach squamous cell carcinomas. In female rats the incidence of adenocarcinoma of the mammary gland was statistically increased. Toxic nephropathy was observed in all treated animals. Under the conditions of this bioassay, DBCP is a stomach carcinogen in rats and mice of both sexes and is carcinogenic to the mammary gland in female rats. (Author abstract)

181. RESULTS OF A TWO YEAR CHRONIC TOXICITY STUDY WITH HEXACHLOROBUTADIENE RATS.

Kociba RJ, Keyes DG, Jersey GC, Ballard JJ, Dittenber DA, Quast JF, Wade CE, Humiston CG, Schwetz BA
Toxicology Res. Lab., Health and Environmental Res.,
Dow Chemical U.S.A., Midland, MI 48640
Am Ind Hyg Assoc J; 38(11):589-602 1977

The possible toxicological effects associated with the chronic ingestion of hexachlorobutadiene (HCB) in the diet of rats were investigated. Male and female Sprague-Dawley rats were maintained for up to 2 yr on diets containing 0.2, 2.0, or 20 mg/kg/day. The kidney was the primary organ affected by the toxin. Ingestion of 20 mg/kg/day of HCB for up to 2 yr caused decreased body wt gain and survival, increased the urinary excretion of coproporphyrin, increased kidney wt, increased renal tubular hyperplasia/proliferation and renal tubular adenomas and adenocarcinomas, some of which metastasized to the lungs. Lesser degrees of toxicity were observed in the rats receiving 2mg/kg/day. They had increased urinary coproporphyrin excretion, and an increase in renal tubular epithelial hyperplasia/proliferation. No neoplasms were found in these rats. No discernible ill effects were observed in the rats receiving 0.2 mg/kg/day for up to 2 yr. Thus, a clear-cut dose-response relationship for HCB-induced toxicity was observed in which the HCB-induced neoplasms occurred at a level higher than that causing discernible renal injury. Irreversible toxicologic effects occurred at a dosage level which caused significant tissue injury and other manifestations of toxicity. No neoplasms occurred at dosage levels which caused no injury or only minor injury that was reversible. (10 Refs)

182. MUTAGENIC AND CARCINOGENIC EFFECTS OF VINYL CHLORIDE.

Bartsch H, Montesano R
International Agency for Res. on Cancer, Unit Chemical
Carcinogenesis, 150 cours Albert Thomas, 69008 Lyon,
France
Mutat Res; 32(2):93-113 1975

The carcinogenic and mutagenic effects of vinyl chloride (VC) are described. VC administered by inhalation is carcinogenic in rats, mice, and hamsters, producing angiosarcoma of the liver and other tissues in all three. In addition, in rats, VC induces tumors of the Zymbal glands and of the skin, nephroblastomas, hepatomas, and neuroblastomas. In mice, tumors of the lung and skin are also observed. The mutagenic activity of VC has been demonstrated by an in vitro technique utilizing the reverse mutation system of *Salmonella typhimurium*, in which the genetic indicator reverts to histidine prototrophy by single base-pair substitutions or by base-pair insertions or deletions. The carcinogenicity of VC in man and animals and its mutagenic action after metabolic conversion by microsomal enzymes from humans and rodents into electrophilic derivatives strengthen the relationship between mutagenesis and carcinogenesis. Despite the fact that there is no direct proof that chloroethylene oxide is the metabolite of VC primarily responsible for its biological effects in vivo, the biological importance of this compound is stressed by circumstantial evidence. The available data concerning the biological hazards of VC demonstrate that it is toxic, carcinogenic, and mutagenic in animals and man. (100 refs)

183. INDUCTION OF PULMONARY ADENOMAS IN STRAIN A MICE BY SUBSTITUTED ORGANOHALIDES.

Theiss JC, Shimkin MB, Poirer LA
Dept. Community Medicine, Sch. Medicine, Univ.
California, La Jolla, CA, 92093
Cancer Res; 39(2,Part1):391-395 1979

An investigation was made of the abilities of 28 organohalides (10 monochlorinated and 18 monobrominated derivatives of alcohols, esters, ethers, carboxylic acids, ketones, and amines that contained 2-4 carbon atoms) to induce lung adenomas in strain A mice. Groups of 20 mice (10 males, 10 females) received ip injections 3x/wk of either the max tolerated dose (MTD), 0.5 MTD, 0.25 MTD, or 0.20 MTD. Except for the more toxic compounds, 24 injections were given when possible. The mice were sacrificed 24 wk after the first injection and their lungs examined. 2-Chloro-N,N-dimethylethylamine hydrochloride, 3-chloropropionic acid, 4-chloro-1-butanol, and 2-bromoethanol produced an elevated pulmonary adenoma response that was significant by two different statistical tests. These substituted derivatives appeared to exert tumorigenic activity at lower doses than those of similar unsubstituted compounds (previous data); thus, nucleophilic substitution may increase the tumorigenicity of linear alkyl halides. Ethyl chloroacetate, 3-chloropropene, 3-chlorobutyric acid, 3-bromopropionic acid, and 3-bromopropylamine hydrobromide produced an elevated lung tumor response that was significant by only one of the statistical tests used. These compounds thus had borderline tumorigenicity in this bioassay. Four of the organochlorides and 15 of the organobromides showed no significant tumorigenicity. Among the negative compounds were three acylating agents, isobutyl bromide, butyl bromide, and benzoyl bromide. In general, the MTD's of the organo-

bromides were substantially lower than those of the organochlorides. The finding that a greater percentage of the chloro compounds showed tumorigenicity than did the bromo derivatives was unexpected, based on chemical activity and on previous studies of mutagenicity and carcinogenicity among organohalides. The greater toxicity of the organobromides toward strain A mice may mask their potential tumorigenicity in some cases, as these compounds could not be administered in sufficient amounts to induce tumor formation. (14 Refs)

G. Factors Modifying Carcinogenicity and Toxicity of Vinyl Chloride and Related Compounds

184. EFFECT OF ETHANOL AND VINYL CHLORIDE ON THE INDUCTION OF LIVER TUMORS: PRELIMINARY REPORT.

Radtke MJ, Stemmer KL, Brown PG, Larson E, Bingham E

Univ. Cincinnati, Inst. Environmental Health, Kettering Lab., Cincinnati, OH, 45267

Environ Health Perspect; 21:153-155 1977

A preliminary report of the effect of ethanol on vinyl chloride (VC) carcinogenicity in 320 male Sprague-Dawley rats is presented. Equal numbers of rats were divided into four groups. Group 1 received a normal diet and breathed filtered air for life. Group 2 received a normal diet plus 5% ethanol in the drinking water and breathed filtered air for life. Group 3 received a normal diet but breathed 600 ppm VC 4 hr/day, 5 days/wk, for 1 yr. Group 4 received a normal diet plus ethanol starting 4 wk before VC exposure. The ethanol exposure lasted until the animal died or was sacrificed. Sixty weeks after the first exposure to VC, 55 rats had died or had been sacrificed. No tumors were noted in eight Group 1 animals that had died. Of six dead Group 2 animals, one had a kidney tumor. Of 13 dead Group 3 animals, 5 had liver tumors (2 of them being angiosarcomas) and 2 had lung tumors. Of 28 dead Group 4 animals, 21 had 26 liver tumors (5 angiosarcomas) and 2 had kidney tumors. These preliminary findings suggest a synergism between VC inhalation and ingested alcohol in tumorigenesis. (6 Refs)

185. EFFECT OF VARIOUS TREATMENTS ON TOXICITY OF INHALED VINYLIDENE CHLORIDE.

Short RD, Winston JM, Minor JL, Seifter J, Lee CC
Pharmacology and Toxicology, Midwest Res. Inst., Kansas City, MO, 64110

Environ Health Perspect; 21:125-129 1977

The acute toxicity of continuously inhaled vinylidene chloride (VDC) was investigated in CD-1 mice and CD rats, and the effects of various treatments on this toxicity were determined. The animals were exposed to varying VDC concentrations for 22-23 hr/day. VDC was more lethal and more hepatotoxic mice than male rats. Furthermore, male mice were more sensitive to the lethal effects of VDC than females; the respective concentrations causing 50% mortality were 98 and 105 ppm. The effects of disulfiram, diethyldithiocarbamate, thiram, cysteine, methionine, N-acetylcysteine, SKF 525-A, cobaltous chloride, dimercaprol, phenoxybenzamine, propranolol, vitamin C, and DL-alpha-tocopherol acetate on VDC toxicity were evaluated. Disulfiram, diethyldithiocarbamate and thiram reduced the acute lethal and hepatotoxic effects of inhaled VDC. Disulfiram also reduced the levels of covalently bound radioactivity in the liver and kidney following ip administration of ¹⁴C-VDC. It is suggested that disulfiram and its metabolites act by not only reducing the activation of VDC, but also by increasing the extent of detoxification. (25 Refs)

ANTIMUTAGENS, ANTITERATOGENS, AND ANTICARCINOGENS IN REDUCING ENVIRONMENTAL HEALTH HAZARDS.

Nashed N

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Environ Health Perspect; 14:193-200 1976

The use of protective agents such as antibiotics, cations, vitamins, sulfhydryl compounds, and amino acids offers a means of dealing with the burden of environmental health hazards facing man. Dietary supplements of appropriate protective agents may protect people working with genetically active agents. Among these are workers in oil refineries and in the manufacture of asbestos, certain pesticides, polyvinyl chloride, and alkylating agents. The use of vitamin C as a preventive measure against nitrosamines in food is only justified if its presence does not also protect bacteria against the antibiotic effect of nitrite. Reducdyn (a combination of N-acetylhemocysteine-thilactone, L-cysteine, and fructose) is already being successfully used against the adverse effects of irradiation and of the clastogenic alkylating agent trenimon. L-Cysteine has been shown to have anticarcinogenic, antimutagenic, and antiteratogenic effects. It should be possible, once the mechanisms of action of both inducers and protectors are known, to be able to protect against a given inducer by selecting the optimal protector and conditions most suited to counter its action. Efforts should be intensified to gain a better understanding of protection mechanisms by using model systems. (71 refs)

187. 1,1-DICHLOROETHYLENE HEPATOTOXICITY: EFFECT OF ALTERED THYROID FUNCTION AND EVIDENCE FOR THE SUBCELLULAR SITE OF INJURY.

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Dept. Physiology, Harvard Sch. Public Health, 665 Huntington Ave., Boston, MA 02115

J Toxicol Environ Health; 3(3):545-555 1977

To study the effect of altered thyroid function on the hepatotoxicity of 1,1-dichloroethylene (1,1-DCE), male Sprague-Dawley rats were exposed for 4 hr to 1,1-DCE by inhalation following an 18 hr fast. The rats were sacrificed 6 hr after exposure. Under these conditions thyroidectomy provided significant protection against the toxic effect of 1,1-DCE. On the other hand, thyroxine pretreatment significantly potentiated the toxicity of this chemical. The thyroidectomized animals had higher values of liver glutathione (GSH) than control animals. Thyroxine pretreatment resulted in a significant reduction in GSH concentration. The antithyroidal agents propylthiouracil and methimazole were comparable to thyroidectomy in their protection against the hepatotoxic effect of 1,1-DCE. The two pretreatments were also associated with significant elevations in liver GSH concentration, showing that decreased thyroid function was associated with increased liver sulfhydryl content. Subcellular fractionation of livers from fed or fasted rats exposed to air or 1,1-DCE showed that mitochondrial GSH concentrations were reduced to a greater extent than those of other fractions. Decreased oxygen uptake by liver homogenate appeared to precede changes in serum alanine-alpha-ketoglutarate transaminase (AKT). Serum sorbitol dehydrogenase, a cytoplasmic marker, was positively correlated with changes in serum ornithine carbamoyl transaminase, a mitochondrial marker, indicating that mitochondrial damage may occur prior to or simultaneously with cytoplasmic membrane rupture. The results suggest that the thyroid gland regulates the concentration of glutathione in the liver and support a previously described hypothesis. A mechanism for the action of 1,1-DCE is proposed. (17 Refs)

188. ORAL TOXICITY OF 1,1-DICHLOROETHYLENE IN THE RAT: EFFECTS OF SEX, AGE, AND FASTING.

Andersen ME, Jenkins LJ

Toxicology Detachment, Naval Medical Res. Inst., Wright-Patterson Air Force Base, OH, 45433

Environ Health Perspect; 21:157-163 1977

The acute po toxicity of 1,1-dichloroethylene (1,1-DCE; vinylidene chloride) was investigated in male and female Holtzman HOT:(SD)BR rats of various sizes. When fasted and fed large, mature, male rats were given 400 mg 1,1-DCE, the hepatotoxic response was four to five times greater in the fasted rats. Determinations of the po LD50 of male rats indicated that for large animals (395 g), mortality increased monotonically from 0% to 100% as the dose increased from 800 to 2,000 mg/kg; the estimated acute LD50 was similar to that reported previously, 1,550 mg/kg. With males weighing 224 g, mortality varied between 10% and 33% following doses of 50-800 mg/kg 1,1-DCE. With rats weighing 73 g, 100% mortality was noted at 300 mg/kg; percent mortality then decreased as the dose was increased up to 800 mg/kg. Maxima and extended plateaus were seen in the survival curves of all males between doses of 100 and 700 mg/kg, making it impossible to calculate an exact LD50. Following a dose of 50 mg/kg, mortality and hepatotoxicity were greatest in rats weighing 100-150 g; smaller and larger males were less susceptible. Female rats did not show this variation in susceptibility with size, and they were less susceptible to the toxic effects of 1,1-DCE: the threshold of toxicity in male rats of 100-150 g occurred near 50 mg/kg, while for females it was closer to 100 mg/kg. These findings suggest that 1,1-DCE is metabolized to a toxic intermediate by some saturable pathway. Based on the effects of pretreatment with microsomal enzyme inhibitors and activators on 1,1-DCE toxicity in rats of various sizes, it appears that there are at least two microsomal reactions involved in 1,1-DCE metabolism. (25 Refs)

189. ENHANCEMENT OF 1,1-DICHLOROETHYLENE TOXICITY BY PRETREATMENT OF FASTED MALE RATS WITH 2,3-EPOXYPROPAN-1-OL.

Andersen ME, Jones RA, Jenkins LJ

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Drug Chem Toxic; 1(1):63-74 1977

The enhancement of 1,1-dichloroethylene (1,1-DCE) toxicity by pretreatment with 2,3-epoxypropan-1-ol (EP) was studied in fasted male Holtzman rats. Pretreatment with 278 mg EP/kg reduced the acute LD50 of 1,1-DCE by a factor of five (to less than 40 mg/kg). Low mol wt epoxides appear to increase the toxicity of 1,1-DCE by interfering with the metabolism of a toxic product of the microsomal oxidation of 1,1-DCE. Other compounds tested showed lower enhancement effects than EP, including styrene oxide, trichloropropane-2,3-oxide, cyclohexene oxide, diethylmaleate, and butadiene monoxide. (18 Refs)

190. POSSIBLE METABOLIC INTERACTION BETWEEN STYRENE AND ORGANIC SOLVENTS (MEETING ABSTRACT). (PP. 10)

Ikeda M, Hirayama T

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Proceedings of the International Symposium on Styrene: Occupational and Toxicological Aspects Held by the Institute of Occupational Health in Helsinki (Finland), 17-19 April, 1978. Institute of Occupational Health, Helsinki, Finland, 56 pp., 1978.

Animal experiments were initiated to examine the possibility that coexposure to organic solvents affects the

metabolism of styrene and modifies its toxicity. Male Wistar rats (about 300 g) were given styrene ip (2.2 moles/kg) dissolved in soybean oil, together with n-hexane, ethyl acetate, methylchloroform, acetone, trichloroethylene or toluene. Phenylglyoxylic and mandelic acid were measured in 24-hr urine samples. A preliminary experiment revealed that most of the metabolites are excreted in urine during the time period studied. The amounts of the urinary metabolites were reduced by about 10% when an equimolar amount of either trichloroethylene or toluene was administered in conjunction with styrene, while the other solvents were essentially ineffective. With a trichloroethylene dose of 11 moles/kg (5 x as much as styrene), styrene metabolism was suppressed by 44-49%; a suppression of 45-46% was observed with 11 mole of toluene/kg. In parallel experiments, the metabolism of benzene after ip injection was suppressed by coadministered toluene, and this observation could be reproduced in mixed vapor exposure experiments as well. Accordingly, inhalation experiments are in progress to confirm the suppressive effect of trichloroethylene and toluene on the metabolism of styrene after vapor exposure. (no Refs)

IV. STRUCTURE-ACTIVITY RELATIONSHIPS FOR VINYL CHLORIDE AND RELATED COMPOUNDS

The reader may also find the following abstracts of interest: 38, 40, 43, 50, 56, 58, 59, 65, 69, 109, 117, 133, 140

191. ALKYLATING AND MUTAGENIC EFFECTS OF ALLYL AND ALLYLOGENIC COMPOUNDS (MEETING ABSTRACT).

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Naunyn Schmiedebergs Arch Pharmacol; 302(Suppl):R21 1978

Some allyl compounds have been found active, others inactive in carcinogenicity testing in intact animals. The carcinogenic activity has been attributed, up to now, to the possible epoxidation of the olefinic moiety in these molecules. However, allylic or allylogenic structures are generally characterized by a rather strong SSUBN-1 as well as SSUBN-2 reactivity; they may alkylate nucleophilic biomolecules and thus initiate chemical carcinogenesis and mutagenesis. We investigated the direct alkylating properties of a series of allyl and allylogenic compounds and tested their mutagenic potential in an in vitro-bacterial testing system (A). The selection of compounds was guided by theoretical evaluation of the influence of various substituents on the reactivity of the molecules. These alkylating properties were determined by reaction with 4-nitrobenzyl pyridine (B). Positive results in A and B were found with: allyl chloride, allyl cyanide, 1-chloro-2-methyl-2-propene, 1-chloro-2-butene; negative, in both tests (A and B) were allyl amine and diallyl sulfide. With allyl alcohol, a high mutagenic potential (A) did not correlate with a negative result in B; this, however, might be due to the fact that OH, under the condition of test, does not represent a good leaving group. These findings clearly indicate the possibility that allyl compounds might exert a direct carcinogenic effect.

CARCINOGENICITY AND TUMOR-ENHANCING ACTIVITY IN VARIOUS CHEMICALS. (PP. 2071-2084)

Van Duuren BL

Lab. Organic Chemistry, New York Univ. Medical Center, New York, NY, 10016

Prevention and Detection of Cancer, Proceedings of the Third International Symposium on Detection and Prevention of Cancer Held by the International Study Group for the Detection and Prevention of Cancer in New York, April 26 - May 1, 1976. Vol. 2(Part I), International Study Group for the Detection and Prevention of Cancer, New York, NY, 2404 pp., 1978.

Structure-activity relationships of direct-acting alkylating agents, tumor promoters, and cocarcinogens are reviewed. Among the 100 alkylating agents examined were epoxides (mono-, bi- and polyfunctional), beta- and gamma-lactones, and a variety of chloro ethers. The beta-lactones are carcinogenic but the gamma-lactones are not. The bifunctional epoxides exhibit carcinogenicity more frequently than the monofunctional analogs. In monofunctional agents, the presence of a reactive adjacent functional group results in carcinogenic activity. Trichloroethylene (TCE) and vinyl chloride (VC) may be metabolized via an epoxide intermediate. TCE is carcinogenic in mice but not in rats, and VC is a known human carcinogen. Because of the wide differences in chemical structure, reactivity, and physical properties of tumor promoters, cocarcinogens, and tumor inhibitors, they probably exert their activities in several different ways. They may simply alter the rate of absorption and disappearance of a carcinogen, or they may alter its metabolic pathway. Tumor-promoting agents, particularly the phorbol esters, are likely to interact at the cell membrane. As a result of structure-activity studies, it has become possible to assign biological activity to certain classes of compounds that have not yet been tested. (41 Refs)

193. STRUCTURAL PROGNOSTICATION OF CARCINOGENICITY AND TUMOR ENHANCING ACTIVITY IN VARIOUS CHEMICALS (MEETING ABSTRACT). (PP. 130-131)

Van Duuren BL

Lab Organic Chem and Carcinogen, Inst Environ Med, NY Univ Med Ctr, NY, NY 20016

Third International Symposium On Detection And Prevention Of Cancer. 1976.

The chemical reactivity and carcinogenicity of epoxides, lactones, their N and S isosteres and haloethers were examined. The findings are important with regard to mode of action of direct-acting carcinogens, and more immediately with regard to environmental carcinogenesis. An example is bis(chloromethyl)ether which was pinpointed in a long list of potential occupational carcinogens and was then shown to be carcinogenic in mice and rats. Subsequent epidemiologic studies in chemical workers led to its designation as a human carcinogen. Thus, the usual pattern of uncovering occupational carcinogens, ie from epidemiologic studies, has been reversed in this instance. It was also suggested that trichloroethylene will be carcinogenic particularly to the liver. Subsequently the National Cancer Institute announced that it caused liver cancer in mice. Structural changes in the tumor-promoting agent phorbol myristate acetate have been made and the products were examined for tumor-promoting activity on mouse skin. Phorbol and phorbol triacetate are inactive; phorbolol myristate acetate showed decreased activity. Long-chain aliphatic hydrocarbons (C10 -C16) and the phenols catechol, resorcinol, hydroquinone and pyrogallol show remarkable differences in cocarcinogenicity. Close

examination of chemical structure, reactivity, stereochemistry and known or suspected metabolic pathways can now be used much more effectively in pinpointing potential carcinogens in the environment. (Author Abstract)

194. CHEMICAL STRUCTURE, REACTIVITY, AND CARCINOGENICITY OF HALOHYDROCARBONS.

Van Duuren BL

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Environ Health Perspect; 21:17-23 1977

The structural and carcinogenic properties of haloalkylhydrocarbons are reviewed, with particular emphasis on trichloroethylene (TCE). Based on studies of the chemical structure, reactivity, and possible metabolic pathways of TCE, the compound was predicted to be carcinogenic, particularly to the liver. These studies also suggested that TCE is metabolized to an epoxide and that this epoxide may be the activated carcinogenic intermediate of TCE in liver carcinogenesis. The binding of TCE to liver microsomal proteins of male B6C3F1 hybrid mice, which are susceptible to TCE-induced liver tumorigenesis, was found to be significantly higher than the binding of TCE to microsomal proteins of male Osborne-Mendel rats, which are resistant to TCE-induced hepatocellular carcinoma. Also, the in vitro binding of TCE to liver microsomal proteins was higher for male than female B6C3F1 mice; females have been reported to show a lower incidence of TCE-induced hepatocellular carcinoma than males. The results of carcinogenicity assays of vinyl bromide and polyvinyl bromide are also given. Neither compound appeared to be carcinogenic when injected sc or when applied to the skin of mice. The carcinogenicity of other chlorinated hydrocarbons that are widely used in the chemical industry and that are structurally analogous to TCE and vinyl chloride is discussed briefly.

195. METABOLISM AND MUTAGENICITY OF HALOGENATED OLEFINS - A COMPARISON OF STRUCTURE AND ACTIVITY.

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Environ Health Perspect; 21:61-64 1977

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

renders the epoxides unstable and mutagenic. High electrophilicity may be a prerequisite for the mutagenic and carcinogenic activity of these chlorinated ethylenes. (20 Refs)

196. MOLECULAR ASPECTS TO THE OXIRANE-FORMATION OF TRICHLOROETHYLENE AND OTHER CHLORINATED ETHYLENES (MEETING ABSTRACT).

Bonse G, Henschler D

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Arch Pharmacol; 293(Suppl): R64 1976

The molecular aspects of oxirane formation from trichloroethylene and other chlorinated ethylenes are discussed. In vitro, chlorinated oxiranes formed from the corresponding ethylenes undergo rearrangement to carbonylic compounds. In all cases except trichloroethylene, the products of thermal rearrangement of synthesized oxiranes are identical to the in vivo metabolites identified in perfused rat liver preparations. With trichloroethylene, the photochemically synthesized oxirane undergoes rearrangement in vitro, in nonpolar solvents, to dichloroacetyl chloride; chloral is formed only under catalysis of Lewis acids. The in vivo metabolites are chloral hydrate and its reduction products trichloroethanol and trichloroacetic acid. These findings indicate an interaction of the oxirane with its biological environment. (1 Refs)

197. STRUCTURAL PARAMETERS ASSOCIATED WITH CARCINOGENESIS (HALOGENATED OLEFINS, VINYL AND ALLYL ANALOGS AND EPOXIDES). (PP. 8-21)

Fishbein L

Natl. Center Toxicological Res., Little Rock, AR, 72207

Structural Correlates of Carcinogenesis and Mutagenesis.

A Guide to Testing Priorities? Proceedings of the Second Food and Drug Administration Office of Science Summer Symposium held in Annapolis, 31 August-2 September 1977. Office of Science, FDA Annapolis, MD HEW Publication No. (FDA)78-1046, 241 pp., 1978.

A number of reportedly carcinogenic industrial compounds (including halogenated olefins, vinyl and allyl analogs, and epoxides) were examined to determine if their structural, biological, and metabolic similarities could help predict their carcinogenicity. The chlorinated olefinic derivatives of major concern are vinyl chloride, vinylidene chloride, trichloroethylene, chloroprene, dichlorobutene, and perchloroethylene, all of which have been proved to be carcinogenic to humans and/or laboratory animals. Evidence suggests that all chlorinated ethylenes are metabolized to oxiranes (epoxides) as a first step. The oxiranes, which are strongly electrophilic, may react directly with cell nucleophiles or they may undergo intramolecular arrangements. No such structure-activity relationship has been demonstrated for the various vinyl and allyl analogs that are carcinogenic and/or mutagenic. In the case of the epoxides, the presence of a reactive functional group (as in epichlorohydrin) or a double bond (as in glycidaldehyde) near the epoxide appears to enhance carcinogenicity by allowing the chemical to act as a difunctional alkylating agent for macromolecules. Greater reliance should be placed on mutagenicity testing and on definitive metabolic and pharmacokinetic studies to augment structure-activity predictions of carcinogenicity. (79 Refs)

198. CARCINOGENIC POTENTIAL OF CHLORINATED ETHYLENES. TENTATIVE MOLECULAR RULES. (PP. 171-175)

Henschler D, Bonse G, Greim H

Institut für Toxikologie und Pharmakologie, Universität Wurzburg, D-8700, Wurzburg, Germany

Environmental Pollution and Carcinogenic Risks. Lyon, International Agency for Research on Cancer, IARC Scientific Publications No 13, INSERM Symposia Series, Vol. 52, 1976.

The mechanisms of bioactivation and the mutagenic activity of the chlorinated ethylenes were studied with a short-term in vitro system using metabolic activating liver microsomal enzymes. Chlorinated ethylenes were activated in mammalian metabolism to oxiranes. Asymmetric chlorine substitution of the ethylenes and oxiranes rendered the molecules unstable and mutagenic. Vinyl chloride was the most active; trichloroethylene and vinylidene chloride were far less active but still significantly so. Chlorinated ethylenes metabolized via symmetric oxiranes (tetrachloroethylene, cis- and trans-1,2-dichloroethylene) were relatively stable and were not mutagenic. It was concluded that mutagenic activity and possible carcinogenic potential were related directly to oxirane stability. (13 Refs)

199. STRUCTURAL CORRELATIONS OF CARCINOGENIC AND MUTAGENIC ALKYL HALIDES. (PP. 163-171)

Simmon VF

SRI International, Menlo Park, CA, 94025

Structural Correlates of Carcinogenesis and Mutagenesis.

A Guide to Testing Priorities? Proceedings of the Second Food and Drug Administration Office of Science Summer Symposium held in Annapolis, 31 August-2 September 1977. Office of Science, FDA Annapolis, MD HEW Publication No. (FDA)78-1046, 241 pp., 1978.

The Ames Salmonella typhimurium microsome assay, using strain TA100, was used to determine the mutagenicity of 23 alkyl halides, 10 of which were unknown carcinogens. Twenty-one of these halides were mutagenic with and without S-9 liver microsome mix. The mutagenic compounds (c denotes proven carcinogen) included methyl bromide, methyl chloride, methyl iodide (c), methylene chloride (c), bromochloromethane, methylene bromide, bromoform (c), dibromochloromethane, bromodichloromethane, vinyl chloride (c), vinylidene chloride (c), 1,1,2-trichloroethylene (c), bis(2-chloroethyl) ether (c), bis(2-chloroisopropyl) ether, 1-chloropropene, 3-chloropropene, epichlorohydrin (c), hexachlorobutadiene, 3-bromopropionic acid, 3-iodopropionic acid, and 3-chloropropionic acid. Two known carcinogens, carbon tetrachloride and chloroform, were not mutagenic in the presence or absence of the S-9 mix. It is likely that an insufficient amount of the mutagenic form was produced or that this form was so unstable it was unavailable to interact with the bacterial DNA. In general, the mutagenicity correlated with chemical reactivity. Of interest was the mutagenicity of methylene chloride, a widely used industrial chemical with broad environmental exposure (via paint removers and aerosol spray cans). (17 Refs)

200. MUTAGENICITY OF DICHLORVOS AND OTHER STRUCTURALLY RELATED PESTICIDES IN SALMONELLA AND STREPTOMYCES.

Carere A, Ortali VA, Cardamone G, Morpurgo G

Istituto Superiore di Sanita, Università di Roma, Rome, Italy

Chem Biol Interact; 22(2/3):297-308 1978

The following pesticides: azinphosmethyl, diallate, dichlorvos, EPTC (S-ethylpropyl thiol + carbamate),

fenchlorphos, mevinphos, monocrotophos, noruron, parathionmethyl, triallate, trichlorphon and vegadex were tested for the ability to induce his+ revertants in four histidine-requiring strains of *Salmonella typhimurium*, TAI 535 (missense), TAI 536, TAI 537 and TAI 538 (frame-shift), and resistance to low levels of streptomycin in *Streptomyces coelicolor*. Dichlorvos, which is a phosphoric ester with a dichlorovinyl group as side chain, and trichlorphon, which is known for its spontaneous conversion in dichlorvos, are both mutagenic in *Salmonella* (strain TAI 535) and *Streptomyces*. Five organophosphorus pesticides similar to dichlorvos but devoid of the vinyl group are not mutagenic. Three carbamates, diallate, triallate and vegadex, which contain a chloroallyl group similar to the vinyl group of dichlorvos are mutagenic in *Streptomyces*; triallate and vegadex are powerful mutagens also in *Salmonella* (strain TAI 535); two other carbamates devoid of the chlorinated group are not mutagenic. The results suggest that the presence of a vinyl chloride or allyl chloride group in the molecule of these pesticides is responsible for the ability to induce point mutations in *Salmonella* and *Streptomyces*. (Author abstract) (27 Refs)

V. EPIDEMIOLOGICAL ASSOCIATIONS OF VINYL CHLORIDE AND RELATED COMPOUNDS WITH HUMAN CANCERS

The reader may also find the following abstracts of interest: 236, 256, 290, 300

201. ANGIOSARCOMA OF THE LIVER IN VINYL CHLORIDE/POLYVINYL CHLORIDE WORKERS: 1977 UPDATE OF THE NIOSH REGISTER.

Spirtas R, Kaminski R

Illness Effects Section, SB/DSHEFS/NIOSH, Robert A. Taft Labs., 4676 Columbia Parkway, Cincinnati, OH, 45226

J Occup Med; 20(6):427-429 1978

Data on 64 cases of angiosarcoma among vinyl chloride (VC) polymerization workers reported as of October 1977 are summarized. The material comprises 23 US and 41 foreign cases from 11 different countries. The age at diagnosis ranged from 37 to 71 yr, with a median of 49 yr. The latency period ranged from 9 to 38 yr (median of 21 yr), duration of exposure from 4 to 31 yr (median of 18 yr). The data suggest that the reported VC-induced angiosarcoma cases gradually increased over time. The 20-to 30-yr lag between the growth of the industry after World War II and the increase in the number of diagnosed angiosarcomas among VC/polyvinyl chloride (PVC) workers during the 1970's roughly coincides with the median latency period of 21 yr. Recent studies have also found VC to be associated with excesses in brain cancer and neoplasms of the respiratory and lymphatic systems. (6 Refs)

202. MORTALITY EXPERIENCE OF WORKERS IN A VINYL CHLORIDE MONOMER PRODUCTION PLANT.

Bufler PA, Wood S, Eifler C, Suarez L, Kilian DJ

Univ. Texas Sch. Public Health, P. O. Box 20186, Houston, TX, 77025

J Occup Med; 21(3):195-203 1979

A mortality follow-up study was conducted of 464 white men employed in a vinyl chloride monomer (VCM) production plant for at least two consecutive mo between 1948 and 1975. Eight of the 28 deaths in this group were due to malignant neoplasms, 4 from lung cancer. No angiosarcomas or other liver tumors were observed. The eight persons who died of cancer were initially exposed to VCM prior to 1963,

and the four with lung cancer, prior to 1958. Six of the 28 deaths, including 2/8 cancer deaths, occurred among a subgroup of 165 workers exposed to 1,4-dioxane. The total number of observed cancer deaths was not significantly different than that expected, but a significant excess was noted for malignant neoplasms of the respiratory system. The effects of smoking, duration of exposure to VCM, and level of exposure and the combined effect of duration and level of exposure were analyzed separately. A 5 yr latency requirement was maintained for all analyses except for the smoking analysis. Using a minimum latency period of 5 yr from the date of initial exposure to VCM, the excess of respiratory cancer was moderate but not significant for the 314 employees satisfying this criterion. Both a longer duration and a higher level of exposure during the first 5 yr were associated with a significant excess of respiratory cancer. However when duration and level of exposure were combined, the results were not significant. In spite of the discrepancy in the results of dose-response analyses, the results suggest that a relationship exists between exposure to VCM and respiratory cancer. (27 Refs)

203. MEDICAL SURVEILLANCE SYSTEM FOR NEOPLASTIC AND NON-NEOPLASTIC OCCUPATIONAL INJURIES DUE TO INDUSTRIAL CHEMICALS (MEETING ABSTRACT).

Tamburro CH, Creech JL, Greenberg RA, Makk L, Whelan JG

Cancer Center, Div. Digestive Diseases and Nutrition, Univ. Louisville, Sch. Medicine, Louisville, KY

Clin Res; 27(2):285A 1979

Following the discovery of a rare liver cancer (angiosarcoma) among vinyl chloride polymerization workers in 1974, a prospective medical surveillance program was designed for the early subclinical detection of occupational injuries, including neoplasia. This prototype program involved the active cooperation of a local hospital, a regional university cancer center, the plant workers, labor leaders, management and regulatory agencies. In the first 4 yr of operation, this program identified an increased incidence of hepatic angiosarcoma among vinyl chloride workers, as well as an increased occurrence of such non-neoplastic, and possibly pre-malignant, lesions as peliosis hepatis, portal fibrosis, portal hypertension, splenomegaly and mid-zonal pleural fibrous thickening of lung. A systematic multi-disciplinary evaluation system was developed to determine if the diseases and disorders detected could be related to occupational chemical exposure. This program identified the job-related nature of hepatic angiosarcoma and its causative agent from among 22 different chemicals via individual chemical exposure histories based on a retrospective rank-order system for the various job classifications. This medical health surveillance system can be applied in any industry effectively without significant interference in workers' life or industrial function, at a cost effective level (av cost less than 5,000 dollars/yr/1000 workers provided that all participating parties actively cooperate. (no Refs)

204. PRIMARY LIVER CANCER DETECTION IN VINYL CHLORIDE WORKERS (MEETING ABSTRACT). (PP. 425-426)

Whelan JG, Creech J, Tamburro CH

Digest Dis and Nutri Sect and Cancer Ctr, Univ Louisville, Sch Med, Louisville, KY 40201

Third International Symposium On Detection And Prevention Of Cancer. 1976.

The recent discovery of hepatic angiosarcoma in vinyl chloride polymerization workers led to a medical screening program which utilized radioisotopic scanning as a primary

screening procedure among asymptomatic workers. Nine hundred employees underwent medical examination, biochemical blood studies and ^{99m}Tc hepatic scanning. Sixty-six of these employees had hepatic angiographic studies and hepatic biopsy. Thirty-five were studied because of pathological abnormalities on liver scan and 30 because of biochemical abnormalities with normal scans. Thirty-one percent of those with abnormal liver scans had angiographic lesions. Five had angiosarcoma, 2 of whom had no biochemical abnormalities at the time their scan indicated a lesion present. Four had cirrhosis and 2 peliosis hepatis. Of the 31 employees with normal scan, only 7% (2) had angiographic lesions; both had peliosis hepatis. Within one year, one developed a positive liver scan associated with the progression of his peliosis hepatis and the development of hepatic arterial-portal venous shunts. The majority of those with positive liver scans without angiographic lesions did have significant histological disease including portal fibrosis, granulomatosis and fatty metamorphosis. In contrast, only minor nonspecific histological abnormalities were found in those with normal scans and negative angiographic studies. These data illustrated the effectiveness of the liver scan as a primary screening procedure both by its early detection of hepatic tumors and its low incidence of false positivity (less than 3%) in this cohort of asymptomatic vinyl chloride polymerization workers. In addition, vascular abnormalities such as peliosis hepatis, possibly a pre-malignant lesion, may also be detected in the absence of biochemical abnormalities. (Author Abstract)

205. VINYL CHLORIDE - PART I.

Potter HR

No affiliation given

Food Cosmet Toxicol; 14(4):347-349 1976

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

206. ANGIOSARCOMA OF THE LIVER IN VINYL CHLORIDE/POLYVINYL CHLORIDE WORKERS.

Lloyd JW

Natl. Inst. Occup. Saf. Health, Rockville, Md.

J Occup Med; 17(5):333-334 1975

Review of recent data on cases of liver angiosarcoma illustrated a clustering within recent years. Although the high risk of the disease for polymerization workers had previously gone unnoticed, an exact estimate of the incidence of liver angiosarcoma among the workers could not yet be determined, pending exposed-to-risk figures. Approximately 5,600 men are currently employed in 36 U.S. facilities, with 15 cases of liver angiosarcoma reported to date. Greater than 70% of the cases were initially employed in polymerization work more than 20 yr ago, setting an average latent period of 19 yr. The age at diagnosis of angiosarcoma among both vinyl chloride workers and polymerization workers was considerably lower than that of the general population, suggesting the possibility of a common etiology. Preliminary

findings from continuing epidemiologic investigations indicated that polymerization workers may also be at high risk for other malignant neoplasms, particularly of the brain. It remains to be determined whether exposure to lower levels of vinyl chloride also represents excessive risk for liver angiosarcoma or other malignancies.

207. EPIDEMIOLOGICAL STUDIES OF VINYL CHLORIDE HEALTH EFFECTS IN THE UNITED STATES (MEETING ABSTRACT).

Falk H, Waxweiler RJ

Center for Disease Control, United States Public Health Service, Dept. Health, Education, and Welfare, Atlanta, GA 30333

Proc R Soc Med; 69(4):303-305 1976

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

208. VINYL CHLORIDE EXPOSURE IN A CONTROLLED INDUSTRIAL ENVIRONMENT: A LONG-TERM MORTALITY EXPERIENCE IN 594 EMPLOYEES

Ott MG, Langner RR, Holder BB

Dow Chemical Co., Corporate Medical Dept., 2030 Dow Center, Midland, Mich. 48640

Arch Environ Health; 30(7):333-339 1975

The relation between tumor incidence and the highest levels of vinyl chloride exposure was examined. Measurements of the work environment began in 1950 by collecting breathing zone samples on silica gel and measuring chlorides by the Volhard method to calculate vinyl chloride. More recently, a combination of gas chromatography and mass spectrometry has been used to identify airborne material. The study population included production employees who worked between 1942 and 1960 in areas of potential vinyl chloride exposure. Each job was classified according to time-weighted average (TWA) concentration of vinyl chloride for an eight-hr day. The high level concentration was defined as over 200 ppm vinyl chloride, and the low level was below 25 ppm. Observed deaths among vinyl chloride workers were 91% of the expected deaths based on the U.S. white male population. Distribution of malignant neoplasms suggests a possible dose-response relationship, since nine of 13 malignancies were observed in the high exposure group. The Chi 2 comparison of the distribution of malignancy deaths between high and all other exposure groups was significant (P is less than 0.01). No adverse malignancy effects are demonstrated in the lower exposure categories.

209. MORTALITY EXPERIENCE OF A COHORT OF VINYL CHLORIDE-POLYVINYL CHLORIDE WORKERS.

Nicholson WJ, Hammond EC, Seidman H, Selikoff IJ

Mt. Sinai Sch. Med., City Univ. New York, N.Y.

Ann NY Acad Sci; 246:225-230 1975

The medical histories and current health status were obtained from 255 of 257 Goodyear Tire and Rubber Company employees who had been exposed to polyvinyl chloride (PVC) and vinyl chloride (VC) for a minimum of five

yr subsequent to 1946. Observation began ten yr after the onset of exposure. The individuals worked in PVC production majority, maintenance, shipping, and in the laboratory. These workers may often have been exposed to peak VC concentrations exceeding 1,000 ppm. Over 50% of the employees were under age 37 as they entered the cohort. Twenty-four individuals were deceased and three of these deaths were due to liver hemangiosarcoma. One glioblastoma, two lymphomas, and one liver cirrhosis with associated bleeding esophageal varices accounted for other deaths. All of these conditions appear to be associated with VC. The three hemangiosarcomas occurred in individuals exposed prior to 1951. Longer periods of observation are thus needed to study the full spectrum of VC-induced malignancies and their incidence among exposed workers.

210. MORTALITY STUDY OF WORKERS IN THE MANUFACTURE OF VINYL CHLORIDE AND ITS POLYMERS.

Tabershaw IR, Gaffey WR

Tabershaw-Cooper Assoc., Ins., Rockville, Md.

J Occup Med; 16(8):509-518 1974

This study of 8384 men who had at least one yr of occupational exposure to vinyl chloride before December 31, 1972, demonstrates that cancers of the digestive system (primarily angiosarcoma), respiratory system, brain, and cancers of unknown site, as well as lymphomas, occurred more often than expected in those members of the study population with the greatest estimated exposure. The mortality from other cancers was lower than that of the general male population with the exception of cancer of the buccal cavity and pharynx. There was an excess of these cancers, which however was inversely related to estimated exposure. No explanation has been found for the latter finding. The other major findings of the study are: 1) the overall mortality of the study population was approximately 75% of what would be expected in a comparable population of U. S. males; 2) no cause of death showed a statistically significant excess over what would be expected in a comparable U. S. male population; and 3) no deaths identified as angiosarcoma of the liver were found other than those previously identified. This is the first epidemiological study suggesting that vinyl chloride may also be associated with human cancer of multiple sites.

211. PROPORTIONAL MORTALITY AMONG VINYL-CHLORIDE WORKERS.

Monson RR, Peters JM, Johnson MN

Harvard Sch. Public Hlth, Boston, Mass.

Lancet; 11(7877):397-398 1974

In a proportional-mortality analysis of 161 deceased workers in two plants using vinyl chloride, a 50% excess of deaths due to all cancer was seen. Specific sites of cancer with the greatest excess included liver and biliary tract, lung, and brain. The excess in fatal cancer was seen mainly in men who died before age 60. Also, there was a trend in time in the ratio of observed to expected deaths: since 1970 the expectancy of deaths from cancer has more than doubled.

212. HEPATIC DISEASE AMONG WORKERS AT A VINYL CHLORIDE POLYMERIZATION PLANT.

Falk H, Creech JL, Heath W, Johnson MN, Key MM

Center Disease Control, Atlanta, Ga.

JAMA; 230(1):59-63 1974

Eleven cases of hepatic disease, including seven cases of hepatic angiosarcoma, have been identified to date among men employed at one vinyl chloride polymerization plant in Louisville. The earliest diagnosis was made in April 1964. The two most recent cases, both angiosarcoma, were diagnosed in February 1974 as a result of systematic medical screening for liver abnormalities among workers at the plant. Ages at

diagnosis have ranged from 36 to 58 yr for the seven patients with angiosarcoma and from 28 to 56 yr for the four patients with nonmalignant disease; durations of employment before diagnosis have ranged from 12 to 28 yr (average 18.0) and from 5 to 29 yr (average 20.6). All 11 persons had worked in close and continuous contact with various phases of the vinyl chloride polymerization process. Review of pathologic material suggests the presence in both tumor and nontumor cases of portal fibrosis and atypical sinusoidal lining cells. A direct causal relationship between exposure to vinyl chloride monomer and pathologic findings is postulated.

213. TEN CASES OF ANGIOSARCOMA OF THE LIVER IN SHAWINIGAN, QUEBEC.

Delorme F, Theriault G

Dept. Pathology, Centre Hospitalier Regionale de la

Maurice, Shawinigan, Quebec, Canada

J Occup Med; 20(5):338-340 1978

Of the 10 cases of angiosarcoma of the liver diagnosed in Shawinigan, Quebec, since 1955, all occurred in men who worked in a vinyl chloride (VC) polymerizing plant. All 10 men were very light drinkers, and only 4 smoked one or more packs of cigarettes per day. The time between the first exposure of VC monomer and the diagnosis of angiosarcoma ranged from 11 to 29 yr, with an av of 20.5 yr. Exposure to VC monomer in the plant, although not documented, is believed to have been very high in the past. The benign liver lesions found in these workers included portal and perisinusoidal fibrosis. (15 Refs)

214. MORTALITY EXPERIENCE OF WORKERS EXPOSED TO VINYL CHLORIDE MONOMER IN THE MANUFACTURE OF POLYVINYL CHLORIDE IN GREAT BRITAIN.

Fox AJ, Collier PF

Office Population Censuses and Surveys, St. Catherine's

House, 10 Kingsway, London WC2B 6Jp, England

Br J Ind Med; 34(1):1-10 1977

The mortality incidence in 7,717 workers in the vinyl chloride industry in Great Britain was investigated. Approx 99% of these workers were traced; 12% had been exposed to constant high levels, but only 34 men had been exposed to constant high levels for greater than 20 yr because of the newness of the industry. The standard mortality ratio was below that expected. Four cases of liver cancer were found, one primary cancer (vs 0.71 expected), and three other liver cancers (vs 0.93 expected). Two were angiosarcomas, and the other two were carcinomas. The two workers with angiosarcoma died 8 and 21 yr after initiation of exposure to high concentrations. Other cancers vs their expected incidences were as follows: stomach 14 vs 15.33; lung, 46 vs 51.23; brain, 2 vs 3.66; and lymphatic and hematopoietic tissues, 9 vs 9.01. The observed death rate from all cancers was 115 compared to an expected 126.77; there is no evidence that cancer at sites other than the liver was associated with exposure to vinyl chloride. Conclusions drawn from this survey must be tempered by the reservation that the full impact of the problem may not yet be in evidence. (18 Refs)

215. ANGIOSARCOMA OF THE LIVER: AN EPIDEMIOLOGIC SURVEY.

Brady J, Liberatore F, Harper P, Greenwald P, Burnett W,

Davies JN, Bishop M, Polan A, Vianna N

Bureau Occupational Health and Chronic Disease Res.,

New York State Dept. Health, Empire State Plaza, Tower

Building, Albany, NY 12237

J Natl Cancer Inst; 59(5):1383-1385 1977

An epidemiology survey of angiosarcoma of the liver (ASL) revealed that the annual incidence rate (cases diagnosed

1970 through 1975) among residents of New York State (excluding New York City) was 0.25 per million. A case-control study of 26 patients indicated that direct exposure to arsenic, vinyl chloride (VC), and thorium dioxide was a significantly important factor in the etiology of ASL (p less than 0.02). Seven patients had documented exposure to these chemicals, but, 19 did not. The fact that 5/19 lived nearer to VC fabrication or polymerization plants than did their matched controls indicated that indirect modes of exposure, not specifically related to occupation, might be an important factor in the etiology of ASL. The possibility that other toxic substances (chlorinated hydrocarbons) may cause ASL was also mentioned. (17 Refs)

216. MORTALITY AMONG EMPLOYEES OF PVC FABRICATORS.

Chiazze L, Nichols WE, Wong O
Div. Biostatistics and Epidemiology, Dept. Community
Medicine and International Health, Georgetown Univ.
Sch. Medicine, Washington, DC 20007
J Occup Med; 19(9):623-628 1977

A cross-sectional mortality study was conducted to identify any angiosarcoma deaths among 4,341 deaths that occurred during 1964-1973 among current or former employees of 17 companies engaged in polyvinyl chloride fabrication. No angiosarcoma deaths were found among the study population. In addition, distributions by cause of death among white male and female employees were compared with those for the entire population of the US, specific for color and sex and adjusted for age by Proportionate Mortality Ratios. Important excesses in total cancer were found among white employees. They appeared to be concentrated in cancers of the digestive system, particularly, cancers of the intestine. In addition, mortality from breast and urinary cancer among white female employees was high. Results suggest the need for continued investigation. (9 Refs)

217. MORTALITY AND CANCER MORBIDITY IN A GROUP OF SWEDISH VCM AND PVC PRODUCTION WORKERS.

Byren D, Engholm G, Englund A, Westerholm P
Kema Nord, 85013 Sundsvall, Sweden
Environ Health Perspect; 17:167-170 1976

Mortality and cancer morbidity data are presented from studies of 750 workers employed in a Swedish vinyl chloride (VC)/poly(vinyl chloride) plant since 1940. Observed/expected deaths from various causes were: 2/0.33 (brain cancer), 3/1.78 (lung cancer), 4/0.97 (cancer of liver/pancreas, including 2 angiosarcomas of the liver), 28/18.26 (total circulatory disease), 6/3.02 (cerebrovascular disease), 15/9.15 (myocardial infarction), and 5/1.48 (cerebral hemorrhage). Observed/expected morbidities were: 3/1.30 (lung cancer) and 2/0.48 (cancer of liver/pancreas). The excess of cancers of the liver/pancreas increased with latency time (time between first employment and end of follow-up). The possible etiology of the cardiovascular deaths is discussed. (7 Refs)

218. THE CARCINOGENIC PROPERTIES OF VINYL CHLORIDE.

de Engelse L, Emmelot P
Netherlands Cancer Inst., Amsterdam
Chem Weekbl; 70(28/29):5 1974

Recent studies on the carcinogenicity of vinyl chloride and related legislation are reviewed in the light of the significantly increased incidence of angiosarcoma of the liver in workers exposed to this compound in the air of polyvinyl chloride (PVC) plants. A total of 19 cases of angiosarcoma of the liver have thus far been detected in workers exposed to vinyl chloride. Angiosarcoma of the liver and other tumors

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

219. CASE STUDY OF VINYL CHLORIDE AS A CARCINOGEN.

Kobayashi Y
Engineering Faculty, Yokohama Natl. Univ., Yokohama,
Japan
J Jpn Soc Saf Eng; 15(2):101-104 1976

Cases of hepatic angiosarcoma associated with vinyl chloride monomer (VCM) and various facets of the VCM problem are summarized. VCM production in Japan began in the 1950's, and, in the United States, in the 1930's. In Japan, since 1975, recommended VCM concentrations in the factory atmosphere range from 2 to 5 ppm, and provisions have been made for adequate ventilation. Governmental surveys of 10 representative Japanese factories from 1974 to 1975 showed that 97.3% of the work areas had atmospheric VCM concentrations of less than 3 ppm. Other factories had atmospheric VCM concentrations greater than 5-10 ppm. One case of hepatic angiosarcoma was recently reported among retired Japanese factory workers. According to the National Institute of Occupational Safety and Health (NIOSH, United States), 38 cases of hepatic angiosarcoma worldwide (United States, Canada, Europe) occurred since 1975 among workers exposed to VCM from 4 to 30 yr.

220. HAZARDS ASSOCIATED WITH EXPOSURE TO VINYL CHLORIDE AND POLYVINYL CHLORIDE MATERIALS.

Diubankova EN, Bykhovskii AV
F. F. Erisman Res. Inst. Hygiene, Moscow, USSR
Gig Sanit; (1):69-74 1979

Current data on the hazards of vinyl chloride (VC), in general, and of the use of polyvinyl chloride packages, in particular, are reviewed. Seventeen cases of liver angiosarcoma have been reported in workers in the VC industry (compared with the total 45 cases reported in the world literature). In addition to liver angiosarcomas, the workers had an increased incidence of cancer of the respiratory, CNS, lymph, and hematopoietic systems. The long-term storage of alcohol in PVC bottles showed distinct organoleptic changes in the alcohol that prompted a ban on the use of PVC containers for food products containing alcohol. (26 Refs)

221. TEN CASES OF ANGIOSARCOMA OF THE LIVER IN VINYL CHLORIDE WORKERS IN CANADA.

Delorme F
Centre Hospitalier Regional de la Mauricie, C.P. 1130,
Shawinigan-Sud, Quebec, Canada
Ann Anat Pathol (Paris); 23(2):97-104 1978

Ten cases of hepatic angiosarcoma were found among employees of a vinyl chloride plant in Shawinigan, Canada. All patients had been exposed to vinyl chloride vapors. The average age of the patients was 50 yr (41-61 yr); the length of occupational exposure to vinyl chloride averaged 16 yr 10 mo (ranging from 5 yr, 8 mo to 26 yr); and the time lapse between first exposure and diagnosis was 20.5 yr (11-18 yr). Survival after diagnosis averaged 4.4 mo (1-8 mo). The risk of hepatic

angiosarcoma appears to be highest among vat cleaners, pipe fitters, and polymerization workers. (16 Refs)

222. VINYL CHLORIDE: EPIDEMIOLOGICAL STUDIES AND PREVENTIVE MEASURES.

Owen R

London, England

Adv Tumor Prev Detect Charact; 3:238-241 1976

Epidemiological studies are being made to assess the effects of occupational exposure to vinyl chloride in Great Britain. Cancer and mortality rates of 6,000-8,000 past and present workers in five polyvinyl chloride plants are being related to vinyl chloride exposure in terms of time and concentration. A retrospective study of cases of angiosarcoma of the liver is underway to evaluate the association between this disease and occupation. The medical and social histories of these cases are also being compiled. The United Kingdom has lowered its interim standards for vinyl chloride exposure to a ceiling value of 30 ppm and a time-weighted average of 10 ppm.

223. CANCER RISK AMONG WORKERS EXPOSED TO CHLOROPRENE.

Lloyd JW

Natl. Inst. Occupational Safety and Health, Public Health Service Center Occupational Safety and Health, Rockville, MD 20852

Ann NY Acad Sci; 271:91-93 1976

The limited information on the potential carcinogenicity of chloroprene is discussed, along with some recently initiated assessments of this carcinogenicity. Chloroprene is used primarily as a monomer for the manufacture of neoprene synthetic rubber (introduced by duPont in 1931). No excess of any disease related to vinyl chloride, including angiosarcoma of the liver, has been observed at duPont upon investigation of employees' records. Although a recent increase in deaths from lung cancer in this population was observed, further investigation revealed no relationship to work assignment. Two studies of approx 45,000 chloroprene workers in Russia are also discussed with respect to the development of lung and skin cancer in these individuals. (2 Refs)

224. LUNG CANCER INCIDENCE AMONG CHLOROPRENE HANDLING WORKERS.

Khachatryan EA

Fifth Clin. Hosp., USSR

Vopr Onkol; 18(6):85-86 1972

A study of 2934 chloroprene-handling workers (working over 25 years) revealed 34 patients (1.24%) with lung cancer. The average age of these patients was 44.5 years and the average length of their service was 8.7 years. In the first control group of 4780 workers including chauffeurs, furniture makers, firemen, benzene storehouse workers, and house painters, there were 22 patients with lung cancer (0.46%). In the second group of 6045 workers including electricians, carpenters, electric welders, tinsmiths, and furnace workers, 11 had lung cancer (0.8%). There were only four patients with lung cancer (0.0064%) among 6220 office workers. Sixteen patients with lung cancer were found among the factory workers studied (number not given). Thus, the workers in contact with chloroprene showed a high incidence of lung cancer as compared with other occupational groups. Of the total 87 patients with lung cancer, 66 (75.8%) had chronic bronchitis, 3 (3.4%) tuberculosis, 1 (1.1%) bronchial asthma, and 4 (3.4%) pneumonia.

225. MORTALITY OF WORKERS EXPOSED TO CHLOROPRENE.

Pell S

Medical Div., E.I. du Pont de Nemours and Co.,
Wilmington, DE, 19898

J Occup Med; 20(1):21-29 1978

A study was undertaken to determine whether exposure to chloroprene increases the risk of lung cancer. Data were obtained from historical prospective mortality studies of two cohorts, one consisting of 270 men first exposed between 1931 and 1948, and the other of 1,576 men first exposed between 1942 and 1957. The number of lung cancer deaths in each cohort (3 in the first and 16 in the second) were about the same as expected. Among maintenance mechanics in the second cohort, there were eight lung cancer cases (4 living and 4 dead). A crude morbidity analysis suggested that this group may have had an excess incidence of lung cancer. However, the absence of excess lung cancer mortality in other high exposure occupational groups indicates that chloroprene exposure does not increase the risk of lung cancer. (Author abstract)

226. CHLOROPRENE: OBSERVATIONS OF CARCINOGENESIS AND MUTAGENESIS. (PP. 205-217)

Infante PF, Wagoner JK, Young RJ

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Incidence of Cancer in Humans, Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation. Vol. 4, Hiatt HH, Watson JD, Winsten JA, ed. Cold Spring Harbor, Cold Spring Harbor Laboratory, Origins of Human Cancer., 602 pp., 1977.

Observations of excessive lung and skin cancer associated with chloroprene production were reported in the Russian literature in 1972. However, it was not until 1974, when an epidemic of liver, brain, and lung cancer among vinyl chloride (VC) polymerization workers was identified, was attention in the US focused on the carcinogenic potential of chloroprene. Chloroprene is mutagenic in bacteria, causes recessive lethality in *Drosophila*, causes dominant lethality and chromosome aberrations in rat bone marrow cells, and has been associated with sterility in mice and rats. A significant excess of chromosome aberrations and a reduction in the numbers and motility of sperm have been reported in chloroprene workers, and a threefold excess of miscarriages has been reported among their wives. In the absence of adequate data, a final evaluation of the carcinogenicity of chloroprene cannot be made. However, given its other effects, the possible carcinogenicity of chloroprene may be only of academic interest from a public health point of view. The data for VC and chloroprene may serve as the basis for a more aggressive role by genetic toxicologists in the assay of industrial chemicals. (35 Refs)

227. A COHORT STUDY ON TRICHLOROETHYLENE EXPOSURE AND CANCER MORTALITY.

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Molina G, De Verdier A

Dept. Occupational Medicine, Regional Hosp., 701 85
Orebro, Sweden

J Occup Med; 20(3):194-196 1978

A cohort of 518 Swedish men exposed to trichloroethylene (TCE) was studied with respect to cancer mortality. The men were divided into high- and low-exposure categories as estimated by the av trichloroacetic acid level in the urine: those with levels greater than 100 mg/liter were in the high exposure group, and those with levels less than 100 mg/liter were in the low-exposure group. Requiring 10 yr of

latency time after the date of first employment (assumed to correspond to the time of first exposure) resulted in 3,643 person-yr of observation. Subdividing the cohort with regard to 10 yr of latency time as to high-/and low-exposure categories resulted in 548 and 3,095 person-yr of observation, respectively. There was a close agreement between expected and observed number of cancer cases in both the high-/and low-exposure groups. No particular type of cancer was overrepresented, although there were two leukemias and two stomach cancers. Both the leukemia and stomach cancer cases were in the low-exposure category. It seems justified to consider TCE as a possible human carcinogen, but one that is not more potent than many other industrial compounds. There is probably no serious hazard at low exposures. (21 Refs)

228. MORTALITY AMONG LAUNDRY AND DRY CLEANING WORKERS (MEETING ABSTRACT).

Blair A, Decoufle P, Grauman D

Environmental Epidemiology Branch, NCI, Bethesda, MD, 20014

Am J Epidemiol; 108(3):238 1978

The possible carcinogenicity of tetrachloroethylene, the predominant dry cleaning fluid used today, led the authors to conduct a preliminary analysis of the causes of death for 315 laundry and dry cleaning workers, identified from union records, in order to determine if this group experienced unusual site-specific mortality. A proportionate mortality ratio (PMR) was calculated using the observed number of deaths in the study group and an expected number derived from the general US population. Statistically significant excesses occurred for all malignant neoplasms (PMR = 1.32) and in particular cancers of the liver (ICD 156) (PMR = 6.08), lung (PMR = 1.81), and leukemia among whites (PMR = 4.20). In addition, non-significant deviations occurred for cancers of the digestive system (PMR = 1.40), breast (PMR = 0.71) and cervix (PMR = 1.98) among females. The excess of cancer of the cervix and deficit of breast cancer among females is consistent with other data for women of a similar socioeconomic level. The increase in the relative frequency of liver cancer and leukemia is particularly intriguing in light of the report by the NCI Carcinogen Bioassay Program of an excess of hepatocellular carcinoma in mice exposed to tetrachloroethylene and a clinical report of five cases of chronic lymphocytic leukemia in a family operating a dry cleaning business. A cohort mortality study is underway to further elucidate the potential risks faced by this group. (no Refs)

229. CARCINOGENS IN DRINKING WATER.

Miller RW

NCI, NIH, Bethesda, MD 20014

Pediatrics; 57(4):462-464 1976

Asbestos, the carcinogenic qualities of which when inhaled are considered the result of its physical properties, has been found in high concentrations in drinking water. On the other hand, animal studies have indicated that when asbestos is ingested, it is not carcinogenic. Human occupational exposure to asbestos, however, is associated with increased frequencies of gastrointestinal cancer, presumably from the swallowing of the compound. The high cancer mortality of whites in New Orleans is reported to be due to the presence of carcinogens in the water, despite the facts that the high cancer incidence is primarily in the lungs, women are less affected than men, and different communities with the same water supply show different effects. Vinylchlorides, pesticides, and polycyclic hydrocarbons are considered the most harmful. Chlorination leads to the formation of four carcinogens (chloroform, bromoform, bromodichloromethane, and dichloromethane). Chloroform is considered potentially the most dangerous, although no human correlations have been

found. The fetus and child may be more susceptible than adults to these carcinogens. No basis for recommending changes in water supply exists.

230. HEALTH EFFECTS OF VINYL CHLORIDE.

Tamburro CH

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Tex Rep Biol Med; 37:126-144 1978

The health effects of vinyl chloride (VC) are reviewed, and a medical surveillance system for detecting and following its effects is described. An early finding in exposed human and animals is activation of morphological changes in the sinusoidal lining cells of the liver without evidence of hepatocellular toxicity. With progressive exposure to VC there is an increase in atypia of the sinusoidal lining cells, progressive worsening of the focal sinusoidal dilatation, and malignant transformation of the sinusoidal lining cells. Most data suggest that it is the endothelial lining cell that becomes malignant and forms the angiosarcoma. Peliosis hepatis is often seen in nontumorous portions of the liver; whether this is a precarcinogenic or preangiosarcomatous lesion in VC workers is under study. Preliminary epidemiological and histological data suggest that the frequency of lung cancer is increased among VC workers. Two cases are reported in which the duration and degree of exposure to VC were almost identical, yet one man developed primary hepatocellular carcinoma and the other angiosarcoma. The man in whom hepatocellular carcinoma developed had a history of extensive alcohol consumption, which may have played a role in the inability of the hepatocytes to detoxify VC metabolites. A prospective medical surveillance system has been designed based on classification of industrial environments into three categories according to the level of possible carcinogens. (10 Refs)

231. ASSOCIATIONS OF CANCER MORTALITY WITH HALOMETHANES IN DRINKING WATER.

Cantor KP, Hoover R, Mason TJ, McCabe LJ

Health Effects Res. Lab., U.S. Environmental Protection Agency, Cincinnati, OH, 45268

J Natl Cancer Inst; 61(4):979-985 1978

Age-standardized cancer mortality rates by site and sex for whites in 76 US counties were compared with levels of chloroform, bromine-containing trihalomethane(s) (BTHM), and total trihalomethane(s) (THM) in the drinking water. The 76 counties are greater than 50% urban, and over half the population is served by a sampled water supply. Using several demographic, socioeconomic, and industrial variables, a predicted mortality rate was computed and compared with the actual rate. The resulting residual mortality rate for each county was compared with the level of one of the three THM indicators by use of the bivariate correlation coefficient. Counties were grouped according to the overall percentage of the county served by the sampled water supply (low, intermediate, or high) and by geographic location. Bladder cancer residual mortality in both sexes showed a strong correlation with BTHM. This correlation persisted in spite of controls for social class, ethnic group, urban vs rural residence, presence of specific high-risk industries, and lung cancer rates (possible surrogate for levels of cigarette smoking). Brain cancer was also correlated in both sexes, but the associations were not as strong, and there was regional variation. Other sites that gave indications of an association were: CHCl₃ levels and male kidney cancer, BTHM and female lung cancer, and THM levels and non-Hodgkin's lymphoma in men. Stomach cancer in women showed a negative correlation. (23 Refs)

VI. CLINICAL AND BIOLOGICAL EFFECTS OF OCCUPATIONAL EXPOSURE TO VINYL CHLORIDE AND RELATED COMPOUNDS

A. Morphological Changes in Humans Exposed to Vinyl Chloride and Related Compounds

232. MORPHOLOGICAL CHANGES OF THE LIVER AFTER CHRONIC VINYL CHLORIDE INTOXICATION.

Muller R, Bechtelsheimer H, Gedigk P, Marsteller HJ, Lelbach WK

Pathologisches Institut der Universitat, D-5300 Bonn-Venusberg, West Germany

Leber Magen Darm; 5(5):204-208 1975

The liver histopathology of 50 workers exposed to vinyl chloride was examined from biopsy material. Three of the probands presented with polycentric hemangioendothelial sarcoma extending along the ectatic sinusoids into the parenchyma. In border areas a transition between proliferating atypical sinusoid cells and tumor cells was apparent, typical of the angiosarcomas reported after chronic arsenic and thorium dioxide exposure. Septal fibrosis of the portal fields and collagenization of sinusoid walls, chainlike proliferation of sinusoid endothelial cells with nuclear polymorphism, hepatocytic hyperplasia with nuclear polyploidy, and focal adaptation of the hepatocytic cytoplasm (with hyperplasia of the smooth endoplasmic reticulum) to hydropic swelling, fat vacuolization, and cell necrosis were signs of generalized hepatotoxicity. Hepatocytic hyperplasia was most pronounced in the areas of the reactive sinusoid endothelium and at tumor interfaces.

233. HISTOPATHOLOGY OF LIVER LESIONS ASSOCIATED WITH EXPOSURE TO VINYL CHLORIDE MONOMER (MEETING ABSTRACT).

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Proc R Soc Med; 69(4):299-303 1976

An outline of the cell characteristics of angiosarcoma of the liver and changes that have occurred, with and without tumor development, in patients exposed to vinyl chloride monomer are presented. The tumors appear as dark hemorrhagic nodules with distortion and fibrosis in the intervening tissue; frank necrosis is often present. There are three types of involvement: the sinusoidal pattern, the papillary type, and the cavernous type. The cells are usually associated with vessel walls and vascular spaces. Near the tumor and sometimes in the absence of tumors, perisinusoidal reticular fibers are prominent and fibrosis in the portal tracts is often reported. Subcapsular fibrosis may also occur. The relevance of these nontumorous changes to the subsequent development of angiosarcoma is unknown at this time.

234. ULTRASTRUCTURE OF LIVER DAMAGE IN CHRONIC VINYL CHLORIDE INTOXICATION.

Schattenberg PJ, Totovic V, Gedigk P, Marsteller HJ

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2120, D-5300 Bonn, Bundesrepublik Deutschland

Virchow Arch Pathol Anat Histol; 373(3):233-247 1977

Liver biopsies taken from 15 workers at a PVC-producing factory were examined by electron microscopy. The hepatocytes showed focal hydropic swelling, disseminated toxic steatosis, peculiar para-crystalline inclusions in enlarged mitochondria, focal cytoplasmic degradations, and occasional single cell necroses. These regressive changes were more prominent in cases with a shorter interval of non-exposure

prior to the biopsy. Further, a focal compensatory hyperplasia of the smooth endoplasmic reticulum was found. With increase of the non-exposure time interval, a regression of the degree of steatosis as well as an age-independent excessive lipofuscin deposition was seen in the hepatocytes. Apparently, these are sequelae of increased autophagia of lipids and increased lipid oxidation by the vinylchloride. In the sinusoids, activation, enlargement and proliferation of Kupffer cells were noted. The tendency of these cells to proliferate is apparently caused by the cancerogenic stimulation by vinylchloride. The prominent hyperplasia of lipocytes is probably connected with the deposition of collagen and the peculiar perisinusoidal fibrosis. (28 Refs) (Author Abstract)

235. CLINICAL AND MORPHOLOGIC FEATURES OF HEPATIC ANGIOSARCOMA IN VINYL CHLORIDE WORKERS.

Makk L, Delmore F, Creech JL, Ogden LL, Fadell EH, Songster CL, Clanton J, Johnson MN, Christopherson WM

Department of Clinical and Anatomical Pathology, St. Anthony Hospital, Louisville, Ky 40204

Cancer Suppl; 37(1):149-163 1976

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.

236. DEVELOPMENT OF HEPATIC ANGIOSARCOMA IN MAN INDUCED BY VINYL CHLORIDE, THOROTRAST, AND ARSENIC. COMPARISON WITH CASES OF UNKNOWN ETIOLOGY.

Popper H, Thomas LB, Telles NC, Falk H, Selikoff IJ

Stratton Lab. Liver Disease, Mount Sinai Sch. Medicine,

City Univ. New York, New York, NY

Am J Pathol; 92(2):349-376 1978

Human hepatic angiosarcomas that occurred following exposure to vinyl chloride, Thorotrast, or arsenic (medicinal and industrial) and cases, including those in children, of unknown etiology were studied to establish diagnostic criteria and evolutionary features. The uniform evolution suggests that there is also an environmental factor in the cases of unknown etiology. The precursor stage is characterized by areas of combined hyperplasia of hepatocytes and a variety of sinusoidal and perisinusoidal cells associated with an excess of

reticulin and with sinusoidal dilatation. Silver stainings indicated reticulum formation by the perisinusoidal cells, presumably the lipocytes. The hepatocytic proliferation suggested a hepatocarcinogenic, but usually not fully expressed, potential. The mixed hyperplasia of the various sinusoidal cells proceeded to an overgrowth of angiosarcoma cells, presumably derived from endothelial cells. In early stages they were usually in contact with hepatocyte (intralobular growth). A trabecular arrangement resulted from loosening of the lobular plate arrangement by dilatation of sinusoids, leading to primary peliosis. With disappearance of the hepatocytes, various growth patterns developed, terminating in nodular, solid angiosarcoma composed of either spindle-shaped or polyhedral cells that underwent necrosis or hemorrhage (secondary peliosis). The interaction between hepatocytes and sinusoidal cells requires elucidation. (110 Refs)

237. HEPATIC ANGIOSARCOMA IN WORKERS FOLLOWING CHRONIC EXPOSURE TO VINYL CHLORIDE. MORPHOLOGICAL DESCRIPTION OF THE LESIONS.

Delorme F, Makk L

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Shawinigan-Sud, Quebec, Canada

Union Med Can; 104(12):1836-1844 1975

The histological characteristics of liver angiosarcomas (2 metastases) in 18 men (36 to 58 yr; mean age 46.7) who had prolonged exposure to vinyl chloride (4 yr to 27 yr 10 mo; mean time 17 yr 4 mo) are presented. Various benign lesions were noted not only in the angiosarcoma cases but also in noncancerous cases who also had prolonged exposure. Many of the perisinusoidal cells of the angiosarcomas resembled, with their elongated nuclei, the small mesenchymatous cells of the benign tumors. The angiosarcomas had different forms: sinusoidal, sarcomatous, nodulopapillary, and cavernous. These cancers are generally preceded by the appearance of ten benign lesions induced by the vinyl chloride. They appear simultaneously in many places and apparently are multifocal. The numerous nodules are not intraparenchymal metastases from a primary tumor but are themselves primary tumors.

238. ENZYME HISTOCHEMICAL, HISTOMETRICAL AND ULTRASTRUCTURAL STUDIES OF SPLEENS IN VINYLCHLORIDE-DISEASE.

Heusermann U, Stutte HJ

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Abteilung Allgemeine Pathologie und Pathologische

Anatomie, Hospitalstr. 42, D-2300 Kiel, W. Germany

Virchows Arch Pathol Anat; 375(4):303-317 1977

By means of histometric, enzyme histochemical, and electron microscopic investigations it was demonstrated that the pathological changes in the spleen in vinylchloride-disease are primary. Fibroblastic cells are the only specific splenic cells involved. Fiber-associated reticulum cells of the red pulp and fibroblastic reticulum cells in white pulp are stimulated to produce excessive amounts of the extracellular elements of connective tissue, especially collagen fibrils. The newly formed connective tissue causes obliteration of extracellular blood channels in the red pulp and thus a reduction in the number of pulp-cord macrophages, and scarring of the periarterial lymphatic sheaths. The results of this fibrosing process are characteristic quantitative changes in the splenic histologic structures. These changes are different from those structural alterations occurring in spleens following extrasplenic hemodynamic changes, such as thrombosis of the splenic veins or cirrhosis of the liver. (Author abstract) (16 Refs)

239. THE CONDITION OF THE SPLEEN DURING VINYL CHLORIDE DISEASE (MEETING ABSTRACT).

Stutte HJ, Heusermann U

Kiel, W. Germany

Zentralbl Allg Pathol; 122(3):284 1978

Contact with vinyl chloride during the production of various synthetic substances is unavoidable and may lead to severe organ alterations, the most frequently observed being splenomegaly with clinical signs of portal hypertension. Morphological examination indicates that the spleen is the target of fibrotic lesions with characteristic types, location, and dissemination. These parameters allow for successful histological confirmation of a clinically occult splenomegaly and the differentiation of a portal occluded spleen in case of hepatic cirrhosis. The most significant differential diagnostic criteria are presented in tabular form. With respect to these criteria, it is thought that the splenic alterations observed during vinyl chloride disease were not caused by portal hypertension due to vinyl chloride induced hepatic alterations, rather by a direct fibrotic process in the red and white pulp and connective tissue of the spleen induced by vinyl chloride or its metabolites. (no Refs)

240. CAPILLARY ABNORMALITIES IN POLYVINYL CHLORIDE PRODUCTION WORKERS. EXAMINATION BY IN VIVO MICROSCOPY.

Maricq HR, Johnson MN, Whetstone CL, LeRoy EC

Div. Rheumatology Immunology, Dept. Medicine, Medical

Univ. South Carolina, 80 Barre St., Charleston, SC 28401

JAMA; 236(12):1368-1371 1976

To determine whether symptomatic vinyl chloride (VC) workers have finger-skin-capillary abnormalities, whether the abnormalities are similar or different from those in patients with idiopathic scleroderma and Raynaud syndrome, whether microvascular abnormalities are related to the type of VC-associated abnormalities (especially liver), whether microvascular abnormalities are related to the nature and duration of VC exposure, and whether microvascular abnormalities are found in workers not exposed to VC, the hands of 152 VC-exposed workers were examined by wide-field capillary microscopy. Examination revealed scattered scleroderma-like microvascular abnormalities in 21 workers and isolated capillary abnormalities in another 27, as compared with only three isolated abnormalities in 50 manual workers not exposed to VC. Thirteen of 17 VC workers with objective evidence of VC-associated abnormalities (angiosarcoma or fibrosis of liver, acro-osteolysis, or scleroderma-like skin lesions) also had microvascular abnormalities. Since microvascular changes occur more frequently than overt VC-associated pathologic conditions, they may represent an early manifestation of the VC effect. Thus, capillary microscopy may become a useful mass-screening procedure in the early detection and prevention of VC-associated disease.

241. PRECURSOR LESIONS IN EXPOSED POPULATIONS AS INDICATORS OF OCCUPATIONAL CANCER RISK.

Maltoni C

Inst. Oncology and Tumour Centre, Bologna, Italy

Ann NY Acad Sci; 271:444-447 1976

Occupational cancer risk was monitored on two separate occasions by cytological examinations. The first involved three groups of workers who were known or suspected of being at risk for developing pulmonary cancer: chromium industry workers, vinyl chloride-polyvinyl chloride (VC-PVC) industry workers, and workers at different chemical factories not directly involved in the production or use of known carcinogens. The results of sputum cytology showed that the

incidence of abnormal cases was higher than expected among chromium and VC-PVC workers, even when compared to populations of heavy smokers. The second occasion was the cytologic investigation of urinary sediments in a group of Italian dye stuff factory workers exposed to aromatic amines and, therefore, at risk for urinary tract tumors. A high incidence of 1% for Class III cytology and over was obtained. These results indicate both the value and need for cytologic examinations as preventive measures that can be taken to overcome occupational risks of carcinogenesis. (no Refs)

B. Cytogenetic Changes in Humans Exposed to Vinyl Chloride and Related Compounds

242. INDUSTRIAL MONITORING: A CYTOGENETIC APPROACH.

Kilian DJ, Picciano DJ, Jacobson CB
Dept. Industrial Medicine and Biomedical Res., Dow
Chemical U.S.A., Texas Div., Freeport, TX 77541
Ann NY Acad Sci; 269:4-11 1975

The authors describe the use of cytogenetic monitoring to detect changes induced by occupational exposures to chemicals, particularly to vinyl chloride. During a 10-yr period, 43,044 shorthand and conventional karyotypes of 1,689 production workers were studied by chromosome analysis correlated with a standardized medical history. Blood samples were drawn from each individual, slides were prepared, and a metaphase spread was located. The selected cells were photographed, the metaphase spread photographs were evaluated, and anomalous chromosomes were classified and tabulated according to the type of structural aberration. Chromosomes were karyotyped to permit detection of aberrations such as small deletions, translocations, and pericentric inversions. Preliminary data from the cytogenetic analysis of blood samples from 121 vinyl chloride workers were compared with preemployment examination records from 75 individuals who served as controls. The following three differences were seen: vinyl chloride workers showed less chromatid breakage, a greater frequency of dicentric chromosomes, and a lower percentage of abnormal cells than the preemployment comparison group. It is concluded that chromosome analysis is the procedure of choice for objective observation and measurement of possible insults to human genetic material and that the techniques described are the best for the detection of genetic injury at a stage when corrective action can be taken. (8 refs)

243. EXTERNAL CHROMOSOME STUDIES UNDERTAKEN ON PERSONS AND ANIMALS WITH VC ILLNESS (MEETING ABSTRACT).

Fleig I, Thiess AM
Occupational Medicine and Health Protection, BASF,
Aktiengesellschaft, 6700 Ludwigshafen, W. Germany
Mutat Res; 53(2):187 1978

A chromosome analysis was undertaken on lymphocyte cultures taken from 30 workers from various polyvinyl chloride (PVC) factories throughout W. Germany, and of 10 control persons who had been matched according to age. The lymphocyte cultures had been incubated for 72 hr. The exposed workers were divided into two groups: (a) 10 persons with no symptoms of VC illness and (b) 20 persons with VC illness symptoms such as acro-osteolysis, Raynaud syndrome, thrombocytopenia, liver function disturbances, etc. One hundred cells per individuals were scored for gaps, breaks, fragments, dicentrics, rings, chromatid and chromosome

translocations, and deletions. Only in the proband group showing symptoms of the VC illness, inclusive as well as exclusive gaps, could a significant increase in the rate of aberrations be seen, in comparison to the control group. At the same time tests were made on the bone marrow of Chinese hamsters. The animals had been previously treated with 2,500 and 5,000 ppm VC respectively taken in by inhalation and then with doses of 600 mg/kg body wt and 300 mg/kg respectively given by ip injection. Both tests showed that the frequency of structural anomalies inclusive and exclusive gaps in the bone marrow cells was significantly higher in comparison to the control group. (no Refs)

244. MUTAGENICITY OF VINYL CHLORIDE. EXTERNAL CHROMOSOME STUDIES ON PERSONS WITH AND WITHOUT VC ILLNESS; AND ON VC EXPOSED ANIMALS.

Fleig I, Thiess AM
Dept. Occupational Medicine and Health Protection,
BASF Aktiengesellschaft, 6700 Ludwigshafen, W.
Germany
J Occup Med; 20(8):557-561 1978

Chromosome analysis was performed on lymphocyte cultures from 6 workers with an estimated degree of exposure to vinyl chloride (VC), 4 workers whose degree of exposure was monitored, 20 workers showing symptoms of VC illness after unknown degrees of exposure, and 1 patient with VC-induced angiosarcoma. Bone marrow cells from Chinese hamsters exposed to VC by inhalation (2,500 or 5,000 ppm for 4 hr/day x 5) or ip injection (300 or 600 mg/kg/day x 5) were also analyzed. The frequency of chromosome aberrations was not increased relative to controls in the exposed workers with no signs of VC illness. The frequency of aberrant metaphases in the workers with VC illness was 5.2% excluding gaps and 11.2% including gaps, these values were significantly higher than the control values of 2.1% and 5.5%, respectively. The rate of aberrant metaphases in the angiosarcoma patient was 7.3% excluding gaps and isogaps and 16.6% including gaps and isogaps. The frequency of structural abnormalities in the VC-treated hamster cells was also significantly higher than that in the control cells, inclusive and exclusive of gaps. (15 Refs)

245. CYTOGENETIC INVESTIGATIONS ON LYMPHOCYTES FROM WORKERS EXPOSED TO VINYL CHLORIDE.

Leonard A, Decat G, Leonard ED, Lefevre MJ, Decuyper LJ, Nicaise C
Lab. Genetics, Dept. Radiology, C.E.N.-S.C.K. B 2400
Mol, Belgium
J Toxicol Environ Health; 2(5):1135-1141 1977

Eleven male workers from the polymerization department of a VC factory, seven people employed in the laboratory of another VC plant, and ten controls from outside the factory environment were examined for the presence of chromosome aberrations in blood lymphocytes and these cytological findings were viewed in light of the occupational and medical histories of the subjects. Most of the workers from the polymerization department had chromosome anomalies such as fragments, rings, translocations, and dicentrics. However, since these workers received frequent radiographs of the hands, feet, vertebral column and digestive tract, it is impossible to determine whether these chromosome anomalies result from vinyl chloride exposure or from diagnostic exposure to ionizing radiations. It is concluded that the risk of significant increase in chromosome aberrations due to occupational exposure to VC seems small and that present working conditions in VC plants are within acceptable safety limits. (17 Refs)

246. CYTOGENETIC INVESTIGATIONS ON LYMPHOCYTES FROM WORKERS EXPOSED TO VINYL CHLORIDE (MEETING ABSTRACT).

Leonard A, Decat G, Leonard ED
Mammalian Genetics Lab., C.E.N-S.C.K., B-2400 Mol,
Belgium
Mutat Res; 53(2):219 1978

Male workers from the polymerization department of a vinyl chloride (VC) factory, people employed in the laboratory of another VC plant and controls from outside the factory environment were examined for the presence of chromosome aberrations in blood lymphocytes. The incidence of chromatid aberrations (gaps and breaks) and of chromosome gaps was not significantly increased after VC exposure, but more severe chromosome anomalies such as chromosome fragments, rings and dicentricies were observed in most of the workers from the polymerization department. The medical history of the workers shows that most people from the polymerization department received several radiographies. The conclusion that the chromosome fragments and chromosome dicentricies result from VC exposure remains, therefore, dubious. It is much more probable that these anomalies originate from the diagnostic exposure to ionizing radiation. (no Refs)

247. CHROMOSOMAL ANALYSES IN VINYL CHLORIDE-EXPOSED WORKERS.

Purchase IF, Richardson CR, Anderson D, Paddle GM, Adams WG
Central Toxicology Lab., Central Medical Group and Mond Div., Imperial Chemical Industries Ltd., Alderley Park, Macclesfield, Cheshire, England
Mutat Res; 57(3):325-334 1978

The chromosomal morphology of cultured peripheral lymphocytes from 81 men 57 employed in plants manufacturing vinyl chloride (VC) or polyvinyl chloride (PVC), 19 on-site controls, and 5 off-site controls) was studied. There was a significant increase in chromosomal abnormalities among the VC/PVC-exposed workers compared with the controls. Total B cells (those with a chromatid break or gap or a chromosome gap), total Cu cells (those with larger unstable chromosomal abnormalities), and total Cs cells (those with larger unstable chromosomal abnormalities) showed the greater increases in autoclave operators, with smaller increases in the other five job categories. The increase in chromosomal aberrations was correlated with length of exposure and with a history of exposure to excursion levels of VC during the year prior to sampling (1973-1974). There were no correlations between results of liver function tests and chromosome aberrations. Quantity of tobacco smoked 18 mo after blood sampling was correlated with total C cells, as was smoker vs nonsmoker status at 18 mo postsampling. It was not possible to determine whether smoking history, length of employment, or exposure to excursion levels of VC was the most important variable in determining C cell abnormalities. (15 Refs)

248. CHROMOSOMAL DAMAGE IN MEN OCCUPATIONALLY EXPOSED TO VINYL CHLORIDE MONOMER AND OTHER CHEMICALS.

Heath CW, Dumont CR, Gamble J, Waxweiler RJ
Cancer and Birth Defects Div., Bureau Epidemiology, Center Disease Control, Public Health Service, U.S. Dept. Health, Education and Welfare, 1600 Clifton Road, N. E., Atlanta, GA 30333
Environ Res; 14(1):68-72 1977

Cytogenetic analyses were conducted on men employed at a rubber and plastics plant who were exposed to vinyl chloride

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

249. VINYL CHLORIDE CYTOGENETICS.

Picciano DJ, Flake RE, Gay PC, Kilian DJ
Occupational Health and Medical Res., Dow Chemical, Freeport, TX 77541
J Occup Med; 19(8):527-530 1977

This report presents cytogenetic findings from a group of 209 workers employed for up to 28 yr in the manufacture of vinyl chloride monomer at the Texas Division of Dow Chemical USA. Cytogenetic evaluation results from this group were compared to results found in examination of individuals being considered for employment. Statistical analyses were performed on a group basis for chromatid aberrations, chromosome aberrations and proportion of abnormal cells; no statistical difference of significance was found between the two groups. Comparison of these results with reported studies suggests that the level of cytogenetic aberrations in vinyl chloride workers is probably related to the length and level of exposure, and that risk of adverse genetic effect can be avoided in controlled, minimal-exposure environments. (Author abstract) (31 Refs)

250. EFFECTS OF VINYL CHLORIDE IN MAN. A CYTOGENETIC FOLLOW-UP STUDY.

Hansteen IL, Hillestad L, Thiis-Evensen E, Heldaas SS
Lab. Genetics, Telemark Central Hosp., Olavsgt. 26, 3900 Porsgrunn, Norway
Mutat Res; 51(2):271-278 1978

For comparison, a second cytogenetic study was made of 37/39 polyvinyl chloride workers 2-2.5 yr later, during which time the workers had minimal exposure to vinyl chloride monomer (VCM). The second study was performed with 32 matched controls selected from office employees at the same factory. Of the original 39 workers, 14 had been chosen at random, 13 because they had heavy exposure to VCM for years, and 12 because of abnormal clinical findings that later proved to be normal. Breaks, gaps, and stable rearrangements were scored as 100 metaphases/person from 48-hr lymphocyte cultures. In the first study, the mean number of chromosome breaks was significantly higher for the workers (3.41%) than for the controls (1.79%). No significant difference was found in the second study. In addition, there was no significant difference in mean number of breaks between the first control group and both groups of the second study. The results of the two studies provide evidence that VCM was the cause of the chromosome damage found in the first study. In the second study, the mean number of sister chromatid exchanges per cell was the same (7.6) for both workers and controls. Studies of bone marrow samples from four workers revealed that these samples had a higher mean number of chromosome breaks (4.2%) than normal bone marrow (literature values, 0.2% 1.7%) or the corresponding lymphocyte cultures. (19 Refs)

251. HIGH RATE OF CHROMOSOMAL ABERRATION IN PVC WORKERS.

Szentesi I, Hornyak E, Ungvary G, Czeizel A, Bognar Z, Timar N
Lab. Human Genetics, Natl. Inst. Hygiene, H-1966
Budapest, Gyali ut 2-6, Hungary
Mutat Res; 37(2-3):313-316 1976

Chromosome examinations were performed on 45 polyvinyl chloride (PVC) workers exposed to vinyl chloride for 0.5 to 12 yr. Two control groups were used. The first was composed of 44 industrial workers who were not exposed to PVC and were only indirectly exposed to other chemicals. The second control group was composed of 49 individuals who had no occupational exposure to chemicals. The rate of numerical chromosome aberrations did not differ significantly between PVC workers and either control group. The frequency of chromatid-type aberrations was higher in PVC workers than in either control group. Unstable chromosome-type aberrations were also significantly higher in PVC workers. The PVC workers who showed a significantly higher frequency of chromatid-type aberrations or unstable chromosome-type aberrations had been exposed to the compound for longer periods than other PVC workers. They are to undergo a clinical check-up to determine whether they can continue in their present occupations. (17 refs)

252. CHROMOSOME STUDIES OF TRICHLOROETHYLENE WORKERS.

Konietzko H, Haberlandt W, Heilbronner H, Reill G, Weichardt H
Institut für Arbeitsmedizin der Universität, Wilhelmstrabe 27, D-7400 Tübingen, W. Germany
Arch Toxicol (Berl); 40(3):201-206 1978

On the basis of lymphocyte cultures, chromosome studies were carried out on 28 employees involved in the purification of trichloroethylene (TCE) who were exposed from 1 to 21 yr to various concentrations of TCE. Nine of these subjects showed pathological percentages of hypodiploid cells, but otherwise they had normal karyotypes; one subject had the karyotype 47,XY,+mar (small metacentric extrachromosome). For these nine employees, it was found that the significantly higher chromosome aberration rate correlated with TCE concentration level but not with duration of exposure. (9 Refs)

253. HEALTH DAMAGE BY TRICHLOROETHYLENE: AN EPIDEMIOLOGICAL AND CLINICAL-EXPERIMENTAL STUDY.

Konietzko H
Institut für Arbeits- und Sozialmedizin, Universität Tübingen, Wilhelmstrasse 27, 7400 Tübingen, W. Germany
Fortschr Med; 97(14):671-674 1979

Trichloroethylene (TCE) levels were measured at 10 industrial sites. The 6-hr av were mainly between 52-94 ppm. The max allowable level (MAL) is 50 ppm. Chromosome aberrations increased in workers as the level of exposure to TCE increased. This finding indicates that the TCE levels observed present a carcinogenic risk and that lowering the MAL to 20 ppm should be considered. (no Refs)

C. Teratogenicity of Vinyl Chloride and Related Compounds in Humans

254. SURVEILLANCE OF SPONTANEOUS ABORTIONS. POWER IN ENVIRONMENTAL MONITORING.

Kline J, Stein Z, Strobino B, Susser M, Warburton D
Columbia Univ. Coll. Physicians and Surgeons, New York, NY 10032
Am J Epidemiol; 106(5):345-350 1977

The advantages of using spontaneous abortions rather than birth defects to monitor environmentally induced carcinomas are discussed. Theoretically, a change in the incidence of spontaneous abortions or of anomalies in spontaneous abortions should be detectable 6 mo or more before a change in the incidence of birth defects. Moreover, teratogens that cause many anomalies cannot be detected by studies of birth defects since the majority of anomalous conceptions lead to spontaneous abortions. Abortion specimens can also be preserved for future studies. The spontaneous abortion approach is illustrated by the potential teratogenic effects of paternal exposure to vinyl chloride (VC). VC may affect male germ cells by causing chromosome breaks, dominant or recessive lethal mutations, and/or chromosome abnormalities. Morphologic and karyotype analyses of a sample series of spontaneous abortions are discussed. (14 Refs)

255. ONCOGENIC AND MUTAGENIC RISKS IN COMMUNITIES WITH POLYVINYL CHLORIDE PRODUCTION FACILITIES.

Infante PF
Ohio Dept. Health, Columbus, OH 43216
Ann NY Acad Sci; 271:49-57 1976

An epidemiologic study was done on the distribution of congenital abnormalities in three cities with polyvinyl chloride (PVC) production facilities. The numbers of children with congenital malformations and rates per 1,000 live births were computed for each city over 4 yr. Mothers in the cities gave birth to an excess number of children with congenital malformations compared to that expected based on the state and county averages. Other county-city combinations matched by population size showed no significant differences in incidence of congenital malformations. Maternal age, race, and possible differences in hospital reporting were not considered accountable for the observed differences. Anomalies of the CNS were of the greatest concern. An excess number of CNS defects was observed among stillbirths and live births from the index cities, with one exception. The excess was largely from two of the cities. Deaths from CNS tumors in adult male residents in the same two cities were also significantly greater than expected. On a community basis, excess deaths from the other cancers were not apparent. Since many underlying factors could be responsible for the mutagenic and/or teratogenic and carcinogenic mechanisms involved, these preliminary findings do not link polyvinyl chloride production with the increased occurrence of congenital malformations and CNS tumors, but indicate the need for further study of possible contributing factors. (13 refs)

256. CARCINOGENIC, MUTAGENIC AND TERATOGENIC RISKS ASSOCIATED WITH VINYL CHLORIDE.

Infante PF, Wagoner JK, Waxweiler RJ
Division Surveillance, Natl. Inst. Occupational Safety and Health, Main Post Office Building, Cincinnati, OH 45202
Mutat Res; 41(1):131-142 1976

Results of an epidemiological survey of cancer, birth defects and fetal mortality in groups of people with some kind

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

D. Other Clinical Manifestations of Occupational Exposure to Vinyl Chloride and Related Compounds

257. FURTHER RESULTS IN POLYVINYL CHLORIDE PRODUCTION WORKERS.

Lange CE, Juhe S, Stein G, Veltman G
Dep. Dermatol., Univ. Bonn, West Germany
Ann NY Acad Sci; 246:18-21 1975

The possible nature and extent of occupational damage in 15 employees of polyvinyl chloride (PVC)-processing industries was investigated. In addition, case studies of two former workers of a PVC-producing plant, who had died of malignant tumors, are presented. Dermatological examinations and the following laboratory tests were performed on all 15 workers: complete blood cell platelet count, RBC sedimentation rate, serum electrophoresis, blood urea nitrogen, and Australia antigen. Employed for an average of five years, the workers had complained of sensations of pressure and/or pain in the upper abdomen, frequent dizziness, cold hands and feet, and increasing weakness in the legs. Clinical changes of Raynaud's syndrome were not observed. Slight to moderate thrombocytopenia (63,000-139,000/microl) was observed in seven patients; increased bromsulphalein retention of 5.2-15.1% at 45 min was noted in another seven patients. Reticulosis of 1.7-4.4% was seen in six patients. Leukopenia (3,250/microl) was seen in one patient, and slight splenomegaly was observed in another patient. Laparoscopy and biopsy results were less distinct, though similar to those observed in PVC-production workers. Despite the small number of workers examined, an increased number of findings were made of a combination of symptoms believed characteristic of vinyl chloride disease. A 38-yr-old man, employed for 12 yr, had a large tumor assigned to the liver and spleen, increased ESR, anemia, and other abnormal laboratory findings; surgical laparotomy and biopsies revealed a hemangioendothelial sarcoma of the liver, and increasing cachexia resulted in death. A 39-yr-old man, employed for 11 yr, had a tumor on the epigastric angle, abnormal laboratory results, a histological diagnosis of hemangioendothelial liver sarcoma, and resulting death.

258. AN EPIDEMIOLOGIC STUDY OF BLOOD SCREENING TESTS AND ILLNESS HISTORIES AMONG CHEMICAL WORKERS INVOLVED IN THE MANUFACTURE OF POLYVINYL CHLORIDE.

Wyatt RH, Kotchen JM, Hochstrasser DL, Buchanan JW, Campbell DR, Slaughter JC, Doll AH
Coll. Med., Univ. Kentucky, Lexington, Ky.
Ann NY Acad Sci; 246:80-87 1975

When five cases of liver angiosarcoma were identified among polyvinyl chloride manufacturing workers in a single

plant, 882 male employees were screened for blood chemistry abnormalities and illness history. The results obtained from 413 of these workers, who had worked for more than one month in the manufacturing unit, were compared with the remaining workers employed in other areas. Two additional cases of angiosarcoma were discovered in the manufacturing workers through this screening. Blood samples were tested for total protein, albumin, calcium, inorganic phosphate, creatine, uric acid, total bilirubin, alkaline phosphatase, LDH, SGOT, cholesterol and creatine phosphokinase. Colorimetric analysis was performed and enzymatic reactions were read in the 340 nm range. Liver-spleen disease and allergic problems were observed more frequently in manufacturing workers than other workers while more genitourinary illness was found in the other workers. Whereas more polyvinyl chloride workers had abnormally elevated albumin levels, more workers in other areas had elevated SGOT and alkaline phosphatase levels. After adjusting for age, both albumin and cholesterol level trends with age were found to be different for the two populations. This was not found in any other test. Further study is indicated.

259. SCINTIGRAPHY OF LIVER AND SPLEEN IN VINYL CHLORIDE WORKERS.

Biersack HJ, San Luis T, Lange CE, Thelen M, Veltman G, Winkler C
Inst. for Clinical and Experimental Nuclear Medicine,
5300 Bonn-Venusberg, W. Germany
Hepatogastroenterol (Stuttg); 24(5):357-361 1977

In 152 vinylchloride(VC)-exposed, workers of whom 124 were employed in the polyvinylchloride (PVC) production and 28 in VC-processing plants, liver and spleen imaging was performed using Tc99m-sulphur colloid and Hg197-BMHP. In 101 (81%) of the 124 workers of the PVC-production plant and in 18 (64%) workers of PVC-processing factories pathological liver and spleen scintigrams were found. The most frequent pathological change in the scintigraphic image was an increase in splenic colloid accumulation, when compared with the liver uptake. Three angiosarcomas of the liver were detected through circumscribed defects of colloid accumulation. Sequential liver scintigraphy was done in 15 cases. In 7 patients with esophageal varices considerable decrease in portal venous blood flow was demonstrated. Scintigraphically detectable changes are sensitive indicators of VC-induced lesions of the liver including liver fibrosis, portal hypertension and angiosarcoma. (Author abstract) (22 Refs)

260. LIVER DISEASE IN POLYVINYL CHLORIDE PRODUCTION WORKERS - CLINICAL AND LAPAROSCOPIC ASPECTS.

Marsteller HJ, Lebach WK, Muller R, Gedigk P, Lange CE
Medizinische Universitätsklinik, D-5300 Bonn-Venusberg,
West Germany
Leber Magen Darm; 5(5):196-202 1975

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

areas were found in laparotomies of the patients with noncirrhotic portal fibrosis after vinyl chloride exposures ranging between 9 mo and 21-3/4 yr.

261. RESULTS OF A STUDY OF 17 CASES OF LONG-TERM EXPOSURE TO VINYL CHLORIDE.

Muller KT, Buchter A, Gross R, Bolt W
Med. Univ.-Klinik, 5 Koln 41, Joseph-Stelzmann-Str. 9,
West Germany
Med Welt; 27(1):21-24 1976

A discussion of the physicochemical properties of vinyl chloride (VC) and its toxicology precedes a review of 17 patients with VC intoxication. Liver pathology and positive Raynaud signs occurred in 11/17, esophageal or fundic varices in 8/17, splenomegaly in 8/17, thrombocytopenia in 10/17, and acro-osteolysis in 8/17. Six probands presented with granulo cytopoiesis and marrow stimulation by sternal puncture. Five patients had various changes in antibody composition, and six were leukopenic. All patients were otolaryngologically negative. A suspicion of hepatic hemangioendothelioma in one subject was disconfirmed on laparoscopy, although the patient had elevated serum iron and distal hypalgnesia. The subjects were men, with a mean 9-yr VC exposure.

262. PORTAL HYPERTENSION IN VINYL CHLORIDE MONOMER WORKERS. A HEMODYNAMIC STUDY.

Blendis LM, Smithe PM, Lawrie BW, Stephens MR, Evans WD
Room 112, Univ. Wing, Toronto General Hosp.,
University Ave., Toronto, Ontario, Canada M5G 1L7
Gastroenterology; 75(2):206-211 1978

Hemodynamic studies were performed in five vinyl chloride monomer workers in whom splenomegaly or thrombocytopenia was detected during a screening program at a major chemical plant. Three patients had portal hypertension and collateral venous circulations, with intrasplenic pressure between 20 and 29 mm Hg and normal wedged hepatic venous pressures, but the gradient between the wedged and free hepatic vein pressures was also increased. Splenic blood flows were increased in both hypertension and normotensive patients. There was no correlation between the splenic blood flow and the portal pressure or the presence of the portal fibrosis. The portal hypertension associated with vinyl chloride exposure is mainly presinusoidal in type, and may be attributed to an abnormality of the portal vein radicles, or hepatic sinusoids. (Author abstract) (23 Refs)

263. PORTAL HYPERTENSION IN VINYL-CHLORIDE PRODUCTION WORKERS.

Smith PM, Crossley IR, Williams DM
Dept. Medicine, Llandough Hosp., Penarth, South Glamorgan, Wales
Lancet; 2(7986):602-604 1976

Portal hypertension was observed in seven patients who had been involved in the production of vinyl-chloride monomer (VCM) for 4-15 yr. The patients were 36-57 yr old at the time of presentation, and they had been exposed to VCM gas for 4-15 yr. Four had hematemesis from esophageal varices, and two of these had had prior splenomegaly and thrombocytopenia. At laparotomy, the liver appeared finely nodular and cirrhotic, but biopsy revealed a noncirrhotic fibrosis in four patients and slight fibrosis in two. Of the four patients who bled from the esophageal varices, one died 2 mo after an esophageal transection from hepatic failure and Escherichia coli septicemia. The other three have done extremely well after end-to-side portacaval shunts. They have

survived so far for 3, 6, and 8 yr, respectively. With improvements in technology, workers should no longer be exposed to VCM gas levels 5 ppm. (15 Refs)

264. PULMONARY CHANGES AMONG VINYL CHLORIDE POLYMERIZATION WORKERS.

Lilis R, Anderson H, Miller A, Selikoff IJ
Mount Sinai Sch. Medicine, New York, NY
Chest; 69(2):299-303 1976

Pulmonary changes uncovered during clinical examinations of three groups of exposed vinyl chloride (VC) polymerization workers are discussed. The examination included chest x-rays, smoking history, a chronic bronchitis questionnaire, and pulmonary function tests. The first group was from a plant known to have high exposure levels to VC and polyvinyl chloride (PVC). The second plant was the first PVC polymerization facility, so that long exposure effects could be expected. The third plant had a relatively low exposure level. In the first group, the overall prevalence of small linear reticular and/or rounded opacities was 22.7%; x-ray changes increased with length of exposure. In the second group the prevalence of chest x-ray changes was 19.4%. The third group had a much lower prevalence of chest x-ray abnormalities (4.3%). The prevalence of positive smoking history was higher in workers with abnormal chest x-ray films in the first two groups, perhaps indicating a multiple factor effect of smoking and VC-PVC exposure. No significant differences were found between the groups with abnormal and normal chest x-rays with respect to chronic bronchitis or age. Pulmonary function tests showed a relatively high prevalence of obstructive changes, but there was no consistent correlation between abnormal chest x-ray and pulmonary function abnormalities. It is possible that chest x-ray changes and obstructive pulmonary function abnormalities reflect different pathologic processes, the chest x-ray changes being mainly related to parenchymal damage, while the obstructive pulmonary function changes reflect airway changes.

265. PRENEOPLASTIC AND COLLAGENIZING CHANGES IN THE LIVER AND BLOOD CLOTTING IN PVC WORKERS.

Bachner U, Etzel F, Muller N, Lange CE, Egli H
No affiliation given
Thromb Diath Haemorrh; Suppl62:319-326 1976

Sixty-five polyvinyl chloride (PVC) workers with thrombocytopenia were divided into three groups: (A) 31 with unremarkable liver histology; (B) 20 with slight liver fibrosis; and (C) 14 with clear periportal and perisinusoidal fibrosis, stellate (Kupffer) cell proliferation, and atypical stellate cells. Twenty-two blood-clotting tests were carried out and related to pathological and histological findings in the liver. PVC workers with strong collagenizing and preneoplastic changes in the liver showed the lowest number of thrombocytes. Groups B and C showed an increase in platelet factor 3 activity, but this increase was statistically significant in Group C only. Factor VIII activity showed a tendency to rise from Groups A to C. Factor V values were normal in Groups A and B, but slightly decreased in Group C. In all three, fibrinogen was at high normal or elevated levels, plasminogen was at the lower level of normal, and aggregability was increased. The reaction time in TEG was slightly shorter in Group C than in A or B. Tissue changes in the liver and spleen were related to hindrance of the microcirculation, which could explain the portal hypertension and esophageal varices observed in 10/14 Group C patients. The availability of phospholipids was increased, as shown by the deposit of lipopigments in the sinusoidal and liver cells. (45 Refs)

266. LYMPHOCYTE TRANSFORMATION TESTS IN VINYL CHLORIDE (VC) WORKERS (MEETING ABSTRACT).

Fortwengler HP, Dever ME, Tamburro CH, Espinosa E
Univ. Louisville Sch. Medicine, Louisville, KY, 40201
Fed Proc; 37(3):362 1978

Previous reports have shown circulating immune complexes in vinyl chloride (VC) workers and a tumor-associated antigen in VC-related liver angiosarcoma. This suggests immune stimulation by a tissue of plasma antigen induced by or conjugated with VC or a metabolite. In this work, the in vitro lymphocyte reactivity for such antigens was tested in 79 VC workers including 25 with liver abnormalities, and 20 normal individuals having no exposure to VC. The liver angiosarcoma antigen preparation included the tumor-associated antigen and other tissue antigens as shown by immunodiffusion. Stimulation indices (SI) were calculated from cellular incorporation of tritiated thymidine. Mean SI in the normal individuals for antigens of angiosarcoma and normal liver tissues were 4.7 (SE+1.7) and 3.8 (+0.9) and in VC workers, 1.8 (+0.2) and 2.5 (+0.3) respectively. Mean SI for phytohemagglutinin and concanavalin A in the normal individuals were 235 (+35) and 209 (+30) and in VC workers 201 (+23) and 180 (+19) respectively. Thus, these results suggest that VC workers have a decreased lymphocyte response to antigens of liver angiosarcoma and normal liver tissues rather than the hypothesized increased reactivity. This appears to be due to a lower overall lymphocyte responsiveness in these chemical workers.

267. IMMUNOLOGICAL MECHANISMS IN THE PATHOGENESIS OF VINYL CHLORIDE DISEASE.

Ward AM, Udnoon S, Watkins J, Walker AE, Darke CS
Hallamshire Hosp. Medical Sch., Sheffield S10 2RX,
England
Br Med J; 1(6015):936-938 1976

To determine the etiology and pathogenesis of vinyl chloride (VC) disease, immunological and immunochemical investigations performed on 58 workers from a VC polymerization plant showed the presence of circulating immune complexes in 19 out of 28 patients with the disease and in 2 of 30 workers exposed to VC. The immunological data were reviewed in relation to the clinical picture of the disease and to the available evidence on the metabolism of VC. The results suggest that VC disease is an immune complex disorder and that the immune response is initiated by the adsorption of VC or a metabolite, presumably the dioxide, onto tissue or plasma protein, producing either a haptenic group or a conformational change within the protein molecule that escapes tolerance and stimulates B cell proliferation.

268. SPERM COUNT DEPRESSION IN PESTICIDE APPLICATORS EXPOSED TO DIBROMOCHLOROPROPANE.

Glass RI, Lyness RN, Mengle DC, Powell KE, Kahn E
Chronic Diseases Div., Bureau Epidemiology, Center
Disease Control, Atlanta, GA, 30333
Am J Epidemiol; 109(3):346-351 1979

Male pesticide applicators who worked with the nematocide dibromochloropropane (DBCP) were examined to determine the possible testicular toxicity from this exposure. Infertility and azoospermia which were first noted among factory workers exposed to DBCP were not observed among the applicators. Sperm count depression, however, was associated with the duration of exposure in the current yr but not with exposure in past yr. The extent of exposure to DBCP in the current yr was also associated with an elevation of serum follicle stimulating hormone (FSH) but not of luteinizing

hormone (LH). Sperm count depression was limited to applicators involved in irrigation setup work and in the calibration of equipment. These results suggest that the testicular toxicity of DBCP for men may occur in a shorter period that was previously reported, that the effect may be reversible in men with mild sperm count depression, and that public health measures might be directed at controlling specific application technique. (Author abstract) (12 Refs)

VII. PUBLIC HEALTH ISSUES, OCCUPATIONAL SAFETY, AND REGULATIONS CONCERNING VINYL CHLORIDE AND RELATED COMPOUNDS

The reader may also find the following abstracts of interest: 187, 204, 219, 223, 227

269. VINYL CHLORIDE: ITS IMPACT ON OCCUPATIONAL MEDICINE PRACTICE IN IRAN.

Aryanpur J
Public Health and Occupational Medical Services, Natl.
Iranian Oil Company, P. O. Box 1863, Tehran, Iran
J Occup Med; 19(10):689-692 1977

Measures taken to protect the workers at the Abadan Petrochemical Company in Iran from the carcinogenic effects of vinyl chloride monomer (VCM) and polyvinyl chloride (PVC) are outlined. Since 1971, all workers have been required to undergo periodic medical examinations with an emphasis on liver function. Factors related to liver disease, such as endemic viral hepatitis, low alcohol and cigarette consumption, and dietary habits, are considered. To date, among 43 workers in the VCM and PVC production units, none have evidence of liver dysfunction or angiosarcoma. The threshold limit value for VCM has been set at 25 ppm time weighted av for 8 hr with revisions expected in the future. No leakage to the community has been detected except for some chlorine release. (11 Refs)

270. CONTROL STATUS OF VINYL CHLORIDE.

Wyatt S
United States Environmental Protection Agency, Research
Triangle Park, NC, 27711
Tex Rep Biol Med; 37:145 1978

The Environmental Protection Agency (EPA) listed vinyl chloride as a hazardous air pollutant in December, 1975, and promulgated a national emission standard for it under the authority of section 112 of the Clean Air Act on October 21, 1976. On November 19, 1976, the Environmental Defense Fund (EDF) petitioned the United States Court of Appeals for review of the standard. On March 24, 1977, EDF and EPA moved to dismiss the court proceedings in view of a settlement agreement requiring EPA to propose certain amendments to the standard. These amendments to the standard were proposed on June 2, 1977. Since that time EPA has received numerous comments from the industry on the proposal. The main issue involved is how carcinogens should be regulated under section 112 of the Clean Air Act. Section 112 of the Act requires that emission standards be set 'at the level which, in the judgment of the Administrator, provides an ample margin of safety to protect the public health from such hazardous air pollutants.' It has not been possible to determine a threshold level of effects for vinyl chloride and it is not certain that such a threshold may be determined in the near future. Therefore, EPA has developed standards which require emission reduction to the lowest level achievable using technological means. (Author abstract) (no Refs)

Downs TD

Dept. Biometry, Univ. Texas Health Science Center at
Houston, Sch. Public Health, P.O. Box 20186, Houston,
TX, 77025

Tex Rep Biol Med; 37:118-122 1978

A simplified account of a statistical method used to assess community risk from environmental carcinogens is presented. The method is called the linear model and is based on the assumption that the probability, or risk, of developing cancer from exposure to a relatively small amount of carcinogen is directly proportional to that amount. The linear model is illustrated with data on vinyl chloride inhalation in rats and subsequent development of liver angiosarcoma. Results from these experiments are extrapolated to humans. Rats were intermittently exposed to vinyl chloride at different ambient air concentrations. Exposures to vinyl chloride were maintained for 4 hr/day, 5 days/wk, for a period of 1 yr. Following this, surviving rats were housed under normal conditions until death. Whenever a rat died an autopsy was performed to determine if the rat had developed liver angiosarcoma. The proportion of rats with liver angiosarcoma increased steadily as the dose concentrations of vinyl chloride increased. The proportion of rats with liver angiosarcoma seemed roughly proportional to the dose concentration. Use of the linear model was extrapolated to humans to quantify the risk of liver angiosarcoma for residents in the vicinity of a hypothetical vinyl chloride plant. (6 Refs)

272. OCCUPATIONAL SAFETY AND HEALTH STANDARDS: TOXIC AND HAZARDOUS SUBSTANCES.

Department of Labor

Occupational Safety and Health Admin., Dept. Labor,
Washington, DC

Fed Regist; 44(29,Book2):8575-8833 1979

Occupational safety and health standards for toxic and hazardous substances which are applicable to construction are presented. The substances discussed include asbestos, coal tar pitch volatiles, 4-nitrobiphenyl, alpha-naphthylamine, methyl chloroethyl ether, 3,3-dichlorobenzidine and its salts, bis-chloromethyl ether, beta-naphthylamine, benzidine, 4-aminodiphenyl, ethyleneimine, beta-propiolactone, 2-acetylaminofluorene, 4-dimethylaminoazobenzene, N-nitrosodimethylamine, vinyl chloride, inorganic arsenic, benzene, coke oven emissions, cotton dust (in cotton gins), 1,2-dibromo-3-chloropropane, and acrylonitrile. (no Refs)

273. PUBLIC HEALTH DECISION-MAKING AND THE LEGAL PROCESS IN THE UNITED STATES: THE REGULATION OF VINYL CHLORIDE (MEETING ABSTRACT).

Cottine BR

U.S. Occupational Safety and Health Review Commission,
Washington, DC

The Scientific Basis for the Public Control of
Environmental Health Hazards, held by the New York
Academy of Sciences in New York, 21-30 June, 1978. The
New York Academy of Sciences, New York, New York,
1978.

Public health decision-making on the hazards of vinyl chloride exposure occurred in the legal process of the United States through two functional systems. At a federal level 'public-ordering' was accomplished prospectively through authority delegated by Congress to several administrative agencies including the Consumer Product Safety Commission and the Occupational Safety and Health Administration. Investigatory hearings, rulemaking action, and enforcement actions were commenced. Public ordering also occurred

retrospectively through state worker compensation systems. However, the retrospective systems do not integrate with, or provide data for, prospective action. Moreover, retrospective ordering has a limited sensitivity and field of view due to statutory limitations on the compensability of occupational disease, variable latency periods, access controls on the system, and data visibility. Though limited retrospective data were available on vinyl chloride, prospective regulatory actions necessarily relied on experimental and epidemiological data. Private ordering also occurred on a limited basis. (no Refs)

274. CASE STUDY 3: VINYL CHLORIDE - BEST AVAILABLE TECHNOLOGY.

Lassiter DV

Occupational Safety and Health Admin., US Dept. Labor,
Washington, DC 20210

Ann NY Acad Sci; 271:176-178 1976

Several tumors have been directly linked with occupational exposure to various carcinogens. Guidelines that determine policy for the regulation of occupational carcinogens, as set forth by the Occupational Safety and Health Administration, are quoted and commented upon. Any regulations should ideally assure minimum risk of cancer to the employee while allowing the manufacturer to remain competitive in a situation in which costly controls must be instituted to restrict exposure. (0 Refs)

275. PRODUCTION AND USE OF VINYL CHLORIDE: IMPACT OF THE LINK BETWEEN VINYL CHLORIDE MONOMER AND CANCER.

Pregaglia GF

Dept. Res. and Technology, Petrochemical Div.,
Montedison, Milan, Italy

Adv Tumor Prev Detect Charact; 3:209-215 1976

Exposure hazards associated with the production and use of vinyl chloride monomer (VCM) are reviewed along with some possible solutions. VCM has recently been associated with the cancer deaths of production workers exposed to the compound, and the Occupational Safety and Health Administration has recommended that the exposure level be reduced to 1 ppm (averaged over an 8-hr period) starting in 1976. Exposure hazards to VCM in polyvinyl chloride manufacturing plants include: VCM loss from valves and pumps to the ambient air at concentrations ranging from a few to a few dozen parts per million; the need for workers to enter reactor vessels periodically for cleaning; monomer escape from the polymer during storage and processing of the latter; and monomer losses through vent gas streams. Possible means of reducing VCM exposure include: the scale-up to larger reactors, resulting in fewer leaks and easier cleaning; remote control operation and the use of highly sensitive vapor detectors; and new processes for the removal of VCM from vent gases, such as the adsorption of VCM on activated carbon and its regeneration with steam.

276. PUBLIC-HEALTH ROUNDS AT THE HARVARD SCHOOL OF PUBLIC HEALTH. VINYL CHLORIDE: CAN THE WORKER BE PROTECTED?

Wegman DH, Peters JM, Jaeger RJ, Burgess WA, Boden LI
665 Huntington Ave., Boston, MA 02115
N Engl J Med; 294(12):653-675 1976

The toxicology, economic and engineering aspects, and regulation of occupational exposure to vinyl chloride are reviewed. Well before 1974, when three cases of a rare neoplasm, angiosarcoma of the liver, were reported in workers exposed to vinyl chloride over a 20-yr period, there was sufficient evidence to support the presumption of a serious occupational hazard. Toxicological studies as early as 1938 indicated that vinyl chloride has little acute lethal action and

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negligible short-term toxicity but is a potent carcinogen in rodents under work-like exposure of 50 ppm and less. Useful toxicologic screening should be carried out in locations other than the workplace and in species other than man. The manner in which workers are exposed to vinyl chloride varies greatly, depending on their occupation in one of three stages: (a) production of vinyl chloride monomer (VCM); (b) reaction of VCM to form polyvinyl chloride (PVC); and (c) the fabrication of plastic products from PVC. Major exposure and the cases of angiosarcoma of the liver occur in the second industrial stage. The most common exposure in the first stage occurs from leaks and faulty equipment maintenance. In the third stage, exposure (1,000 ppm) occurs when workers periodically crawl into the reactor to clean the inside surface. The Federal occupational standard for vinyl chloride exposure (issued in October 1974), although accepting in principle 1 ppm as the maximum possible exposure, permits temporary exposures of up to 25 ppm without respiratory protection.

277. VINYL CHLORIDE, PVC AND CANCER.

Anonymous

Lancet; (7870):1323-1324 1974

To date, 19 workers throughout the world have reportedly developed angiosarcoma of the liver following a history of intermittently heavy exposure to vinyl chloride (VC) over periods of 12-27 years in polyvinyl chloride (PVC) manufacturing plants. Experimental work indicating a relationship between VC and cancer has heretofore gone unheeded because the experimental exposure levels were very high in comparison to those to which PVC workers are exposed and because experimentalists have often warned of hazards where no adequate evidence of real hazard exists. There is no indication that PVC is itself dangerous or that it depolymerizes to produce VC. Unreacted VC which is present in newly manufactured PVC may, however, be released during storage and when the material is heated during the manufacture of PVC products. There have been no cases of angiosarcoma of the liver among PVC processors. In Great Britain, the current upper limit for exposure to VC in PVC manufacturing plant is 50 ppm with a maximum time-weighted average exposure of 25 ppm. In light of evidence that rats develop angiosarcoma of the liver following exposure to 50 ppm VC, these limits may be lowered. More systematic evaluation of industrially used chemicals is needed to determine the carcinogenic risks to workers.

278. VINYL CHLORIDE POLYMERS IN CONTACT WITH FOOD.

Schmidt AM

No affiliation given

Fed Regist; 40(171):40529-40537 1975

Proposed regulations restricting the uses of vinyl chloride (VC) polymers in contact with food, as suggested by the Food and Drug Administration, are reviewed. In general, the proposal permits the continued use of VC polymers in food packaging when the migration potential of VC is diminished, includes an interim regulation for the use of water pipes made from VC polymers, and prohibits all other use of VC polymers in food-contact articles. The chemical structure and properties of CC and VC homopolymers and copolymers are described. Earlier studies have indicated that polyvinyl chloride (PVC) is insoluble in various solvent systems used to simulate food. However, later migration studies have revealed residual VC from PVC bottles in distilled spirits and wines. No animal feeding studies have established a safe level of consumption when VC is extracted from containers into food. The existence of residual VC in articles made from VC polymers has been found to be related to the manufacturing process and the physical structure of the polymers; a model explaining the VC

migration phenomenon is presented. Viewed as a simple diffusion phenomenon, experimental data indicate that while no VC is extractable from packaging materials, the greatest likelihood for migration of VC appears to be from PVC articles intended for one-time use. However, there is little likelihood that residual VC from PVC water pipes will become a component of potable water. Considerable data exist concerning the toxic effects of VC from atmospheric exposures, especially by inhalation and occupational contact; it is also suggested that VC is carcinogenic when ingested. Although a variety of uses of VC polymers in food-contact articles was previously approved, it is now suggested that widespread use be prohibited. It is concluded that no migration of VC from thin plasticized film is expected, nor is any migration expected from jar and bottle cap liners and gaskets. No residual VC reported in beer and soft drink can linings, but VC polymers used as coatings for fresh citrus fruits present the possibility of ingestion. Data also indicate that rigid and semirigid PVC articles intended to contact food may transmit VC to the food they contact. Proposed federal regulations and amendments are presented.

279. SORPTION OF VINYL CHLORIDE BY SELECTED FOOD CONSTITUENTS.

Biran D

Rutgers Univ., The State University of New Jersey, New Brunswick, NJ

Diss Abstr Int B; 38(5):2105-B 1977

The association of vinyl chloride (VC) with carcinogenic effects has caused a proposal by the FDA to restrict the use of rigid unplasticized polyvinyl chloride for food packaging. A major area of concern involves the possible interaction between the VC and food. This study deals with parameters affecting the sorption of VC in the gaseous state by selected food constituents and particularly the mechanism of VC sorption by dry casein particles. Partition coefficients for VC distribution between head space and oil, water, oil/water emulsions and casein were determined. It was found that at concentration levels studied the partition coefficients are fairly constant for all cases. Chemical nature of the substrate, starting head space concentrations and temperature were found to be important factors affecting the extent of VC sorption. Dipole moment of the sorbate gas as well as the chemical nature and moisture content of the protein were found to be important parameters determining the sorption of VC by casein. Particle size affects the sorption to a lesser degree. Transient state sorption measurements as well as the inverse gas chromatographic technique showed an active site binding as the major component in the binding interaction between casein particles and VC. An empirical kinetic model for the sorption VC by dry casein particles is proposed. The model suggests a possible clustering effect at the low temperature and most likely a monolayer sorption at the higher temperatures tested. An active site adsorption model is suggested. A correlation between the two models is shown. (no Refs)

280. THE POTENTIAL HEALTH HAZARD OF SUBSTANCES LEACHED FROM PLASTIC PACKAGING.

Carter SA

Environmental Science and Public Health, Cornell Univ., Ithaca, NY

J Environ Health; 40(2):73-76 1977

The health issues surrounding the leaching of four different groups of chemical compounds from plastic products are presented. These groups include: lead and ink from the printed material on plastic wrapping, stabilizers from soft plastic wraps, vinyl chloride from polyvinyl chloride (PVC)

products, and plasticizers from various PVC products. Analysis of PVC peanut oil containers revealed vinyl chloride levels of 0.3-3.3 ppm. Traces of vinyl chloride have been detected in vinegars and alcoholic beverages packaged in PVC bottles. Plasticizers such as di-2-ethylhexyl phthalate and dimethoxyethyl phthalate were found in human and rat blood which had been circulated in PVC tubing, and in tissue samples taken from human patients who had received transfusions of blood stored in PVC bags. These findings and others are discussed in light of pertinent animal and human studies. (28 Refs)

281. VINYL CHLORIDE: A REPORT OF A EUROPEAN ASSESSMENT.

Van Esch GJ, Van Logten MJ
Natl. Inst. Public Health, Bilthoven, Netherlands
Toxicology; 4(1):1-4 1975

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

282. EXPERIENCE IN INDUSTRIAL EXPOSURE CONTROL.

Rowe VK
Dow Chem. U.S.A., Health Environ. Res., Midland, Mich
Ann NY Acad Sci; 246:306-310 1975

Industrial hygiene methods employed by the Dow Chemical Company provide a model upon which future environmental control systems can be based. The results of toxicological studies of vinyl chloride and vinylidene chloride since 1959 indicated an increased need for monitoring of these substances in the air. Dow widely uses combustion-conductivity analysis but gas chromatography and infrared spectrophotometry have also been recently employed. Time-weighted averages of vinyl chloride exposure that an employee would have in a given job can be computed. In 1959, it was established that this average exposure should not exceed 50 ppm vinyl chloride or 25 ppm vinylidene chloride for an eight-hour five-day week. Exposure was 1-10.4 ppm for most employees in three monomer plants, but laboratory personnel were exposed to 30 ppm. While levels were only 1-5 ppm for most employees in the polymer plant, some areas showed as high as 150 ppm. Safe levels of any hazardous material must be established and maintained through appropriate engineering and monitoring. Corrective measures should be taken when breakdowns occur and a medical surveillance program must

be supported. Vinyl chloride is processed in closed vessels with maximum ventilation, and process automation and remote operation are emphasized. The number of samples for control analysis is minimized, manual collection is reduced by using on-line gas chromatography, and a closed-loop sampling system is used. Polymerization vessels must contain vinyl chloride concentrations of less than 50 ppm before entry for cleaning and air purge must be maintained during the operation.

283. ENVIRONMENTAL CONCERNS BEYOND THE WORKPLACE.

Schweitzer GE
Off. Toxic Subst., Environ. Prot. Agency, Wash., D.C.
Ann NY Acad Sci; 246:296-302 1975

Preliminary investigations were undertaken by the Environmental Protection Agency on vinyl chloride monomer (VCM) and polyvinyl chloride (PVC) activities, especially their migration beyond the manufacturing plants. A nationwide sampling program to determine VCM levels in ambient areas was initiated at ten PVC plants. The need for the proposed Toxic Substances Control Act which would require reporting of industrial data is emphasized. Over 200 million and 50 million pounds of VCM and PVC, respectively, are estimated to be discharged into the air, water, effluents and sludge annually. A materials loss of 6% in the PVC production process was reported. Leakage typically occurs during opening of polymerization kettles, transfer, drying and disposal of oversize polymer particles. Increased maintenance has reduced loss to 4% in some plants. Many compounding and fabrication plants are attempting to reduce the amount of monomer associated with the polymer following polymerization since monomer concentration ranges between 500-1,000 ppm and may reach 7,000 ppm. Epidemiological studies of populations near PVC plants and toxicological tests in vivo are necessary in assessing effects of VCM exposure on the nonworker population. In vitro experiments on the significance of impurities in VCM, synergistic effects due to exposure to other chemicals, and metabolic reactions induced by VCM are necessary. The persistence and migration of VCM in the environment should also be studied. Physical properties of PVC must be considered with regard to disposal. Landfill disposal presents problems because long-term PVC stability cannot be guaranteed and HCl is produced when it is incinerated.

284. OCCUPATIONAL DISEASES IN CONNECTION WITH THE MANUFACTURE OF PLASTIC BOTTLES FROM POLYVINYL CHLORIDE.

Duport J, Andlauer P, Gattelet M, Chalabreysse J, Archimbaud M, Teulon F, Bertrand R
Centre de Recherches de l'I.N.R.S., B.P. 27, 54500 Vandoeuvre-les-Nancy, France
Arch Mal Prof; 36(4-5):225-241 1975

Because of an outbreak of eczema, the blood and urine from workers in a factory that manufactures plastic bottles from vinyl chloride were examined. The chemical pollutants of the surrounding area, all industrial chemicals and cleansing solvents, and the heat decomposition of the polyvinyl chloride (PVC) bottles were studied. Over a 6-mo period, 677 blood samples from 159 workers revealed depressed levels of RBC and polynuclear neutrophils, elevated levels of WBC, and variable levels of polynuclear eosinophils. It is concluded that the manufacture of vinyl chloride bottles causes dermatitis and hematological abnormalities characterized by leukocytosis with relative lymphocytosis. Analysis of the air by gas phase chromatography and mass spectrometry revealed only slight traces of aromatic hydrocarbons. No aromatic hydrocarbons were found in the cleansing solvents. Industrial forms of PVC began to decompose slowly between 215 and 220 C; benzene was one of the byproducts of decomposition. Because this

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temperature is reached for short periods only and because decomposition is slow, it is unlikely that it is a major factor. Neither benzene nor phenol were found in the blood or urine, respectively. There were significant levels of hippuric acid, a possible metabolite of organic toxins, in the urine. Since none of these compounds was considered the cause of the dermatitis or hematological abnormalities, *a*-phenylindole, the only compound detected in high concentrations in the air, will be studied.

285. INDUSTRIAL MEDICINE AND VINYL CHLORIDE.

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Berufsdermatosen; 25(2):67-77 1977

After a short review of the history of some other occupational diseases, the institutions and government agencies in West Germany concerned with regulating industrial medicine and occupational hazards are listed. The vinyl chloride (vc) syndrome is recognized as an occupational hazard, and patients are eligible for workmen's compensation. Directions for dealing with vc are described: teaching the employees the hazards of vc, criteria for selecting new employees, regular medical examinations, and recommendations and rules governing hazard-free working conditions. New products of economic importance should be examined carefully before being commercialized. (4 Refs)

286. THE VINYL CHLORIDE MONOMER HEALTH PROBLEM.

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Chem Ind ; 5(11):466-470 1976

Proceedings of the British Plastics Federation conference on 'Vinyl Chloride and Safety at Work' of May 18, 1975 and the conference of the Occupational Health Section of the Royal Society of Medicine of September 12, 1975, were reviewed, as were recent developments on the vinyl chloride health problem in the UK, Europe, and the US. The health hazards associated with polyvinyl chloride manufacture seem to be entirely related to the vinyl chloride monomer (VCM). During 1969-71 the first fibrosarcoma due to VCM was produced in experimental animals. Soon after, another investigator found that VCM exposure produced a considerable yield of tumors of many types in the glands and liver of rats exposed to varying dosages, with a linear relationship between the log concentration and the number of tumors. Numerous epidemiological surveys have turned up over 40 cases of angiosarcomas connected with VCM in the world. Nearly all of these cases were autoclave cleaners who experienced high exposures to VCM. Much more statistical data will be necessary to assess the threshold for plant exposure so that a proper perspective can be placed on those standards now being used by manufacturers. (No refs)

287. VINYL CHLORIDE: A CASE FOR THE USE OF LABORATORY BIOASSAY IN THE REGULATORY CONTROL PROCEDURE. (PP. 1797-1805)

Wagoner JK, Infante PF

Industry-wide Studies Branch, Div. Surveillance, Hazards Evaluations and Field Studies, Natl. Inst. Occupational Safety and Health, Cincinnati, OH, 45202

Human Risk Assessment, Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation. Vol. 4 (Book C). Hiatt HH, Watson JD, Winsten JA, ed. Cold Spring Harbor, Cold Spring Harbor Laboratory, Origins of Human Cancer., 583 pp., 1977.

The need for laboratory bioassays in the regulatory control of chemicals is illustrated using vinyl chloride (VC) as

an example. The induction of skin, lung, and bone tumors in rats exposed by inhalation to high VC levels (levels not infrequently approached in the industrial setting) was first reported in 1971, 40 yr after VC's commercial introduction but 3 yr before three cases of liver angiosarcoma were reported among workers at a VC polymerization facility. A follow-up study, initiated as a result of these initial angiosarcoma cases, showed a significant excess of deaths from malignant neoplasms among VC workers, compared with US white male death rates. Excess cancer mortality was found for four organ systems: brain and CNS, respiratory system, hepatic system, and lymphatic and hematopoietic system. The cancer risk increased with increasing years of exposure. In the follow-up study, 11/14 confirmed cases of biliary or liver cancer were hepatic angiosarcoma. Among 8 bronchogenic carcinomas, 5 were large-cell undifferentiated and 3 were adenocarcinomas, which is not consistent with distributions previously reported for inhaled carcinogens. A recent bioassay was predictive not only for the carcinogenicity of VC but also for several of the target organs. VC is mutagenic in microbial test systems, and VC metabolites have induced mutations in mammalian cells. Wives of VC-exposed men have a significantly high risk of fetal loss. Thus, both mutagenic and carcinogenic assays predicted the potential hazards of VC. (34 Refs)

288. THE POSSIBLE USE OF A BIOLOGICAL EXPOSURE TEST TO DETERMINE HEALTH STANDARDS FOR WORKERS.

Teisinger J

Srobarava 48, Prague 10, Czechoslovakia
Zentralbl Arbeitsmed; 28(1):13-21 1978

The blood and urine of factory workers exposed to lead, mercury, cadmium, trichloroethylene, benzene, or xylene were tested for metabolites of these agents, and max acceptable values were established. The classification of industrial toxicants in Czechoslovakia corresponds to the classification proposed by the World Health Organization and the International Labor Office and includes the following categories: (A) exposure to the toxic agent causes no deleterious effect on the worker; (B) toxic effects are reversible and cause no long-term damage; (C) exposure causes reversible disease; and (D) exposure often causes irreversible damage or death. Lead levels in the blood of persons not continually exposed to lead were measured at 10-40 microg/100 ml blood; the upper limit was established at 70 microg/100 ml blood. Blood lead levels corresponding to category A are 10-40 microg %, B 40-70 microg %, C 70-100 microg % and D greater than 100 microg %. The level of coproporphyrin in the urine is an effective indicator of exposure to lead and should not exceed a max value of 0.8-1 mg/liter. For aminolevulinic acid, another indicator of lead exposure, a max urine value was established at 20-25 mg/liter. Max allowable concentrations for mercury and cadmium in urine were established at 0.1-0.3 mg Hg/liter and 10-20 microg Cd/liter. A previously set standard for max concentration of benzene in air (25 ppm) corresponds to a phenol level of 70-100 mg/liter in the urine. Similarly, max air concentrations for toluene and xylene (200 microns/liter air and 200 mg/m³, respectively) correspond to 550-850 mg benzoic acid/24 hr and 930 mg toluic acid in urine. Max air concentration for trichloroethylene is 50 ppm. (34 Refs)

289. VINYL CHLORIDE POISONING IN THE USSR: LITERATURE SURVEY.

Matufuji H

Occupational Health Service Center, Inst. Science Labor, Japan

Rodo Kagaku; 54(11):585-592 1978

Among workers exposed to vinyl chloride in western countries about 70 cases of hepatic angiosarcoma have been reported in Western countries, while none have been reported

in the Soviet Union (USSR). However, many cases of chronic vinyl chloride poisoning have been reported in the USSR, while few have been reported in Western countries. The USSR requires poisoned workers to change to work unrelated to vinyl chloride and limited exposure time on the job. Tolerated limits of vinyl chloride are set at 10.7 ppm in the USSR, while the limit has been 500 ppm (1959-1971) to 200 ppm (1971-1975) in the United States. Inspection of USSR factories between 1953 and 1969 revealed that unacceptable levels (greater than 10.7 ppm) occurred in 2-80% of cases. Exposure regulations and the low tolerance limits in the USSR may explain why patients with chronic vinyl chloride poisoning with characteristic symptoms have not progressed to the point of developing hepatic angiosarcoma. (42 Refs)

290. THE RISK OF CONSUMERS AND PVC WORKERS TO VINYL CHLORIDE.

Schlatter CH

Institut für Toxikologie, Schorenstrasse 16, CH-8603

Schwerzenbach bei Zurich

Schweiz Med Wochenschr; 106(19):647-650 1976

The signs and symptoms of vinyl chloride intoxication, the epidemiology of hepatic hemangiosarcoma, the results of animal experimentation, current estimates of occupational risk, and the danger of polyvinyl chloride packaging to the general population are topically reviewed.

291. THE COSTS OF CANCER.

Nisbet IC

No Affiliation Given

Technol Rev; 78(3):8-9 1975

Social and economic problems arising when a cancer-causing substance is identified are discussed, with particular emphasis on the case of vinyl chloride. Prior to the discovery of its hazards, an estimated 100 million pounds a year were lost to the environment during manufacture and a further 40-50 million pounds were released through deliberate dispersive uses. Although the most hazardous of these uses - as a propellant in spray cans - was banned in 1974, and although attempts are being made to reduce manufacturing losses, human exposure continues. The most serious problem is that trace quantities of unpolymerized vinyl chloride are found in polyvinyl chloride. Both nonoccupational and occupational exposure can be hazardous. Although federal law requires strict regulation of occupational exposure to carcinogens, the proposed standard for vinyl chloride offers little or no assurance of safety.

292. NEW IMPETUS FOR PROBE.

Anonymous

No affiliation given.

Chem Week; 114(9):14 1974

Two former employees of B. F. Goodrich's Louisville, Ky, polyvinyl chloride (PVC) plant were afflicted with angiosarcoma of the liver. This has added new urgency to the investigation into the possible carcinogenicity of vinyl chloride monomer (VCM). At the same time Union Carbide also found that a former employee at its South Charleston, W. Va, PVC plant, died in 1968 of angiosarcoma. Reacting to the Goodrich problem, the Kentucky Safety and Health Standards Board had added VCM to the list of 14 restricted industrial carcinogens issued by OSHA and lowered the employee VCM exposure level from the federal standard to 75 ppm, with a time-weighted average of 50. Because of the lack of solid scientific data on the chemical and the possible huge economic impact, OSHA has not yet issued temporary emergency standards. Investigations pertinent to this matter continue.

293. BATTLE LINES DRAWN ON VINYL CHLORIDE ISSUE.

Anonymous

Chem Eng News; 52(8):16 1974

Controls on the occupational exposure to vinyl chloride or other chemicals used in making the monomer or in polymerizing it to polyvinyl chloride have been requested by the labor unions. These controls include no measurable exposure to the carcinogen, safer work practices, closed systems, use permits, periodic medical and lab tests, plus a cut of residual vinyl chloride in PVC resins to less than 0.01% (100 ppm). The deaths of 4 polymerization section workers at the Louisville, Ky plant of B. F. Goodrich have been attributed to angiosarcoma of the liver. These workers had average exposures of some 19 years to vinyl chloride and 10 years to vinylidene chloride with variable exposure to vinyl acetate, methyl acrylate, ethyl acrylate, methanol and chlorinated solvents. Angiosarcoma of the liver is a rare occurrence, accounting for only 20 to 30 deaths per year in the entire U. S., and can be mis-diagnosed as cirrhosis of the liver. Liver angiosarcomas have been experimentally created in rats inhaling vinyl chloride down to the 250 ppm level. The rats also developed zymbal (sic) glands carcinomas and kidney nephroblastomas.

294. DRINKING WATER AND HEALTH: RECOMMENDATIONS OF THE NATIONAL ACADEMY OF SCIENCES.

Blum B

Criteria and Standards Div., Office of Water Supply,
Environmental Protection Agency, Washington, DC
20460

Fed Regist; 42(132):35764-35779 1977

Recommendations of the National Academy of Sciences concerning the contamination of water supplies with harmful substances are summarized. Four principles relevant to the assessment of risk from long-term exposure to carcinogenic substances at low doses are outlined: (1) effects in animals, properly qualified, are applicable to man; (2) methods to establish a threshold for long-term effects of toxic agents are not in existence; (3) the exposure of experimental animals to high doses of toxic agents is a necessary and valid method of discovering possible carcinogenic hazards in man; (4) materials should be assessed in terms of human risk, rather than as safe or unsafe. Risk estimates have been made for some known water supply contaminants for which data were available. Estimates of lifetime cancer risks (with a 95% upper confidence limit) are 5.1×10^{-7} , 2.6×10^{-6} , 4.4×10^{-6} , 1.2×10^{-6} , 3.1×10^{-6} , and 3.7×10^{-7} (expressed as risk/ug/liter) for vinyl chloride, dieldrin, kepone, DDT, polychlorinated biphenyls (with data for arochlor 1260), and carbon tetrachloride, respectively. The highest observed concentrations in drinking water of these substances are 10, 8, unknown, unknown, 3, and 366 ug/liter, respectively. The max observed levels of a large number of organic pesticides and other organic contaminants in drinking water are listed, together with recommended acceptable daily intake levels. (no Refs)

295. ASSOCIATION OF BIOREFRACTORIES IN DRINKING WATER AND BODY BURDEN IN PEOPLE.

Laseter JL, Dowty BJ

Center for Bio-Organic Studies, Univ. New Orleans, New Orleans, LA 70122

Ann NY Acad Sci; 298:547-556 1977

The accumulation and body burden of biorefractories found in municipal water supplies was investigated. The organic chemicals with a mol wt less than 250 are included in this discussion. The major constituents most frequently

observed in a 1 liter sample of tap water from New Orleans were benzene, carbon tetrachloride, dichloroethane, bromodichloromethane, and chloroform. The results suggest that many of the halogenated and aromatic organics pass through the treatment plant unchanged. The water treatment process appears to enhance the concentrations of other compounds. The results indicate that the quality of water in cities using underground artesian wells is several orders of magnitude lower with respect to concentration of low-mol-wt organic compounds than is that of cities such as New Orleans which relies on the Mississippi River for its water supply. The low-mol-wt organic compounds in the blood of adults and newborn humans are reported and tabulated. A bioaccumulation mechanism is suggested because the concentrations of some of these compounds were found at levels in excess of those commonly reported in drinking water. These compounds are acquired transplacentally by the fetus since carbon tetrachloride, chloroform, and benzene were present in cord blood in quantities equal to or greater than their levels in maternal blood. Drinking water can, therefore, contribute to environmentally derived biorefractories found to accumulate in human tissue. The origin of such compounds must be unequivocally established and their significance for health determined. (14 Refs)

296. VINYL CHLORIDE AND THE PRODUCTION OF PVC (MEETING ABSTRACT).

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Proc R Soc Med; 69(4):277-281 1976

The polymerization characteristics of vinyl chloride are described, and the process for producing polyvinyl chloride (PVC) is outlined. Interfaces of exposure of humans to PVC are outlined, and theoretical exposure levels for workers at various stages in the production process and for the average UK civilian are calculated. Average annual dietary ingestion is calculated as 0.0001 g/yr. Atmospheric exposure for polymerization workers has decreased from approximately 1,000 ppm in 1940 to approximately 5 ppm in 1975, although certain workers might have been exposed to as much as 3,000 ppm in 1940. The daily dose of the polymerization plant worker who had been exposed to 1,000 ppm is calculated at 0.36 g/kg, the dose for the polymerization plant worker presently exposed to 5 ppm is 0.0018 g/kg, and that of the average citizen 0.000000004 g/kg.

297. CURRENT INTELLIGENCE BULLETIN 20: TETRACHLOROETHYLENE (PERCHLOROETHYLENE).

National Institute for Occupational Safety and Health
Natl. Inst. Occupational Safety and Health, Cincinnati, OH
Current Intelligence Bulletin 20: Tetrachloroethylene (perchloroethylene). Available Through National Technical Information Service, Springfield, Va., as PB-278 055/9GA.; DHEW/PUB/NIOSH-78/112, 14 pp., 1978.

Based on a recent study indicating that tetrachloroethylene causes liver cancer in mice, the National Institute for Occupational Safety and Health (NIOSH) recommends that it is prudent to handle the compound in the workplace as if it is a human carcinogen, while its carcinogenic potential at work is being further evaluated. The recommended NIOSH tetrachloroethylene exposure limit of 50 ppm and the Occupational Safety and Health Administration standard for occupational exposure of 100 ppm, may not provide adequate protection from potential carcinogenic effects because they were selected to prevent toxic effects other

than cancer. It is estimated that about 500,000 workers employed in dry cleaning establishments and other industries are currently at risk of exposure to the compound in the United States. Suggested procedures for control of overexposure to tetrachloroethylene, and guidelines for personal protective equipment and personal hygiene are outlined. (Author abstract)

298. LEGAL DECISIONS AND OPINIONS IN POLLUTION CASES.

Hills JP

Messenger, Lynch, Hills and Miller, Attorneys and Counselors at Law, Beltsville, MD 20705

Environ Sci Technol; 10(3):234-238 1976

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

299. CARCINOGENIC RISK ASSESSMENT: ETHYLENE DIBROMIDE.

Ramsey JC, Park CN, Ott MG, Gehring PJ

Toxicology Res. Lab., Health and Environmental Res.,

Dow Chemical Co., Midland, MI, 48640

Toxicol Appl Pharmacol; 47(2):411-414 1979

The incidence of cancer following ethylene dibromide (EDB) exposure predicted by a one-hit carcinogenesis model using parameters derived from a bioassay in rats was compared with that observed in a group of 156 workers employed in EDB production. The parameter estimates were derived from the age-specific incidence of tumor formation in male rats treated with 40 mg/kg/day EDB by gavage in corn oil. The one-hit model estimated that an almost 100% lifetime incidence of cancer should be expected in workers exposed for 40 yr to 0.4 ppm EDB at citrus fumigation centers. The duration of exposure to EDB at two locations (at 1 of which employees were also exposed to carbon tetrachloride and chloroform) was determined by work history records of each employee and by an industrial hygiene survey of airborne

concentrations of EDB at one of the locations. Time-weighted av (TWA) concentrations of EDB were conservatively assumed to be 3.0 ppm (23 mg/m(3)). The effect of a different exposure concentration was also conducted at an assumed TWA of 0.9 ppm (6.9 mg/m(3)). The one-hit model predicted either 85 or 54 neoplasms above the normal background incidence at TWA EDB concentrations of 3.0 or 0.9 ppm, respectively, compared with the 8 neoplasms observed to date in both employee groups combined. It is concluded that the use of the one-hit model results in highly exaggerated risk estimates in humans. (8 Refs)

300. DIBROMOCHLOROPROPANE (DBCP) (MEETING ABSTRACT).

Legator M, Biles R, Connor T
Univ. Texas Medical Branch, Galveston, TX, 77550
The Scientific Basis for the Public Control of
Environmental Health Hazards, held by the New York
Academy of Sciences in New York, 21-30 June, 1978. The
New York Academy of Sciences, New York, New York,
1978.

Dibromochloropropane (DBCP) represents another example of a growing list of industrial chemicals where available animal data were disregarded and workers were needlessly exposed to a hazardous substance. This chemical further illustrates the need to establish a meaningful surveillance program in industry to identify potential carcinogenic and mutagenic agents. Fifteen yr prior to the accidental discovery of azoospermia in workers, animal toxicity data concerning gonadal effects were available. Structurally related compounds were known to effect reproductive systems in the late 1960's. Carcinogenic data were reported in 1973 and 1975. This information was disregarded by both industry and governmental agencies. Furthermore positive mutagenic studies were reported in 1975. Recent investigations indicate that sperm from exposed workers show a significant increase in YY bodies indicating that this chemical may cause segregation errors. Utilization of animal data and industrial populations monitoring should, in the future, prevent exposures to other hazardous chemicals. (no Refs)

301. CRITERIA FOR A RECOMMENDED STANDARD-OCCUPATIONAL EXPOSURE TO ALLYL CHLORIDE.

NIOSH

National Inst. Occupational Safety and Health, Cincinnati,
OH

Gov Rep Announce Index; 77(17):84 1977

The recommended standards include an exposure limit of 1.0 ppm as a time-weighted concentration for up to 10-hr work shift in a 40-hr work wk, with a ceiling concentration of 3.0 ppm for 15 min. Provisions are included for sampling, collection, analysis, pre-employment medical examination, periodic examinations, first-aid, medical records, labeling and posting, personal protective equipment (respiratory protection including respirator requirements, eye protection and skin protection), informing employees, emergency procedures involving allyl chloride, control of airborne allyl chloride, storage, handling and general work practices, waste disposal, confined spaces, sanitation, monitoring and recordkeeping. Criteria include the purpose of the standards, biologic effects of exposure (including the extent of exposure, historical reports, effects on humans, epidemiologic study, animal toxicity, correlation of exposure and effect, carcinogenesis, mutagenesis and teratogenesis), environmental data and analytical methods, basis for previous standards and for the present recommended standard and research needs. (Author abstract) (no Refs)

VIII. REVIEWS AND OTHER RELATED STUDIES INCLUDING VINYL CHLORIDE AND RELATED COMPOUNDS

The reader may also find the following abstracts of interest: 52, 108, 139, 159, 288

302. POTENTIAL HALOGENATED INDUSTRIAL CARCINOGENIC AND MUTAGENIC CHEMICALS. I. HALOGENATED UNSATURATED HYDROCARBONS.

Fishbein L

National Center Toxicological Res., Jefferson, AR, 72079
Sci Total Environ; 11(2):111-161 1979

Data on the carcinogenicity and mutagenicity of several of the most industrially significant halogenated unsaturated hydrocarbons are reviewed to assess the nature of their present potential risk. These compounds are vinyl chloride, vinylidene chloride, trichloroethylene, perchloroethylene, chloroprene, trans-1,4-dichlorobutene, hexachlorobutadiene, and allyl chloride. Aspects of their synthesis (primarily in terms of the nature of possible hazardous trace impurities), production volumes and use patterns, chemical and biological reactivity and stability, environmental occurrence, and national permissible worker exposure levels are considered. Experimental and human epidemiologic evidence of the carcinogenicity and mutagenicity of the hydrocarbons is reviewed, as are data concerning their in vivo and in vitro metabolism. (302 Refs)

303. POTENTIAL HALOGENATED INDUSTRIAL CARCINOGENIC AND MUTAGENIC CHEMICALS II. HALOGENATED SATURATED HYDROCARBONS.

Fishbein L

Natl. Center for Toxicological Res., Jefferson, AR, 72079
Sci Total Environ; 11(2):163-195 1979

The carcinogenic and mutagenic potentials of the industrially significant halogenated saturated hydrocarbons are reviewed. These compounds possess considerable utility as solvents, drycleaning fluids, refrigerants, fumigants, degreasing agents, propellants, and intermediates in the production of other chemicals, textiles, and plastics. They include methyl chloride, methylene chloride, chloroform, carbon tetrachloride, methyl chloroform, 1,1,2-trichloroethane, hexachloroethane, ethyl chloride, and the fluorocarbons. They are discussed principally in terms of their synthesis or occurrence, areas of application, stability, distribution, reactivity, exposure levels, populations at risk, carcinogenicity, mutagenicity, and metabolism. (164 Refs)

304. VINYL CHLORIDE-ASSOCIATED LIVER DISEASE.

Berk PD, Martin JF, Young RS, Creech J, Selikoff IJ, Falk H, Watanabe P, Popper H, Thomas L

Room 4D-52, Building 10, Section on Diseases of the Liver,
Digestive Diseases Branch, Natl. Inst. Arthritis,
Metabolism, and Digestive Diseases, NIH, Bethesda, MD
20014

Ann Intern Med; 84(6):717-731 1976

The association of vinyl chloride exposure and liver diseases is reviewed. Polyvinyl chloride has been produced from vinyl chloride monomer for over 40 yr, but recognition of toxicity among vinyl chloride polymerization workers is more recent. In the mid 1960's, acro-osteolysis was found in workers involved in cleaning polymerization tanks. In 1974, the same population of workers was found to be at risk for an unusual type of hepatic fibrosis and angiosarcoma of the liver. Two cases of vinyl chloride-associated liver injury, one of hepatic fibrosis and one of angiosarcoma, are presented. The histologic features of these lesions are similar to the hepatic

R&S 111279

fibrosis and angiosarcomas resulting from chronic exposure to inorganic arsenicals. Preliminary studies suggest that the toxicity of vinyl chloride may result from formation, during high-dose exposure, of active metabolites by mixed-function oxidases of the liver. Epidemiologic studies indicate an increased incidence not only of liver disease, but also of cancers of the brain, lung, and possibly other organs. (51 refs)

305. TOXIC EFFECTS OF VINYL CHLORIDE.

Veltman G, Lange CE, Stein G
Univ.-Hautklinik Bonn-Venusberg, D-5300 Bonn 1, W.
Germany
Hautarzt; 29(4):177-182 1978

The toxicological aspects of vinyl chloride (VC) are reviewed on the basis of examinations of workers occupationally exposed to VC over long periods of time. The liver histology revealed periportal, septal, and intralobular fibrosis; focal and reticular collagenization of the sinusoid walls; hepatocyte degeneration; and activation and proliferation of the sinusoid cells, with cell atypia and transition into angiosarcoma occurring in some cases. The metaphase analysis revealed no remarkable pathological changes; ie, no mutagenic effect of VC. (35 Refs)

306. TOXICOLOGY OF VINYL CHLORIDE.

Heuse A
Laboratoire de Medecine du Travail et Hygiene du Milieu,
Universite Libre de Bruxelles, Brussels, Belgium
Brux Med; 58(1):13-34 1978

A review of the literature on vinyl chloride (VC) traces the history of the toxicity of the compound. Also reviewed are the toxic effects of polyvinyl chloride (PVC), relative risk of industrial exposure to VC and PVC, and potential danger of exposure of the general population to PVC. (196 Refs)

307. INDUSTRIAL HAZARDS DUE TO VINYL CHLORIDE.

Hublet P
Ecole de Sante publique de la Faculte de medecine,
Universite libre de Bruxelles, rue Belliard 100, 1040
Brussels, Belgium
Arch Belg Med Soc; 33(2):73-89 1975

Various aspects of vinyl chloride are reviewed: its physical and chemical properties, methods of synthesis, means of identification, uses, evidence of toxic effects, and industrial risks due to exposure. Because of its toxicity, greater efforts should be made to reduce the concentration in factory air, and workers exposed to the chemical should be examined often. More detailed studies of vinyl chloride and other toxic chemicals should be undertaken.

308. NEW DISCOVERIES AND OBSERVATIONS ON THE PROGRESS OF VINYL CHLORIDE DISEASE (MEETING ABSTRACT).

Veltman G, Lange CE, Stein G
Bonn, W. Germany
Z Hautkr; 52(6):196 1977

The symptomatology of vinyl-chloride (VC) disease with special attention to newer discoveries and the danger to the worker in VC-related industries are discussed. Various periodic checks on skin and bone changes, thrombocytes and liver functions are available. The preventive measures that have arisen from this knowledge have generally removed the immediate threat at the factory. (no Refs)

309. AN OVERVIEW OF THE VINYL CHLORIDE HAZARD IN CANADA.

Basuk J, Nichols A
Science Council Canada, Ottawa, Canada
Chem Can; 29(7):24-38 1977

The effects of occupational exposure to vinyl chloride monomer (VCM) are emphasized in this review, which also includes a discussion of the properties and processing of VCM. VCM came to attention as a health hazard in 1973, when three cases of a rare form of liver cancer, angiosarcoma, were reported in workers from a VCM factory. Since then, 48 victims have been identified; others who may have died from angiosarcoma are unknown because of difficulty in diagnosing the disease. VCM has chronic effects on human beings at high levels of exposure. It causes a specific occupational disease known as acro-osteolysis, in which there is both Raynaud's syndrome and sclerodermiform lesions. In animal studies VCM has produced a wide range of tumors in rats, mice, and hamsters: Zymbal gland carcinomas, nephroblastomas, angiomas and angiosarcomas of the liver and other sites, trichoeplitheliomas, hepatomas, lung adenomas, mammary adenomas and carcinomas, and lymphomas. Recent findings suggest that mammary carcinomas can be induced in laboratory animals at less than or equal to 1 ppm. Efforts to control the adverse health effects of VCM include the setting of standards for occupational exposure to VCM, improved manufacturing techniques to minimize VCM exposure and residual VCM in polyvinyl chloride resin, and increased research on the epidemiology of VCM-related diseases and on diagnosing preangiosarcoma tumors. (65 Refs)

310. CARCINOGENICITY OF VINYL CHLORIDE: CURRENT RESULTS. EXPERIMENTAL EVIDENCE.

Maltoni C
Inst. Oncology and Bologna Tumour Centre, Bologna,
Italy
Adv Tumor Prev Detect Charact; 3:216-237 1976

Partial results are presented from a series of experiments designed to study the effect of vinyl chloride (VC) administered through different routes at different concentrations, for varying periods of time, by continuous or intermittent treatment, on animals of different species (rats, mice, hamsters), strains (Sprague-Dawley and Wistar rats), sex, and age (adults, newborns, embryos). A complete autopsy was made on each animal, which was kept under observation until spontaneous death. Histological examinations were performed on Zymbal glands, interscapular brown fat, salivary glands, tongue, lungs, liver, kidneys, spleen, stomach, different segments of the intestine, bladder, brain, bones of the legs and feet, and any other organ with pathological lesions. Animals exposed to the highest doses (30,000 and 10,000 ppm), with or without tumors, were examined radiologically. When given by inhalation, VC produced the following tumors: in rats, Zymbal gland carcinomas, nephroblastomas, angiosarcomas, mammary carcinomas, and forestomach papillomas; in mice, lung adenomas, mammary carcinomas, angiosarcomas and angiomas of the liver and other sites, skin epithelial tumors, and forestomach papillomas; and in hamsters, liver angiosarcomas, skin trichoeplitheliomas, melanomas, forestomach papillomas, acanthomas, hepatomas, and lymphomas. The response was affected by the length of exposure and by the strain. The onset of tumors in the offspring of breeders exposed during pregnancy for 7 days suggests a transplacental effect. When given by stomach tube at high doses, VC induced angiosarcomas of liver and other sites and Zymbal gland carcinomas in rats. The doses producing these tumors, however, were extremely high when compared to possible human exposure. Thirty cases of liver

angiosarcoma have been identified among workers of VC-PCV (polyvinyl chloride) industries in the US and several European countries. The majority of cases did not occur until 15 yr or more after the first exposure to VC. An excess mortality for cancers of the respiratory tract, blood-forming tissues, and brain has also been observed among workers of VC polymerization plants in the US. It is concluded that VC carcinogenesis has shown the value of experimental bioassays in predicting oncogenic risks. (7 refs)

311. CHLOROPRENE (2-CHLORO-1,3-BUTADIENE) - WHAT IS THE EVIDENCE FOR ITS CARCINOGENICITY?

Haley TJ

Dept. Health, Education, and Welfare, Food and Drug Admin., Natl. Center Toxicological Res., Jefferson, AR, 72079

Clin Toxicol; 13(2):153-170 1978

The biochemistry, metabolism, and toxicology of chloroprene (CP: 2-chloro-1,3-butadiene) were reevaluated to establish whether it is a potential carcinogen. The po LD(50)'s of CP in mice and rats are 260 and 251 mg/kg, respectively. The pathologic changes in these animals included hemorrhages and dystrophic changes in the CNS, lungs, kidneys, and spleen. Chronic inhalation of CP by dogs resulted in changes in higher nervous activity, the nerve cells of the cerebral cortex, and the brain vasculature. Blood histamine increased and histaminase activity decreased in 103 Soviet workers exposed to CP, and the changes were related to duration of exposure. During chronic CP intoxication, there was dysfunction of both the CNS and peripheral nervous system, particularly the cholinergic branch. Cytogenetic analysis of somatic cells from exposed workers aged 23-59 yr revealed both chromosome and chromatid aberrations. Immunization of 208 CP workers with typhoid vaccine produced low immunologic reactivity and no increase in phagocytic activity. In mice, the growth of transplanted Crocker's sarcoma was accelerated by sc CP injection. During 1956-1970, 137 cases of skin cancer were diagnosed in 24,989 Soviet patients; CP workers had the highest skin cancer incidence (21/684), followed by persons working with CP derivatives (38/2,250). In the same period, 87 lung cancers were found in 19,979 workers; 18 of the patients had direct and prolonged exposure to CP and 16 had a history of exposure to CP latexes. Worldwide epidemiology studies should be undertaken to validate the Soviet reports of CP carcinogenicity in humans. Additional metabolic studies are also necessary to define the neurohumoral mechanism of CP action. (149 Refs)

312. VINYL HALIDES: CARCINOGENICITY. VINYL BROMIDE, VINYL CHLORIDE, AND VINYLIDENE CHLORIDE.

Bahlman LJ, Alexander V, Infante PF, Wagoner JK, Lâne JM, Bingham E

Natl. Inst. Occupational Safety and Health, 5600 Fishers Lane, Rockville, MD, 20857

Am Ind Hyg Assoc J; 40(4):A-30-A-40 1979

Laboratory studies demonstrating the carcinogenicity and mutagenicity of vinyl chloride (VC), vinylidene chloride (VDC), and vinyl bromide (VB) are reviewed, together with studies demonstrating the carcinogenicity and mutagenicity of VC in humans. Liver angiosarcomas have been induced in rats or mice by vinyl halide concentrations of 25-55 ppm. It is recommended that VB and VDC be considered in the workplace as potential carcinogens to humans and controlled with the same degree of prudence as VC. (35 Refs)

313. TRICHLOROETHYLENE. (PP. 263-276)

IARC Working Group

IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man. Cadmium, Nickel, Some Epoxides, Miscellaneous Industrial Chemicals and General Considerations on Volatile Anaesthetics. International Agency for Research on Cancer, Lyon France, Vol 11, 1976.

The chemical and physical data; production, use, occurrence, and analysis; and biological data relevant to the evaluation of carcinogenic risk to man of trichloroethylene are examined. In the US, approx 90% of the trichloroethylene produced is used for vapor degreasing of fabricated metal parts. Gastric intubation of 2.4 or 1.2 g/kg body wt trichloroethylene 5 x/wk in male B6C3F mice and of 1.8 or 0.9 g/kg in females induced hepatocellular carcinomas in 30/98 mice given the low dose and in 41/95 mice given the higher dose. Hepatocellular carcinomas occurred in 1/40 control mice. Gastric intubation of either 1.0 or 0.5 g/kg of the compound in both sexes of Osborne-Mendel rats, 5 x/wk for an unspecified period, produced no hepatocellular carcinomas. (61 Refs)

314. A REVIEW ON THE TOXICITY OF TRACE AMOUNTS OF TETRACHLOROETHYLENE IN WATER.

Utzinger R, Schlatter C

Inst. Toxicology, Swiss Federal Inst. Technology, CH-8003 Schwerzenbach, Switzerland

Chemosphere; 6(9):517-524 1977

The toxicity, metabolism, mutagenicity, carcinogenicity, and environmental concentrations of tetrachloroethylene (C2Cl4) are discussed. The ingestion or inhalation of 50 mg/day C2Cl4 is considered acceptable; therefore, the trace amounts of C2Cl4 in air and drinking water are not a serious health problem. Mice exposed to the compound for 12 mo (300 or 600 ppm, 6 hr/day 5 days/wk) developed liver cancers, but these results could not be extrapolated to humans. (22 Refs)

315. VINYLIDENE CHLORIDE: A REVIEW OF THE LITERATURE.

Haley TJ

US Dept. Health, Education and Welfare, Food and Drug Admin., Natl. Center Toxicological Res., Jefferson, AR Clin Toxicol; 8(6):633-643 1975

The literature concerning the chemistry, industrial hygiene, and toxicology of vinylidene chloride (VC) is reviewed. The po administration of 2 mg/kg VC to rats decreases liver glucose-6-phosphatase and increases liver alkaline phosphatase and tyrosine transaminase and also plasma alkaline phosphatase and alanine transaminase. The threshold limit value of VC is 5 mg/cubic meter. The liquid or the vapor form is highly irritating to the eyes and skin, but the chemical is most dangerous when inhaled. In rats, the signs of toxicity upon inhalation include continuous blinking, lacrimation, nasal irritation, roughened coat, excessive salivation, accelerated respiration, gasping, tremors, convulsions, incoordination, prostration, and narcosis. Human exposure to VC results, within 8-30 hr, in irreversible lesions of the trigeminal nerve. VC exerts its primary effects on the CNS, peripheral nervous system, and, particularly, the liver and kidneys. More detailed long-term studies are needed to determine the possible carcinogenicity of this compound. (38 refs)

316. ETHYLENE DIBROMIDE. (PP. 195-209)

IARC Working Group

IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man: Some Fumigants, the Herbicides 2,4-D and 2,4,5-T, Chlorinated Dibenzodioxins and Miscellaneous Industrial Chemicals. Lyon, International Agency for Research on Cancer, Vol. 15, 1977.

The experimental evidence on the carcinogenicity of ethylene dibromide is reviewed. When the compound was administered po to (C57Bl x C3H)F1 mice and Osborne-Mendel rats, squamous cell carcinomas of the forestomach were noted. Ethylene dibromide injected ip in rats induced damage to the spermatogenic cells; however, no data on embryotoxicity or teratogenicity are available. Mutations were induced in *Neurospora crassa* and *Drosophila melanogaster* receiving the compound. Ethylene dibromide has been shown to be toxic to man, but no data are available on its carcinogenicity in humans. (62 Refs)

317. REVIEW OF SELECTED LITERATURE ON ETHYLENE DIBROMIDE (EDB).

Kover FD

Environmental Protection Agency, Office Toxic Substances, Washington, D.C.

Gov Rep Announce (US); 76(26):157 1976

A review of some of the literature on ethylene dibromide is presented. Among the topics discussed are: its uses, properties, production, environmental aspects, sampling and analysis methodology, emission estimates, biological and toxicological considerations, mutagenic potential, reproductive effects, carcinogenic activity, regulations, and substitutes. (no refs)

318. OCCUPATIONAL CHEMICAL CARCINOGENESIS: NEW FACTS, PRIORITIES AND PERSPECTIVES. (PP. 127-149)

Maltoni C

Environmental Pollution and Carcinogenic Risks. Lyon, International Agency for Research on Cancer, IARC Scientific Publications No 13, INSERM Symposia Series, vol. 52, 1976.

The results of experiments on the carcinogenicity of vinyl chloride (VC) are presented in 18 tables as part of a paper calling for a more active approach to the problem of environmental oncogenesis. VC was inhaled at doses from 30,000 ppm to 1 ppm for 4 hr/day, 5 days/wk for 52 wk by rats (Sprague-Dawley, Webster), mice (Swiss), and hamsters (Chinese); 50 ppm was the dividing dose in carcinogenic potential, and a variety of cancers resulted from the higher dosages. VC was also administered by inhalation at 10,000 ppm and 6,000 ppm, 4 hr/day for 1 wk. The resulting cancers were monitored in the animals and their offsprings. In addition, VC was ingested at 50.00, 16.65, and 3.33 mg/g body weight, once daily, 4-5 days/wk for 52 wk; liver angiosarcomas were the predominant resulting neoplasms. Lower dosages of 1, 0.3, and 0.03 mg/g body weight produced no tumors. Subcutaneous administration into rats of 30 mg of compound in 1 cc of water of chromite, neochromium, chromium alumina, lead chromate, molybdenum orange, cadmium sulphide, iron oxide, zinc chromate, and titanium oxide resulted in rhabdomyosarcomas and fibrosarcomas in all cases but chromite, iron oxide (red), titanium oxide, and zinc chromate. Adriamycin was tested in rats by sc injection of 2 mg in 1 cc olive oil. Tumors resulted in 35% of females and 30% of males after an average latency of 31-32 wk. Plans of experiments to test the oncological effectiveness of styrene, vinylidene chloride, and acrylonitrile are also given in tabular form. (14 Refs)

319. CANCER AND CONGENITAL ANOMALIES ASSOCIATED WITH ANESTHETICS.

Corbett TH

US Veterans Admin. Hosp., Ann Arbor, MI 48105

Ann NY Acad Sci; 271:58-66 1976

Certain anesthetics in general use may be carcinogenic, embryolethal, teratogenic, and/or mutagenic. Spontaneous abortion rates as high as 38% have been reported among nurse anesthetists, compared to a rate of 9% among general duty nurses, and 16.4% of 434 children born to nurse anesthetists who had worked during pregnancy had birth defects, compared to only 5.7% of 261 children born to nurse anesthetists who had not worked while pregnant. Three studies have indicated an increased cancer risk in operating room personnel; a recent survey involving 50,000 such personnel and 30,000 non-operating room female medical personnel controls revealed an increased prevalence of cancer in the former, ranging from 1.3 to 2 times the control rate. Halogen ether anesthetics such as isoflurane, methoxyflurane, and enflurane are similar in chemical structure to the proved carcinogen bis(chloromethyl) ether, and trichloroethylene is likewise similar to the carcinogen vinyl chloride. Isoflurane has been shown to be carcinogenic in mice. When pregnant Swiss/ICR mice were exposed to 0.5% isoflurane for 2 hr on days 12, 14, 16, and 18 of pregnancy and the offspring were exposed to 0.1% isoflurane every other day from age 5 days for 25 exposures, 10/37 male offspring killed after 15 mo had hepatic neoplasms, with three animals having multiple tumors. No neoplasms were observed among 23 control animals. Isoflurane, and the structurally similar halogenated ether and alkane anesthetic agents, must be regarded with suspicion and studied for carcinogenic properties as soon as possible.

320. GENETIC EFFECTS ASSOCIATED WITH INDUSTRIAL CHEMICALS. (PP. 100-113)

Wagoner JK, Infante PF, Brown DP

Industrywide Studies Branch, Div. Surveillance, Hazard Evaluation and Field Studies, Natl. Inst. Occupational Safety and Health, Cincinnati, OH

Proceedings Conference on Women and the Workplace, June 17-19, 1976, Washington, D.C. Society for Occupational and Environmental Health, Washington, DC, 364 pp., 1977.

The carcinogenicity and mutagenicity of various chemicals found in the workplace are reviewed, with emphasis on their genetic effects. Women have been excluded from workplaces where vinyl chloride (VC) may be inhaled, but studies have also shown an increased fetal death rate in the offspring of men exposed to VC. Two structural analogs of VC, vinylidene chloride and trichloroethylene, which have wide industrial use, have been shown to be carcinogenic in rodents and mutagenic in microbial and plant assays. However, human data for both are lacking. Functional disruption of spermatogenesis occurred among men occupationally exposed to chloroprene (2-chlorobutadiene) for less than or equal to 10 yr, and morphological disruption of spermatogenesis occurred among men exposed for greater than 10 yr. Wives of workers exposed to chloroprene have a threefold excess of miscarriage. (38 Refs)

321. EFFECTS OF ENVIRONMENTAL CHEMICALS ON THE GENETIC REGULATION OF MICROSOMAL ENZYME SYSTEMS.

Nebert DW, Levitt RC, Orlando MM, Felton JS

Room 13-N-234, Bldg. 10, Natl. Inst. Child Health and Human Development, Bethesda, MD 20014

Clin Pharmacol Ther; 22(5,part2):640-658 1977

Examples of the interaction of environmental carcinogens (polycyclic hydrocarbons, halogenated hydrocarbons, 2-

acetylaminofluorene and acetaminopen) with the genetic regulatory system controlling the monooxygenase response are presented. Studies have indicated that because of the small number of genes involved in a chemical's metabolism, an individual's response to a given environmental chemical can vary, even among siblings. (79 Refs)

322. INDUSTRIAL MUTAGENS AND POTENTIAL MUTAGENS. 1. HALOGENATED ALIPHATIC DERIVATIVES.

Fishbein L

Natl. Center Toxicological Res., Jefferson, AR 72079
Mutat Res: 32(3/4):267-307 1976

Many industrially and environmentally significant halogenated aliphatic derivatives are discussed in terms of their use patterns, residue levels and distribution patterns, chemical and physical properties, and metabolism. Halogenated hydrocarbons are discussed in general, while mutagenic and potential mutagenic halogenated aliphatic derivatives are specifically discussed. These derivatives include vinyl chloride, vinylidene chloride, trichloroethylene, tetrachloroethylene, ethylene dichloride and dibromide, chloroprene, chloroform, carbon tetrachloride, fluorocarbons, epichlorohydrin, 2-chloroethanol, and haloethers. (242 refs)

323. VINYL CHLORIDE AND VINYL BENZENE (STYRENE) - METABOLISM, MUTAGENICITY AND CARCINOGENICITY.

Vainio H

Dept. Industrial and Toxicology, Inst. Occupational Health, Haartmaninkatu 1, SF-00290 Helsinki 29, Finland

Chem Biol Interact; 22(1):117-124 1978

The metabolism, mutagenicity, and carcinogenicity of vinyl chloride (VC) and vinyl benzene (styrene) are reviewed briefly. VC and styrene are mutagenic in bacterial test systems, *Drosophila*, yeast, and mammalian cells. The mutagenicity of VC in bacterial test systems depends, at least partially, on metabolic activation by microsomal enzymes. Chloroethylene oxide, the primary biotransformation product of VC, is a potent mutagenic and alkylating agent. Styrene is mutagenic to *Salmonella typhimurium*, but only after metabolic activation, whereas styrene oxide, its primary biotransformation product, is mutagenic to *Salmonella* without activation. In several studies, an excess of chromosome aberrations (compared with controls) was found in the lymphocytes of workers exposed to VC monomer. In addition, an excess fetal loss occurred among women whose husbands are heavily exposed to VC. Workers exposed to styrene also had increased chromosome aberrations in their lymphocytes. Both chloroethylene oxide and styrene oxide bind covalently to cellular macromolecules. VC is carcinogenic in rats (skin, lung, bone, liver) and humans (liver, brain, lung, and lymphatic tissue). Styrene oxide was a weak carcinogen when applied to mouse skin. Styrene is currently being tested in animals. These findings raise concern about the possible genetic risks of VC and styrene to humans. (55 Refs)

324. RECENT FINDINGS ON THE CARCINOGENICITY OF CHLORINATED OLEFINS.

Maltoni C

Inst. Oncology and Tumor Center, Bologna, Italy
Environ Health Perspect; 21:1-5 1977

Major factors affecting the carcinogenicity of vinyl chloride (VC) and vinylidene chloride (VDC) are discussed. Although the two compounds have very similar molecular structures, they have widely different biological effects. VC is a

multipotential carcinogen, but VDC has produced tumors only in the murine kidney. Dose, concentration, length of treatment, route of administration, and animal species, strain, sex, and age also significantly affect the neoplastic response. These factors may alter the metabolic pathway of the test compounds. The carcinogenicity of VC and VDC is due to their active metabolites, probably epoxy derivatives. Animal species, strain, and sex greatly affect the production of active metabolites of VDC. In Swiss mice and Sprague-Dawley rats, there is a parallelism between the toxic and carcinogenic effects of VDC in relation to species and sex. Confirmation of this parallelism in other strains would indicate new routes for establishing experimental animal models, and for understanding the mechanisms of action of many organic carcinogens.

325. MUTAGENIC AND CARCINOGENIC RISKS ASSOCIATED WITH HALOGENATED OLEFINS.

Infante PF

Industry-Wide Studies Branch, Div. Surveillance, Hazard Evaluations and Field Studies, Natl. Inst. Occupational Safety and Health, Center Disease Control, Dept. Health, Education and Welfare, Cincinnati, OH, 45202

Environ Health Perspect; 21:251-254 1977

The mutagenicity and carcinogenicity of vinyl chloride (VC), vinylidene chloride, trichloroethylene, perchloroethylene, and chloroprene are reviewed. Of the first four compounds, all except perchloroethylene have been shown to be mutagenic in test systems, and all have induced tumors in experimental animals. Studies with chloroprene have indicated that it causes sterility in male mice and rats. Rat studies have also indicated that concentrations ranging from 0.04 to 1.0 ppm result in a dominant lethal effect, affect sperm, cause testicular atrophy, and cause chromosomal aberrations in bone marrow cells. Human studies have indicated both an increase in chromosomal aberrations and a decrease in mobility of the sperm of exposed workers. Several studies have indicated an excess of lung and skin cancer in exposed workers, and one report confirmed a case of angiosarcoma of the liver in a worker with extensive exposure to finished polychloroprene. Studies with VC have indicated that in addition to angiosarcoma, there appears to be a dose-response relationship between exposure and the induction of mammary cancer in rats. A study of women employed in the VC industry indicated a 38% excess of breast cancer in those exposed. These findings could indicate another site of VC carcinogenesis. (29 Refs)

326. SESSION II. CARCINOGEN SCREENING: OBSTACLES AND OPTIONS. IN VITRO TESTING OF ENVIRONMENTAL MUTAGENS/CARCINOGENS. (PP. 27-33)

Ames BN

Berkeley, CA, 94720, Univ. California

Structural Correlates of Carcinogenesis and Mutagenesis A Guide to Testing Priorities? Proceedings of the Second Food and Drug Administration Office of Science Summer Symposium held in Annapolis, 31 August-2 September 1977. Office of Science, FDA, Annapolis, MD, HEW Publication No (FDA)78-1046, 241 pp., 1978.

The development, accuracy, and recent applications of the Ames *Salmonella* mutagenesis test are discussed. Chemicals tested for mutagenicity and carcinogenicity have included flame retardants in children's pajamas, pesticides, vinyl chloride, and dibromo compounds in citrus-flavored soft drinks. (9 Refs)

327. THE RELEVANCE OF DOSE-DEPENDENT PHARMACOKINETICS IN THE ASSESSMENT OF CARCINOGENIC HAZARD OF CHEMICALS. (PP. 187-203)

Gehring PJ, Watanabe PG, Young JD

Toxicology Res. Lab., Health and Environmental Res.,
Dow Chemical, Midland, MI, 48640

Incidence of Cancer in Humans, Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation. Vol. 4, Hiatt HH, Watson JD, Winsten JA, ed. Cold Spring Harbor, Cold Spring Harbor Laboratory, Origins of Human Cancer., 602 pp., 1977.

The use of data obtained after the lifetime daily administration of max tolerated doses of an agent to animals (usually rats or mice) to predict the hazard of low-level exposure to the agent is not justified. Changes in the fate of the chemical or in the metabolic status of the animals preclude the use of routine statistical processes to predict hazards from low doses. Metabolic thresholds may lead to a disproportionate increase in toxicity, including carcinogenesis. This concept is illustrated by pharmacokinetic studies with 1,4-dioxane and vinyl chloride (VC). The marked dose-dependent fate of dioxane and the strong metabolic induction by high doses, together with toxicologic data, negate extrapolation of high-dose carcinogenesis to predict the hazard of low doses. In rats, cancer induction occurs only at doses sufficient to cause marked pathology, metabolic alteration, and even death. These effects, including carcinogenesis, are correlative with the dose-dependent fate of dioxane. In light of this correlation, the hazard of low-level exposure to dioxane appears to be nil. Studies indicate that VC is metabolized by at least two different pathways. The fate of VC changes with dose because the primary pathway for its metabolism is saturated at high doses or exposures. However, both pathways for the metabolism of VC produce reactive metabolites that lead to the same end products. A correlation appears to exist between doses of VC that cause tumors and those that saturate metabolic or detoxifying pathways. There is a threshold of exposure in rats, in which the physiologic defense mechanisms remain fully operative. Thus, dose-dependent alterations in the fate of chemicals must be considered when using toxicological or carcinogenic data obtained at high doses to assess the hazard of low doses. (21 Refs)

328. REVIEW OF ANIMAL STUDIES (MEETING ABSTRACT).

Williamson KS

ICI Ltd., Central Medical Group, Fulshaw Hall,
Wilmslow, Cheshire, SK9 1QB, England
Proc R Soc Med; 69(4):281-283 1976

The author reviews several studies that have been conducted on animals exposed to vinyl chloride gas. It appears that the proportion of the dose retained and metabolized is greater following small doses than large ones. The amount that is inhaled is eliminated in three ways: unchanged from the lungs, in the carbon dioxide from the lungs, and by the excretion of metabolites in the urine. Although many studies are incomplete, there is substantial evidence to indicate that vinyl chloride is oncogenic.

329. MUTAGENICITY TESTS IN CHEMICAL CARCINOGENESIS. (PP. 229-240)

Bartsch H

Unit of Chemical Carcinogenesis, International Agency for Research on Cancer, 150 cours Albert Thomas, 69008 Lyon France.

Environmental Pollution and Carcinogenic Risks, Lyon, International Agency for Research on Cancer, IARC Scientific Publications No 13, INSERM Symposia Series, vol. 52, 1976.

The use of mutagenicity tests in the assessment of chemical carcinogenicity is assessed. The validity of this application is demonstrated with the vinyl chloride experiments in rats, mice, human liver, and *Salmonella typhimurium* and the N-nitrosamine activities in rats, human liver, and *S. typhimurium*. The usefulness of mutagenicity tests in predicting possible carcinogenic effects of chemicals in man is valid only if the short-term bioassay is corroborated by data from long-term tests in experimental animals and is then taken together with epidemiologic studies. Mutagenicity tests, therefore, although effective in predicting the carcinogenic potential of chemicals, are not able to indicate organ and species specificity of the carcinogenic activity of the chemical or correlate mutagenic potency with carcinogenic potency. (50 Refs)

330. OCCUPATIONAL CANCER DISCUSSED AT NEW YORK CONFERENCE.

Englund A, Holmberg B

Landsorganisationen, Sweden

Lakartidningen; 72(38):3487-3488 1975

The proceedings of a conference on occupational cancer organized by the New York Academy of Sciences in cooperation with National Cancer Institute and NIOSH (held on March 24-27, 1975, New York) are reviewed. Increased incidence of lung cancer was found among workers exposed to very small glass-fibers in glass-fiber manufacturing plants. A suspected relationship between asbestos exposure and cancer of the larynx was verified. Increased incidence of skin and lung cancer was found among workers exposed to chloroprene (Neoprene). Vinyl chloride, trichlorobenzene, and benzoyl chloride were found to be carcinogens. Increased incidence of lung and kidney cancer was observed among coke oven operators. The high time requirements and the high expenses involved in carcinogenicity testing, and the correlation existing between carcinogenic and mutagenic properties justifies short-term mutagenicity tests for screening for carcinogenic substances. Because of the many factors involved in the carcinogenic response, a zero exposure to carcinogenic substances is recommended.

331. CARCINOGENESIS INDUCED BY TRACE CONTAMINANTS IN POTABLE WATER.

Kraybill HF

Div. of Cancer Cause and Prevention, NCI, Bethesda, MD
Bull NY Acad Med; 54(4):413-427 1978

The following are some recognized and suspect carcinogens in US drinking water and their concentrations (in ug/liter, when given): aldrin (5.4), benzene (50), benzo(a)pyrene (0.0002-0.002), bis(2-chloroethyl) ether (0.42), lindane, carbon tetrachloride (2.0-3.0), chlordane (0.1), chloroform (0.1-311), 1,2-dibromoethane, dieldrin (8.0), dichlorodiphenyltrichloroethane (DDT), dichlorodiphenyldichloroethylene (DDE) (0.05), 1,4-dioxane (1.0), endrin (0.004), heptachlor, trichloroethylene, and vinyl

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

332. PROSPECTS FOR A REVOLUTION IN THE METHODS OF TOXICOLOGICAL EVALUATION.

De Serres FJ

Natl. Inst. Environmental Health Sciences, Research Triangle Park, NC

Mutat Res; 38:165-176 1976

The impact of research programs to develop efficient assay systems for mutagenic activity to screen untested environmental chemicals and to develop better methods to determine their effect on man is considered. Food and feed additives in widespread use such as sodium nitrite, sodium bisulfite and other nitrofurans derivatives are mutagenic in experimental organisms. A nitrofurans derivative called AF-2, which was used widely as a food preservative in Japan for 10 yr, was found to be a potent mutagen and its use as a food preservative was banned. Most pesticides are also potent mutagens in experimental organisms, and ethylene dibromide, heptachlor, and chlordane are also carcinogenic in mice and rats. Atrazine, a herbicide used widely on most commercially grown corn, is converted to a potent mutagen. Hycanthone, a drug used to treat schistosomiasis, is a supermutagen in experimental organisms. Its long-term genetic effects on treated populations have not been evaluated adequately. The majority of commercial hair dyes available in the United States, England, and Japan are potent mutagens in various short-term tests for mutagenicity. Industrial chemicals that are mutagenic in experimental organisms and have been associated with occupational carcinogenesis include b-propionolactone, ethyleneimine, 4-aminobiphenyl, 4-nitrobiphenyl, bis(chloromethyl) ether, benzidine, and vinyl chloride. Vinyl chloride has produced significant levels of chromosome damage in somatic cells of exposed workers. The primary concern over the effects of environmental mutagens on man is that exposure may produce damage in germ cells that will be transmitted to future generations. Newly developed short-term tests for mutation induction include assays for both forward and reverse mutation at specific loci and tests for inhibition of DNA repair. In the assays for mutation induction, the best correlation between carcinogenic and mutagenic activity is with *Salmonella*; at least 70%-75% of the carcinogens tested with this system show mutagenic activity. It is generally agreed that these short-term tests provide a mechanism for identifying potential mutagenic and carcinogenic agents and that they are most effectively used to establish priorities for testing in higher organisms. (39 refs)

333. PREDICTIVE VALUE OF CARCINOGENESIS BIOASSAYS.

Maltoni C

Inst. Oncology and Tumour Centre, Bologna, Italy
Ann NY Acad Sci; 271:431-443 1976

Bioassays provide an important means of predicting the oncogenic risk of particular occupational and environmental agents to man. In fact, the three most important occurrences of environmental and occupational tumors discovered after 1970 were directly or indirectly predicted by animal studies. The first was the adolescent clear-cell vaginal adenocarcinoma found in girls born to mothers treated during pregnancy with synthetic nonsteroid estrogen therapy. As long ago as 1938, it was demonstrated that stilbestrol had carcinogenic properties, with mammary tumors arising in male mice treated with the compound; several years later, the same hormone was shown to produce a variety of tumors among different animal species. The second occurrence was that of pulmonary carcinoma among workers exposed to bis(chloromethyl) ether, which had previously been shown to produce sc fibrosarcomas and skin carcinomas when injected sc into rats or applied topically to mice. When the compound was inhaled by rats, it induced squamous cell carcinomas of the lung. The third example was provided by the identification of liver angiosarcomas in workers occupationally exposed to vinyl chloride (VC), after the carcinogenicity of the compound had been demonstrated in rats. Data from inhalation experiments with VC in rats, mice, and hamsters and from ingestion experiments in rats are reported in detail. Sixty Swiss mice of both sexes were treated by inhalation of VC in air at 10,000 ppm for 4 hr/day, 5 days weekly for 30 wk. After 81 wk 55 developed pulmonary tumors, 13 had mammary carcinomas, 8 had liver angiosarcomas, 9 had vascular tumors, and 3 had epithelial tumors of the skin; of 150 untreated mice, 8 developed pulmonary tumors and 1 a vascular tumor after the same length of time. Bioassays can also be used to predict the carcinogenicity of inorganic substances. Various inorganic materials were tested by sc injection of 30-mg quantities into Sprague-Dawley rats. Of 40 animals in each group, 9 developed rhabdomyosarcomas and fibrosarcomas with neochromium, 8 with chromium allumen, 26 with chromium yellow, 27 with molybdenum orange, 16 with cadmium yellow, and 1 with iron yellow, after 125-150 wk. None of 140 control animals developed neoplasms. Of 49 male and 48 female Sprague-Dawley rats, 34 and 31 developed peritoneal mesotheliomas following the endoperitoneal injection of 25 mg of crocidolite.

334. OCCUPATIONAL LUNG CANCER. (PP. 25-51)

Frank AL

Mount Sinai Sch. Medicine, New York, NY

Pathogenesis and Therapy of Lung Cancer. Harris CC, ed.
New York and Basel, Marcel Dekker, Inc., Lung Biology in Health and Disease, Vol. 10, 762 pp., 1978.

An overview is presented of factors that contribute to lung cancers associated with working areas. Major occupational respiratory carcinogens discussed are arsenic, asbestos, chloromethyl ethers, chromium, carbon compounds including coke and tar, mustard gas, nickel and radiation. Additional agents are discussed with proven, suspected, or possible carcinogenic risk: beryllium, carbamates, chloroprene, fibrous glass, isopropyl oil, methylene-bis-ortho-chloroaniline and nitrosamines. Also discussed, in connection with lung cancer, are smelting operations, various vegetable dusts, vinyl chloride and woodworking. The review concludes with a brief consideration of directions in occupational carcinogenesis. Despite the interest of various professional and legislative groups, it is pointed out that there will still be a need for the astute clinician to note unexpected associations. (146 Refs)

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