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OCCUPATIONAL EXPOSURE

TO

VINYL CHLORIDE

October 1979

PREPARED BY:

Teresa McGrath, M.D.,
Special Studies and Services Branch.

STATISTICAL EVALUATION:
R. Kusiak.

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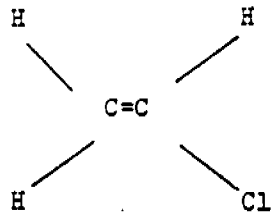
VINYL CHLORIDE

$CH_2 = CH\ Cl$



BACKGROUND:

Vinyl Chloride is a chemical used in the synthetic production of polyvinyl chloride - a widely used plastic material. It is produced by thermal dechlorination of ethylene dichloride or by hydrochlorination of acetylene. Under normal conditions vinyl chloride is a colorless, almost odorless, flammable gas with a boiling point of 13.8°C. At higher concentrations it has a sweetish odor. It is virtually insoluble in water, but is soluble in alcohol, carbon tetrachloride and ether. It is usually stored and transported under its own vapor pressure. The explosive limits are 4% to 22% by volume in air. The auto-ignition temperature is 472.2°C. At concentrations of 8% and above, it is an anesthetic. Because of these properties, it was suggested for use as an anesthetic agent in the early 1930's. It was, however, found unsuitable because of its flammability.

In 1930 large scale production of vinyl chloride was undertaken. At this time it was believed to be one of the safest chemicals on the market. In 1937 Dublin[11] reported two cases of acute intoxication in exposed workers, without serious consequences. In 1949 Tribukh[57] reported problems in Russian workers in a plastics factory. Hepatitis without jaundice, hypertension, anemia, chronic gastritis, skin and respiratory lesions were the main complaints. In 1958 Filatova[15] reported toxic angioneuropathy in exposed workers and in 1965 Puskin[51] reported liver and biliary tract disease in Russian workers. In the mid 1960's several researchers reported Raynaud like changes and acro-osteolysis in vinyl chloride reactor cleaners.[6][54][62] This disorder subsequently became known as polyvinyl chloride disease. Viola,[58] in an attempt to reproduce acro-osteolysis, found that vinyl chloride was capable of

inducing tumors in the exposed animals. In 1973 reports from Germany described findings in exposed workers which included thrombocytopenia, splenomegaly, liver damage, circulatory obstruction and skin and bone alterations.(30)

Despite all these reports vinyl chloride was still considered to be a reasonably safe chemical until 1973 when two cases of hepatic angiosarcoma, a rare liver tumor were found in exposed workers in the B.F. Goodrich plant in Kentucky.(8) Since then, 62 more cases have been reported, worldwide, in exposed workers.(34) (53)

PHARMACOKINETICS OF VINYL CHLORIDE:

Low doses of vinyl chloride are believed to be metabolized by a rapid metabolic pathway to polar products which are excreted predominantly in the urine. These products are thought to be derived after initial metabolism of vinyl chloride and subsequent conjugation of the products with glutathione and/or cysteine, by covalent binding with sulfhydryl groups. A small but significant amount is metabolized to CO_2 and expired. An even smaller but significant amount of ^{14}C activity of labelled vinyl chloride appears to be retained, primarily in the liver but also in other tissues, for as long as 75 hours after exposure.(22) Very little is excreted unchanged in the expired air.

Vinyl chloride binds to albumin and is transported by it. Albumin is synthesized around the portal vein. As the exposure dose of vinyl chloride increases and the detoxifying pathways are over loaded, one would expect more vinyl chloride to bind with albumin in the periportal area. Because of its irritant properties local irritation may occur which may lead to subsequent fibrosis.

The pathway of metabolism is thought to be as follows:

$$Cl\,HC = CH_2 \longrightarrow Cl\,H_2\,C\text{-}CH_2OH \xrightarrow[\text{dehydrogenase}]{\text{alcohol}} Cl\,H_2\,C\text{-}CH\,O \longrightarrow Cl\,H_2\,C\text{-}COOH$$

Vinyl chloride	2-Chloroethanol	Chloroacetaldehyde	Monochloroacetic acid

Only small amounts, if any, of monochloroacetic acid are believed to be formed at low doses, as chloroacetaldehyde rapidly reacts with the sulfhydryl groups of glutathione and cysteine. It is thought that when higher doses are encountered the primary pathway is saturated and metabolism takes place via other less rapid pathways. One postulation is that the accumulating 2 chloroethanol is oxidized by peroxidases and catalases with eventual formation of chloroacetaldehyde. Another is that direct epoxidation occurs with the formation of chloroethylene oxide, which subsequently rearranges to chloroacetaldehyde.

Both the epoxide and chloroacetaldehyde are reactive metabolites, capable of binding with macromolecules, (RNA, DNA, proteins and lipids) with resultant toxic and carcinogenic effects.

Animal studies indicate that a threshold may exist for the takeover by the secondary metabolic pathways, and that this threshold may be around 50 ppm vinyl chloride. Exposure of rats to concentrations of vinyl chloride of 150 ppm or greater resulted in a depression of the hepatic non protein sulfhydryl content, which is believed to be responsible for the detoxification of the metabolites. Exposure to 50 ppm resulted in an inconsistent depression, and exposure to 10 ppm caused no such depression.(60)

ANIMAL TOXICOLOGY:

Acute

Vinyl chloride has a low acute toxicity. The acute LD_{50} for rats exposed by inhalation is 47,600 ppm,(48) and for guinea pigs similarly exposed is 70,000ppm or greater.(48)

Chronic

Chronic exposure of guinea pigs to 100,000 ppm vinyl chloride by inhalation resulted in growth disturbances, and severe liver, kidney, spleen and lung lesions.(49)

CARCINOGENIC EFFECTS:

Tumorigenesis has been reported in rats exposed to concentrations of or in excess of 50 ppm;[39][40][58][31][32] in mice exposed to concentrations of or in excess of 50 ppm[39][29] and in hamsters exposed to concentrations of or in excess of 50 ppm.[39][32] Recent reports indicate that exposure to concentrations as low as 1 ppm have resulted in tumorigenesis in rats though there is no confirmation of this to date.[38] The results of these experiments are presented in Tables I, II, III, and IV. These results suggest that the neoplastic response is related to the exposure concentration, the duration of exposure and possibly the strain of animal.

Twenty two of fifty nine Sprague Dawley rats exposed to 500 ppm for 52 weeks and observed for 135 weeks developed tumors, whereas, sixteen and ten of similar size groups exposed and observed for similar durations to 250 and 50 ppm respectively, developed tumors. (Table I).

Comparison of the total number of tumors observed in groups of Sprague Dawley rats exposed for 52 weeks and observed for 66 weeks, with the number in groups exposed for 17 weeks and observed for 66 weeks, shows a difference of 4 versus 1 at 500 ppm exposure level and 3 versus 1 at 250 ppm exposure level (Table IV),[39][37] thus indicating a possible relationship between exposure duration and tumorigenesis. No tumors were observed in either group at 50 ppm at that stage of the experiment.

A variety of tumors was observed in the various species of animals tested. Hepatic angiosarcomas were observed in Sprague Dawley rats exposed to concentrations of 50 ppm and over; in mice exposed to 50 ppm and over and in hamsters exposed to 500 ppm.[39] Other tumors included nephroblastomas, brain neuroblastomas, skin tumors, pulmonary adenomas, mammary carcinomas and zymbal gland tumors.

Tumor induction was observed in mice and rats at the lowest reported dose tested - i.e. 50 ppm. A dose response function emerges from the animal studies for hepatic angiosarcomas in Sprague Dawley rats between 500 and 50 ppm and for nephroblastomas in Sprague Dawley rats between 250 and 50 ppm. Seven hepatic angiosarcomas were observed in the group of 59 rats exposed to 500 ppm; 4 in the group exposed to 250 ppm and 1 in the 59 exposed to 50 ppm. Six nephroblastomas were observed in the rats exposed to 250 ppm and 1 in the rats exposed to 50 ppm. This will be discussed again in the section relating to derivation of a standard. None of the control rats or mice developed hepatic angiosarcomas or nephroblastomas.

A transplacental effect was suggested by the finding of two subcutaneous angiosarcomas in the offspring of breeder rats exposed between days 12 to 18 of pregnancy to 10,000 and 6,000 ppm vinyl chloride.[37]

Lee et al[32] studied the carcinogenic effects in mice and rats of exposu to vinyl chloride. Four groups comprised of male and female rats and mice were exposed to 0, 50, 250 or 1000 ppm vinyl chloride, six hours per day for 5 days per week. Four animals of each species, sex and exposure level were terminated at the end of 1,2,3,6 and 9 months. The surviving animals were terminated at 12 months. This excluded observation over the natural lifespan of the animals. The sacrifice schedule and the small number of animals, as well as other peculiarities of the study made the data unsuitable for the derivation of a safe exposure limit. It is of interest to note that hepatic angiosarcomas were observed in mice exposed to 50 ppm and in both species exposed to 250 and 1000 ppm. The number of tumors observed in both cases increased with the dose. Extra-hepatic angiosarcomas were observed in both species. Mammary gland tumors were observed in female mice but not in the control animals. It is difficult, however, to evaluate the significance of the development of any of these tumors in a quantative way, as already mentioned, because of the small number of animals and the sacrifice schedule.

McNamara et al[40] undertook a lifetime cancer study in mice and rats exposed either to single doses of vinyl chloride monomer ranging between 50 and 50,000 ppm or to multiple doses of either 50 or 500 ppm with a total dose of 5,000 ppm. Serial sacrifice was performed with final sacrifice at 20 months for the mice and 24 months for the rats. The authors report no changes attributable to vinyl chloride in the rats but report an increased incidence of pulmonary adenomas in mice exposed to 500 ppm for 10 exposure periods. Progression to malignancy is reported in mice exposed subchronically to a total dose of 5,000 ppm. The findings are however unconvincing as the tables do not adequately describe the findings reported in the text and the numbers that progressed to malignancy are not significantly different from the numbers observed in the control group.

No changes attributable to vinyl chloride exposure were observed in the multigeneration study on rats. The authors did not describe the method of selection of offspring for this study which encompasses four generations. As the number of offspring remains fairly constant some method of selection must have been used.

MUTAGENIC EFFECT:

Vinyl chloride has been found to be carcinogenic in animals. As many carcinogens are also mutagenic, and as it is currently believed that tumorigenesis may be the result of somatic mutation, studies have been undertaken to evaluate the mutagenicity of vinyl chloride and its metabolites, two of which are believed to be mutagenic (chloroethylene oxide and chloracetaldehyde).

Mutations have been induced in vivo by vinyl chloride in yeast systems in host mediated assays (using mice as hosts),[35] and in somatic cells of Chinese hamsters.[16] [35] They have also been induced in vitro in bacterial[20] and yeast systems[35] in the presence of liver microsomal preparations. Both metabolites have induced mutations in vitro in Chinese hamster V79 cells, the response increasing with the concentration of the metabolites in the medium.[23]

Mutagenic effects on germ cells have not been established by dominant lethal studies in rats and mice,[1] though in Drosophila, the number of recessive lethals was increased in subsequent generations following exposure.[36]

TERATOGENIC EFFECTS:

There is no evidence at the present time to suggest that vinyl chloride is teratogenic in animals. Exposure of rats and rabbits to 2,500 ppm or 500 ppm and mice to 500 ppm,[28] 7 hours per day during organogenesis did not result in teratogenic effects in the offspring, despite slight maternal toxicity in the rats and rabbits at the higher dose and in mice at 500 ppm. Mice appeared to be more susceptible to the maternal effects of the compound.

No other information has been located on teratogenic effects resulting from animal exposure to vinyl chloride.

HUMAN TOXICOLOGY:

Acute Human Exposure

Single exposure to high concentrations of vinyl chloride can result in euphoria, a feeling of inebriation, somnolence, narcosis and in some cases prolonged sleep. When acute exposures are repeated, headaches, irritability, diminution of memory, insomnia, general asthenia and paraesthesia may develop.[43]

Chronic Exposure

Exposure to vinyl chloride has long been associated with the development of toxic effects. The full implications were not appreciated, however, until it became clear in 1974 that some workers exposed to vinyl chloride developed hepatic angiosarcoma. Earlier reports had associated vinyl chloride with a variety of effects, amongst which were hepatic damage, gastritis, skin and respiratory lesions. Later it was found that workers exposed to high concentrations while cleaning reactors developed a disease involving skin, bone and blood vessels. This became known as "occupational acro-osteolysis". It was soon realized that there was in fact involvement of other organs and the syndrome subsequently became commonly known as"vinyl chloride disease". Presently it is thought that exposure to vinyl chloride may result in the induction of tumors other than hepatic angio[illegible]

namely hepatocellular carcinomas, tumors of lung, lymphatic system, brain and possibly angiosarcomas in other sites. It is also postulated that exposure to vinyl chloride may induce an immune complex disorder with multisystem involvement.

ACRO-OSTEOLYSIS:

Acro-osteolysis was the first well recognized toxic effect of vinyl chloride. Dissolution of the bones of the terminal phalanges of one or more of the fingers is accompanied by clubbing, swelling and shortening of the nail beds, and scleroderma-like changes of the skin. Associated closely with these changes are vascular changes ranging from slight narrowing to segmental occlusion or even complete absence of vessel filling. A classic Raynaud's phenomenon is seen to develop frequently in workers with chronic exposure. Lange et al[30] noted the occurrence of a thrombocytopenia which was the first objective finding in the majority of cases.

Ward[59] suggests that the thrombocytopenia observed may have been an "apparent" one. He postulates, that as the result of an immune response a cryoprecipitable complex is formed which is capable of initiating complement sequence with subsequent platelet aggregation, an apparent thrombocytopenia, fibrinogen/fibrin conversion and vascular occlusion.

PULMONARY EFFECTS OF VINYL CHLORIDE EXPOSURE:

There are several reports of pulmonary changes associated with vinyl chloride exposure. Lilis et al[33] noted the presence of linear reticular and, less frequently, nodular opacities in chest X-rays of workers exposed to vinyl chloride many of whom had also been exposed to polyvinyl chloride dust in polymerization plants. The prevalence of abnormal chest X-ray findings was related to the duration of exposure and to the exposure concentrations. It should be noted that age was unrelated to the prevalence of the changes. The prevalence of a positive smoking history was found to be related to abnormal chest X-ray findings in those with greater exposures. Pulmonary functions changes indicated a relatively high prevalence of obstructive changes in these workers.

Berk[3] noted a significant reduction in forced vital capacity in a

30-year old patient with hepatic fibrosis who had been exposed to vinyl chloride.

Miller[41] noted a 57.8% impairment in pulmonary function, as measured by 1.0 FEV/FVC, in workers exposed to vinyl chloride monomer and polyvinyl chloride dust in a polyvinyl chloride plant in a heavily industrialized city. The impairment correlated with age and duration of exposure but was unrelated to smoking.

Gamble[19] et al however, found no association between exposure to vinyl chloride and decreased pulmonary function or increased respiratory symptoms in workers exposed to vinyl chloride in the production of polyvinyl chloride resin and to polyvinyl chloride dust in the plastic products division of a plant.

The finding of changes may well be consistent with other cellular and subcellular changes which have been seen in other organs of workers exposed to vinyl chloride and may add substance to the concept that exposure to vinyl chloride may result in a systemic disease with manifestations in many organs.

Epidemiological studies have indicated a possible relationship between vinyl chloride exposure and the induction of lung cancers. This is discussed in the section on epidemiological studies.

IMMUNOLOGICAL CHANGES:

Ward et al[59] postulate that vinyl chloride disease is an immune complex disorder and that the immune response is initiated by the incorporation of vinyl chloride or one of its metabolites into protein synthesis to produce a haptogenic effect and the incitement of antibody synthesis. Antigen stimulates B cell proliferation and immunoglobulin production. Antigen plus antibody from a soluble complex which is cryoprecipitable and capable of initiating complement sequence with subsequent platelet aggregation, apparent thrombocytopenia, fibrinogen/fibrin conversion and vascular occlusion. Ischemia which follows, results in collagen biosynthesis. Collagen and complement interact causing further activation of the complement pathway.

Ward studied immunological changes in workers in a vinyl chloride polymerization plant where exposures had been high. Findings of hyperimmunoglobulinaemia, cryoglobulinaem[illegible] and in vivo complement [illegible]

decreased and B lymphocytes were increased. Circulating immunoglobulin complement were seen. Fibrin - fibrinogen conversion and adherence to the vascular wall and narrowing of the dermal vessels with subintimal fibrosis were seen. Removal of these workers from exposure did not influence the persistence of disease activity as evident by the presence of cryoprecipitate and conversion of complement.

HEPATIC CHANGES ASSOCIATED WITH VINYL CHLORIDE EXPOSURE:

Some of the earlier reports from Europe indicated hepatic effects resulting from vinyl chloride exposure. However,serious consideration was not given to the possibility of liver effects until the finding of hepatic angiosarcoma in exposed workers in 1974.

Berk[3] et al reported the case of a 30-year old worker, who had been exposed to vinyl chloride for 5½ years cleaning reactor tanks. Persistent abnormal hepatic function tests and hepato splenomegaly were observed and finally a laparotomy was performed. The liver showed multiple areas of fine nodularity and fibrosis. The spleen showed lymphoid and reticuloendothelial proliferation. Removal from exposure was ensured on his return to work. Follow up of 2½ years later showed that liver function tests had returned to normal despite a possible progression of the hepatic fibrosis.

Popper[47] has described the pathological changes resulting from exposure to vinyl chloride and has observed that the changes are very similar to those resulting from exposure to thorotrast or arsenicals.

A precursor stage exists, characterized by a conspicuous subcapsular fibrosis, a non pathological progressive portal fibrosis and a borderline increase in intralobular connective tissue all associated with focal stimulation of the sinusoidal lining cells and the hepatocytes. This is frequently accompanied by splenomegaly and in some instances by a portal hypertension. Transition to angiosarcoma is preceded by focal dilatation of the sinusoids and even greater activation but dedifferentiation of their lining cells. It is postulated that this may result from stimulation of hepatic and splenic cells by vinyl chloride and or its metabolites

HEPATIC TUMORS:

Since the first report of hepatic angiosarcomas in vinyl chloride exposed workers in 1973, more than 62 occupationally exposed cases have been reported worldwi in the literature, 10 of these occurring in Quebec. In all but one case[53] exposur had been to high concentrations, usually in excess of 100 ppm and frequently much higher than that.

Delorme[10] reported finding a hepatic angiosarcoma and a hepatocellular carcinoma in an employee exposed for 23 years to vinyl chloride. Histological evidence suggested coincidental development of both tumors as though in response to the same stimulus. He believes that a similar response by other cells in contact with the carcinogenic agent may result in tumors of other sites. This seems to be consistent with the findings of Maltoni in his animal studies. It also may explain, the finding of angiosarcomas in more than one site in humans and the reports of epidemiological studies which suggest increased incidences of tumo[illegible] of sites other than liver in exposed populations.

ANGIOSARCOMAS OF OTHER ORGANS:

Popper and Thomas[47], report finding angiosarcomas in other organs in 3 patients with hepatic hemangiosarcomas. Duodenum was the site in one, lung in another and lung, heart, kidney and lymph nodes in the third. They were uncertain as to whether these were metastatic lesions, or whether there was multifocal primary involvement. In none was the spleen a site of angiosarcomatous change.

Couderc et al[7] report on a patient who presented with backache. A tumor involving the posterior arch of 4th, 5th and 6th ribs was found to be an angiosarcoma. Further investigation revealed the presence of a hepatic angiosarcom Multiple other sites were found on death following rupture of the liver lesion. These included vertebra and left adrenal. Again it is not known whether thi[illegible] as a case of multifocal primary sites or secondary spread.

TUMORS OF OTHER ORGANS:

Epidemiological studies suggest a greater than expected incidence

of tumors of the central nervous system, lymphatic system and lung in populations exposed to vinyl chloride. The evidence, though suggestive, is far from conclusive. These studies are discussed later in the text.

EPIDEMIOLOGICAL STUDIES:

As vinyl chloride is carcinogenic in both animals and man, and as it has been found to be mutagenic in bacterial test systems, several epidemiological studies have been undertaken in an effort to establish findings relative to such effects in populations exposed to vinyl chloride either occupationally or environmentally. Such studies include examination of peripheral lymphocytes for chromosomal abnormalities, cancer mortality in exposed populations, incidence of fetal loss in wives of exposed workers, incidence of congenital abnormalities in the offspring of exposed populations. As exposure concentrations are largely unknown, in most instances they have been estimated and hence reliable dose response functions cannot be derived.

I. OCCUPATIONAL EXPOSURE:

Chromosomal Studies

Peripheral lymphocytes have been studied for chromosomal abnormalities in an effort to establish whether vinyl chloride induces such abnormalities in man. Some of these studies conclude that such changes are induced by vinyl chloride while others report negative findings (see Table V). In the majority of these studies the study populations were very small and hence it is difficult to draw firm conclusions. The largest group studied, 209 men, was exposed to low concentrations of vinyl chloride, estimated to be between 12 and < 1 ppm.[40] No chromosomal abnormalities were observed. Using the techniques described by the authors, Purchase[50] noted a positive correlation between chromosomal aberration observed in the study group and the duration of employment, history of exposure to excursion levels and smoking. Again, however, the study group was small. Fleig[16] reports positive findings only in workers who had symptoms of vinyl chloride disease, and in one patient previously treated for his hepatic angiosarcoma with chemotherapy.

These results, whilst inconclusive, suggest that vinyl chloride may indeed be capable of inducing chromosomal abnormalities, and that the effect may be dependent on the severity of the exposure experienced. Vinyl chloride, probably, is one of many agents capable of inducing somatic mutations.

MORTALITY STUDIES IN VINYL CHLORIDE EXPOSED WORKERS:

In response to the report that vinyl chloride was responsible for the induction of hepatic angiosarcoma in two workers in the B.F. Goodrich plant in Kentucky in 1973 many studies were set up to establish the role played by vinyl chloride monomer in the development of this tumor and whether in fact, it is responsible for the development of other tumors in exposed workers.

All of the studies undertaken have been carried out in the absence of definitive exposure data. Estimates of past exposures have been arrived at by using information from various sources. None of these are reliable enough to provide quantitative exposure data. In many cases exposure to copolymers of vinyl chloride, polyvinyl chloride and in some cases other chemicals occurred in addition to exposure to the monomer. As these studies lack quantitative data, they cannot be used to derive a dose-response function. However, the qualitative information that is forthcoming does give some indication of cause and effect relationships.

Hepatic angiosarcoma is the only tumor that has so far been definitely associated with exposure to vinyl chloride monomer in man. Available studies indicate that those workers who have developed hepatic angiosarcomas had experienced exposure to high concentrations of vinyl chloride in the past.(5) (17) (61)(55) (9)(43) Frequently, they had been employed as autoclave operators or reactor cleaners, and experienced exposure concentrations in the hundreds and frequently in the thousands of ppms.

Ott (44) was, however, unable to find an association between malignancies of the liver and biliary tract and exposure to vinyl chloride, although, he did observe an association between exposure and deaths from all malignancies,

particularly in those with an estimated high exposure. Monson and Peters[42] and Waxweiler[61] also observed a relationship between deaths from all malignancies and exposure to vinyl chloride monomer.

The importance of interval between initial exposure and the observation of a tumor was illustrated by Waxweiler,[61] who observed a significant excess only in tumors of the hepatic system at the first time of observation (i.e. 10 years post initial exposure) as compared with significant excesses in tumors of brain and central nervous system, respiratory system and hepatic system when the observation period was extended by 5 years. Monson and Peters[42] report an increasing excess of deaths from all cancers over that expected during the 5 years of their study.

Some studies[61] [55] have indicated an association between exposure to vinyl chloride and the development of brain tumors - particularly glioblastoma multiforme in type. Waxweiller's study[61] suggests that the latent period for the development of tumors of brain is longer than that required for the development of hepatic angiosarcomas. Tabershaw and Gaffey[55] failed to find a relationship between the estimated dose and the development of these tumors. Both of these studies suggest a relationship between vinyl chloride exposure and the development of respiratory cancers. However, in neither study were the effects of smoking considered.

From these studies we can conclude that high maximum exposure to vinyl chloride is associated with the development of hepatic angiosarcomas. An association between exposure and the development of tumors of the brain and respiratory tract is suggested but so far there is no proven cause and effect relationship. The possibility that the latent period required for the development of either of these tumors may exceed that required for the development of hepatic angiosarcoma is supported by the studies. If this is the case then it may not be possible to draw conclusions about the role of vinyl chloride in the induction of these tumors until a lengthier observation period, if not lifetime observation, has elapsed.

STUDIES ON GERM CELL EFFECTS:

The question of germ cell effects of vinyl chloride was studied by Infante et al.[24] Germ cell effects on exposed males were taken to be expressed as fetal loss in the respective wives. The authors report an excess fetal loss in the group of wives whose husbands had had a primary vinyl chloride monomer exposure as compared with controls, whereas prior to exposure no such excess was seen.

The results indicate a possible germ cell effect, however, the study has several shortcomings. The ages of the wives were presumed to be similar to the husbands' ages, a presumption which is not necessarily valid; details pertaining to conception, fetal loss, etc. were obtained from the husbands and no direct contact was made with the wives. The interval between such episodes and the time of recall was not mentioned, but one would presume it would influence the quality of the information. Fetal death rates for wives of vinyl chloride monomer workers prior to exposure are compared with the rates for this group after exposure. The two rates are however not comparable as they have been adjusted to different standards; the first to the control before "exposure" and the second to controls after "exposure".

II. ENVIRONMENTAL EXPOSURE:

Much concern has arisen that populations residing in the vicinity of vinyl chloride plants may experience increased rates of (1)congenital abnormalities, and (2) tumorigenesis in offspring.

Several studies have been undertaken to evaluate such effects. The results of these studies are not unanimous and at the present time no firm conclusions can be drawn on either of these questions.

CONGENITAL MALFORMATIONS:

Infante et al[26] studied the rate of occurrence of congenital abnormalities amongst live births in three Ohio cities, each of which housed a polyvinyl chloride facility. They observed that the rate of occurrence of such abnormalities was significantly greater for each of these cities than the Ohio State rate. Comparison of the rate for each city with the rate for its corresponding county showed that in two cases there was a significant difference. Such a difference was not observed when other city/balance of county rates were compared.

When the data were analysed it was evident that significant excesses were seen for several abnormalities, one of which was defects of the central nervous system. A further study of data on defects of this system included data from stillbirth records, as both may be closely connected. A significant excess of central nervous system defects was observed for one of the cities with a polyvinyl chloride facility. It is note worthy that no cases were seen in another of the cities.

Although these findings suggest association between vinyl chloride exposure and an increased rate of occurrence of congenital malformations they are not conclusive.

In an effort to examine the relationship between exposure to vinyl chloride and an increased rate of central nervous system defects suggested by Infante's study, Edmonds et al undertook two studies. In the first they[14] compared the rates of occurrence of central nervous system malformations (1970-1974) in two hospitals (one in Painesville* and one in Pittsburg both involved with the Birth Monitoring Defects Program) with rates for the respective states. Both cities had polyvinyl chloride facilities. No increase was seen in the rates in the Pittsburg hospital, but there was an increase in the Painesville hospital.

* Painesville was one of the cities studied by Infante.

When occupation and place of residence of the families of these cases was analysed and compared with 2 control groups derived from the hospital registry, no association could be established between the cases and vinyl chloride exposure.

The second,[13] was a more comprehensive study using data on Kanawha County obtained from the Birth Defects Monitoring Program and from the State Department of Vital Statistics, for the period 1970-74. Kanawha county was chosen because its rate of occurrence of central nervous system defects for that period was significantly higher than national Birth Defects Monitoring Program rates for the same period. Two sets of controls were matched to the cases. Results of the study show no case-control differences regarding parents possible occupational exposure to vinyl chloride at that time or five years prior to the child's conception. It is interesting to note that several case families residing within three miles of the polyvinyl chloride plant were located to the North East of the plant and controls to the South West. Data on wind patterns and air pollution do not correlate with these observations. The observed clustering of cases residing within three miles of the polyvinyl chloride plant is not satisfactorily explained by proximity to the plant. Consideration should be given to the fact that several sources of other chemicals are also present in this geographical area, thus making it unrealistic to implicate vinyl chloride monomer as the causative agent in these cases.

A study conducted in Quebec[56] reports a higher frequency of birth defects in a community with a vinyl chloride polymerisation plant, than in a comparable city without such a facility. The ages of the mothers in both cities was comparable, however, occupational histories of the mothers were not considered. It is not possible to draw any conclusive association between the observations and vinyl chloride exposure, as the city which had the polyvinyl chloride facility had several other industries and hence exposure to many other chemicals was a real possibility

It is interesting to note an increased frequency of malformations in the latter years of the study, when in all probability the levels of vinyl chloride had fallen.

TUMORIGENESIS:

Saric et al[52] examined the incidence of malignant tumors of bronchus and liver over a four-year period (1968-1971) in a city with several industries, one of which was a polyvinyl chloride facility. They found that the incidence of both types of tumor was only slightly higher than expected, based on the incidence in Croatia over the same period. No cases of hepatic angiosarcoma, but eight cases of hepatocellular carcinomas were reported. However, no relationship was established between these cases and either occupational or residential exposure to vinyl chloride.

One hundred and thirteen cases of bronchogenic cancer were reported. Ninety three percent of the 158 males and 47% of the 35 females in the study group were smokers, and 39% were between 45-64 years and 58% were 65 or older. No relationship could be established between these cases and exposure to vinyl chloride either occupationally or residentially.

In Wisconsin residents between 1964 and 1976 ten cases of angiosarcoma of liver were identified. This is twice the expected rate based on estimates of the crude incidence of angiosarcoma of the liver for the entire United States.[2] These cases were scattered across the state; the ages ranged from 36-71 years (mean 58); 9 were male and 9 white. One had a history of thorium di oxide exposure; two or possibly four had had an arsenic exposure; 7 of the 10 had lived on farms during their life. Only 1 had exposure to a vinyl compound - polyvinyl acetate, and 1 had lived near a chemical company which made plastics and resins.

A study undertaken by Brady et al[4] indicated that the incidence of hepatic angiosarcoma in residents of New York State, excluding New York City, exceeded the incidence of such tumors in the total U.S. population (0.25 per million versus 0.14 per million respectively 1970-1975).

Twenty six cases of hepatic angiosarcoma were reported to the Tumor Registry of the Cancer Control Brueau (N.Y. State Department of Health) in the years 1958 through 1975. Nineteen of these had no known exposure to any of the three agents known to induce such tumors (arsenic, thorium dioxide and vinyl chloride). Five, however, had lived for long periods (8-62 years) close to either a vinyl chloride or a polyvinyl chloride plant. In the other fourteen cases no pertinent residential or occupational history was obtained. The authors remark that all matched controls* lived at a distance of more than one mile from the respective plants. However, the place of residence for the 14 cases is not mentioned, nor is the question of wind direction, or other possible chemical exposure addressed.

This study at best, indicates a possible relationship between ambient exposure to vinyl chloride and hepatic angiosarcoma induction.

Infante et al[26] [25] reported a greater than expected number of deaths from central nervous system tumors among residents of 4 United States cities combined (38 vs 24.7). Three of the cities had polyvinyl chloride facilities and 1 did not, but was 8 miles from one of the other 3 cities. Expected rates were based on the Ohio State rates. The Standard Mortality Ratios for cancers was increased in 2 of the cities. However, the number of cases involved was small and makes it impossible to draw any firm conclusion from the study.

*Controls were derived from the same Tumor Registry and consisted of cases with an internal malignant tumor, other than a primary liver tumor.

THE EXPERIENCE WITH VINYL CHLORIDE IN ONTARIO:

Ontario has been involved in the production and polymerisation of vinyl chloride for many years. The first plant started up in 1954, a second in 1957 and a third in 1960. Since 1954, as far as can be ascertained, approximately 1,000 workers have been exposed to the chemical for a period of 3 months or more. In the earlier years it is presumed that exposure concentrations would have been high, with certain job categories experiencing very high exposures. Once it was recognized that the chemical caused health effects, measures were taken to reduce exposure concentrations and when the chemical was linked to hepatic angiosarcomas in 1973, further steps were taken to reduce exposure concentrations even further. At the present time it is estimated by the companies that exposure concentrations run around 2-3 ppm for the majority of the time.

Medical programmes were set up by the involved companies as the need became obvious. Preplacement examination and regular assessment are undertaken by the plant physician. When workers retire or resign they are asked to notify the Ministry of Labour of their whereabouts and subsequent moves. The Ministry of Labour in cooperation with the companies, set up a nominal roll for all workers in the three major companies who were exposed to vinyl chloride for three months or more. When an employee retires or resigns from the company he is asked to notify the Ministry of Labour so that follow-up can be maintained. However, due to the human factor involved, this notification is less than 100% and follow-up is thus incomplete. This must be remembered when one states that to date, to the best of our knowledge no cases of vinyl chloride induced hepatic angiosarcoma have been seen in Ontario.

Also to be remembered is the small number of workers who would have a sufficient latent period for development of a hepatic angiosarcoma, the decreasing exposure concentrations over the years, the fact that one plant is an open one, the small number of workers in the annual work force and the even smaller number who would have had jobs such as reactor cleaners. It is possible also that

recognized cases of hepatic angiosarcomas were classed as such, only when reviewed with the knowledge of the association between vinyl chloride and this tumor. It may well be that we have just entered into the time period when one would expect to see these tumors because of long latent period, and if, as the reported studies suggest, the latent periods for tumors of other organs are longer, we may still not have reached this time.

While to date we are not aware of any cases of vinyl chloride induced tumors in Ontario, we must remember that this picture may change in the future.

THE DERIVATION OF AN ACCEPTABLE CONCENTRATION OF VINYL CHLORIDE FOR OCCUPATIONAL EXPOSURE:

Ideally the derivation of an acceptable concentration for occupational exposure to vinyl chloride should be made using data from epidemiolcgical studies which describe the dose response function in humans. In the case of vinyl chloride, this type of data are not available and it, therefore, becomes necessary to use animal studies which do provide quantitative data. In the case of vinyl chloride, the animal studies of Maltoni are the only ones suitable for this purpose and as such have been used exclusively for the derivation of an acceptable concentration of vinyl chloride for occupational exposure.

It must be recognized that when animal data are used for such a purpose many assumptions must be made. It has been assumed that no threshold exists; that the function is a linear one; that the effects observed at high doses can be extrapolated to lower doses in the same species; that if the chemical is inhaled it is possible to extrapolate directly from animal to man; that the risk for both animal and man is similar,if a similar fraction of their life is spent in a smaller exposure concentration; that the latent period for the development of a specific tumor takes the same fraction of both species lifetimes if they have experienced similar exposures; an acceptable risk has been taken to be 5×10^{-4} per year.

Based on the animal data and recognizing fully the assumptions that have been made, it has been calculated that an acceptable concentration of vinyl chloride for the air in the workplace is 2 ppm. See appendix I.

SUMMARY:

Workers have been exposed to vinyl chloride since the early 1920's. Because of the large demand for its products, production has increased enormously since its introduction to the market place. Vinyl chloride was up to 1973, considered to be of low toxicity despite some published reports of toxicity in exposed workers. Up to 1974 exposure concentrations frequently reached hundreds of ppms and often thousands of ppms as ascertained by reported acute effects. Once it was recognized that vinyl chloride was capable of inducing hepatic angiosarcomas in those exposed to it, the workmen [illegible]

lowered. However, some of the workers had already been exposed to high concentrations of the chemical.

Since 1973 it has been recognized that vinyl chloride has been responsible for the induction of hepatic angiosarcoma in exposed workers. Current information suggests that, in addition, tumor induction may occur in other organs and may include angiosarcoma of sites other than liver, hepatomas, tumors of lung, brain, respiratory tract, lymphatic system. Presently, however, hepatic angiosarcoma is the only tumor definitely associated with vinyl chloride exposure in man. The epidemiological studies suggest that in the cases known to date high exposure concentration and period between initial exposure and observation are related to the development of the tumor.. The lack of quantitative human data make it impossible, however, to derive a dose response relationship for this effect in man.

Maltoni's animal studies have shown the induction of hepatic angiosarcoma in rats, mice and hamsters, with the former two species of animal developing the tumor at the lowest tested dose. A dose response relationship was observed for the rat over the three lowest doses tested. Tumor induction was also related to the duration of exposure and interval between initial exposure and observation. Tumors of other sites were also reported. Because the data from this study comprise the only quantitative data available, they have been used to derive an acceptable occupational standard for exposure to vinyl chloride.

Besides carcinogenesis, exposure to vinyl chloride can result in a variety of toxic effects involving blood vessels, lungs, skin, spleen and liver. It has been suggested that these effects may be the result of an immunological response with multi system involvement. Immunological studies add some support to this theory.

Vinyl chloride has been found to be mutagenic in bacterial test systems. Chromosomal studies on human peripheral lymphocytes indicate a possible mutagenic effect in man.

Some reported studies indicate a possible germ cell effect on male workers exposed to the chemical. The studies are however, inconclusive.

Studies undertaken to evaluate the effects of environmental exposure to vinyl chloride suggest a possible relationship between exposure and increased incidence of tumorigenesis, especially of the central nervous system, and congenital abnormalities in exposed populations. Whilst these studies suggest such relationships they also are inconclusive.

There have been, to the best of our knowledge, no known cases of vinyl chloride induced hepatic angiosarcoma among the estimated 1,000 workers exposed to the chemical in Ontario since the inception of the industry in 1954. However, as follow up has been less than one hundred percent and as the interval between initial exposure and observation may be shorter than the interval required for the development of tumors, particularly, if the group exposed is small, it may be too early to fully assess the full impact of vinyl chloride in the exposed population.

CONCLUSION:

Epidemiological studies have demonstrated a definite cause and effect relationship between exposure to vinyl chloride and the development of hepatic angiosarcoma in exposed workers. In addition they suggest a relationship between exposure and the development of other tumors. As the exposure data are ill defined and frequently are only estimates using a variety of sources of information, the data arefar from quantitative and as such are unsuitable for use in the derivation of a dose response function and subsequently for the derivation of a safe exposure level. At best the data suggest that past exposure concentrations have been high for those who have developed tumors and that the interval between initial exposure and the time of observation may influence the observed response.

The animal studies of Maltoni provide the only quantitative data available which is suitable for use in the derivation of a safe exposure dose.

The utilization of animal data for such a purpose is not without problems. Many assumptions must be made and findings have to be extrapolated from animal to man. In view of the assumptions taken, a conservative approach must be adopted. Using such an approach a conservative estimate [illegible]

a tumor by being exposed to 1 ppm of vinyl chloride is derived. By assuming an acceptable annual risk for man the exposure concentration which would incur this risk is calculated.

Based on the experimental data and using the assumptions described, it was calculated that the risk resulting from lifetime exposure of workers to 2 ppm vinyl chloride would be acceptable.

RECOMMENDATIONS:

The time weighted average exposure limits shall be 2 ppm vinyl chloride.

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TABLE I

..s and ...	Exposure concentration ppm	Exposure duration weeks.	Observation period weeks.	Number of animals that developed hepatic angiosarcomas	Latent period weeks.	Number of animals that developed nephroblastomas.	Latent period.	Total number of animals that developed tumors (2)	Ref.
:ats	500	52	135	7	81	4	83wks	22	(38)
.ts	250	52	135	4	79	6	80wks	16	(39)
.ts	50	52	135	1	135	1	135wks	10	(37)
ts	0	0	135	0	0	0	0	None	(39)

(1) S.D. - Sprague Dawley

(2) Some animals developed more than one tumor.

TABLE II (BT_4)

al cies Number	Exposure Concentration	Exposure duration	Observation Period	Number of Pulmonary Tumors	Latent Period	Number of Mammary Cancers	Latent Period	Site of other tumors and types	Total number of animals with tumors.	Ref
ss e 3	500 ppm	30 wks	41 wks	16	34	2	33	4 hepatic angio-sarcomas. 1 subcutaneous. 1 skin acanthoma	17	(34)
s 1	250 ppm	30 wks	41 wks.	11	34	6	30	3 hepatic angiosarcomas. 1 hepatic angioma.	15	(34)
s	50 ppm	30 wks	41 wks	-	-	7	35	2 hepatic fibroangiomas. 2 subcutaneous angiosarcomas.	8	(34)
s 1	0	-	41 wks	1	39	0	-	-	1	(34)

TABLE III (BT_8).

Animal Species and Number	Exposure Concentration	Exposure Duration	Observation Period	Angiosarcomas Liver	Site of other tumors and types.	Reference
Golden Hamsters X 33	500 ppm	28 wks	28wks	(1 at later stage).	1 lymphoma.	(39)
Golden Hamsters X 32	250 ppm	28 wks	28wks	0	0	(39)
Golden Hamsters X33	50 ppm	28 wks	28 wks	0	1 lymphoma	(39)
Golden Hamsters X70	0	-	28 wks	0	0	(39)

TABLE IV (BT_3 + BT_4)

Animals Surviving Rats	Exposure concentration weeks	Exposure duration weeks.	Observation During weeks.	Animals with tumors.	Ref.
Sprague Dawley rats x 54	500ppm	17	66	1 animal:- lymphoma	(34)
Sprague Dawley rats x 39	250ppm	17	66	1 animal;- nephroblastoma	(34)
Sprague Dawley rats x 59	500ppm	52	66	4 animals: 1 hepatic angio-sarcomas - 3 other types.	(38)
Sprague Dawley rats x 59	250ppm	52	66	3 animals: 2 hepatic angiosarcomas - 1 other type	(34)

TABLE V

ɔn studied.	Exposure duration (range in years.)	Exposure concentration (range in ppms).	Chromosomal Effects	Comments	Conclusions	Ref.
·s ɔls from ɹ·nt.	1-24 years	2000 -80 ppm	Significant increase in breaks over controls.	Comparison of the control groups indicated similar rates of chromosomal breaks in both groups	Vinyl Chloride Monomer is mutagenic though a dose response function could not be derived.	27
;ginal :s .ed ·ears later	1-26 years	2000 -80 ppm initially, 80 - 1ppm during the subsequent 2 to 2.5 yrs.	No difference between study group and controls.			
ɔls from ;e plant.						
·rs ·ols ng of ·esenting mployment ɔns) No ·f exposure ·somal agents.	1-28years	Estimated as 12 -< 1ppm	No significant difference between exposed group and controls.		Vinyl Chloride Monomer at low doses may not induce changes.	46
s.	9-29 years	20-30ppm at time of study but presumably higher in earlier years	Significant difference between exposed group and controls.	The highest frequency of abnormal cells was observed in those with the shortest exposure. 2 cases did not vary from controls.	No conclusions can be drawn from this study as the groups are too small.	18

TABLE V (continued)

tion studied	Exposure duration (range in years.)	Exposure concentration (range in ppms)	Chromosomal Effects	Comments	Conclusions	Ref.
kers poly- chloride,	1-17 years (average 6-5 years)	+500 ppm	A significant increase was not observed in either exposed groups.	All those exposed in polyvinyl chloride industry had been exposed to X-ray examinations in the recent past.	The risk of such changes occurring as a result of exposure to vinyl chloride is low.	35
ratory rs.	2-15 years (average 9-5 years)	estimated maximum 50ppm	The severity of the lesions observed was greater in the polyvinyl chloride workers than in the laboratory workers.			
side plant ols.	-	-				
/vinyl ride workers	18-29 years (average 24years).	"High"	An increased frequency of breaks was observed in the three groups as compared with the 4 control cases. There was little difference in the frequency of breaks between the three groups.		These results confirm that vinyl chloride monomer may be one of many causes of cyto-genic damage.	21
vinyl ride workers	21-29 years (average 26years)	"Low"				
: ufacturing	9-36years (average 25 years)	none to vinyl chloride, but exposure to other chemicals occurred.				
ols	-	none				
/vinyl ride workers trols plant - 6 f plant)	4-28years (average 15 years) —	500ppm or more.	A significantly higher frequency of unstable chromosome changes was observed in exposed workers. Breakage rates did not vary with duration of exposure.	This is a small study group.	These results indicate that vinyl chloride induces mutagenic effects.	12

TABLE V (continued)

:tion studied	Exposure duration (range in years).	Exposure concentration (range in ppms).	Chromosomal Effect	Comments	Conclusions	Ref.
›osed workers ›sclave 'kers. :. and Kers l chloride ators. yvinyl ride tenance ! chloride tenance :llaneous .rols	 (average) 10-7years (average) 12-7 years (average) 6-3 years (average) 15-5 yrs (average) 6-1 years (average) 8-6 years -	 Ranges – 1000-300ppm (1945-1979) 15-5 ppm (thereafter)	A significant increase was observed in the exposed groups as compared with the controls. Those with a history of short term exposure to the excursion values had a higher percentage of abnormal cells.	A positive correlation was observed between duration of employment; smoking and exposure to excursion values.	The results indicate that vinyl chloride induces mutagenic effects in exposed workers.	50
.ers :ymptoms) wn ure ored ure rols.	not stated.	1000-150 ppm (assumed) 28 - < 1 ppm 28 — < 1 ppm	No significant difference between exposed and controls.		An increased rate of chromosomal aberrations was observed only in those with symptoms of vinyl chloride illness.	16
:rs /mptoms :ntrol		[illegible]	A significant difference between workers with symptoms and control group.			

APPENDIX 1

R&S 113396

Calculation of an Acceptable Concentration of Vinyl Chloride in Air in the Workplace

Data

The results of several animal experiments involving the inhalation of vinyl chloride were used in these calculations. The exposed animals were made up of six exposure groups of approximately equal numbers. Exposure levels were 50, 250, 500, 2500, 6,000 and 10,000 ppm of vinyl chloride. The control animals and all of the exposed animals were observed for the same time. In the case of the Sprague-Dawley rats, which were exposed for 52 weeks, the animals were observed until all had died and, in all other cases, survivors were present at the end of the observation period. The data used in the calculations are in Appendix 2 and a more complete description of the experiments is contained in reference 1.

The data contained in reference 2 consisted of results obtained from animals which were sacrificed long before the end of their natural lives as well as results obtained from animals which were allowed to die naturally. Since, in the published reports, the results from the two groups were combined, any calculation based upon the data would under-estimate tumour risks. Hence, the data were not used.

Methods of Results

The relative frequencies of specific tumours in control animals and in all animals exposed to vinyl chloride were compared. Table 1 contains the probability that the tumour frequencies in control and all exposed animals were the same. Comparisons which were not statistically significant at the 5% level were not reported.

Also, the relative frequencies of specific tumours in control animals and in animals in the lowest exposure level were compared. Statistically significant differences at the 1% level were found in Swiss Mice for mammary carcinoma, angiosarcomas of sites other than liver and other vascular tumours, and also all tumours. In all other cases, there were no statistically significant differences in tumour frequencies in control animals and in animals exposed to the lowest exposure level.

Two methods were used to make estimates of the excess tumour risk factor.

In the first method, it was assumed that the excess tumour risk corresponding to vinyl chloride concentration, C, was less than the risk, R, calculated using the following formula:

$$R = \frac{Ro \times C}{Co}$$

where Ro = upper confidence limit of the excess tumour risk corresponding to vinyl chloride concentration Co.

Co = highest vinyl chloride concentration at which no excess tumour risk was discernible (no effect level).

Excess tumour risk was the fraction of exposed animals which developed the tumour during the experiment less the fraction of unexposed animals which developed the tumour during the experiment.

The upper 95% and 99% confidence limits of excess tumour risk were used. The upper 95% confidence limit and the upper 99% confidence limit were calculated so that the probabilities that the excess risk was, in fact, higher were 5% and 1% respectively.

The factors Ro/Co were calculated when the tumour frequencies in control animals and in all exposed animals were statistically significantly different. Calculations concerning the risks of Zymbal Gland carcinoma were not reported because such glands are not present in humans. Table 2 contained the upper 95% and upper 99% confidence limits on excess tumour risks per ppm of vinyl chloride based upon the data observed at the no effect level.

In the second method, it was assumed that the excess tumour risk depended linearly on the concentration of vinyl chloride in air when the concentration was sufficiently low.

Unweighted linear regression calculations were made in order to fit the observed excess risk to the following equation:

$$R = A \times C + B$$

where R = Excess tumour risk at vinyl chloride concentration C

A = Calculated slope of the regression line (excess tumour risk per ppm of vinyl chloride).

B = Calculated intercept of the regression line (excess tumour risk at 0 concentration of vinyl chloride)

C = Vinyl chloride concentration in air (ppm).

The calculations were made when the tumour risks in control animals and in all exposed animals were found to be statistically significantly different. As will be shown later, the linear dose response function applied only over the lower dose ranges and therefore risk estimates derived from higher exposure groups that did no longer satisfy a linear dose response function were omitted from this calculation.

The calculated slope of the regression line was an estimate of the excess tumour risk per ppm of vinyl chloride and the calculated intercept of the regression line was an estimate of the excess risk at zero vinyl chloride concentration. If the intercept was not statistically significantly different from zero and the slope of the regression line was statistically significantly different from zero then the data were compatible with a linear risk function with no threshold. A negative intercept which was statistically significantly different from zero together with a slope which was statistically significantly different from zero would indicate that the data were compatible with a linear risk function with a threshold.

In no case was the calculated intercept negative and statistically significantly different from zero. For mammary carcinoma in Swiss Mice, the intercept was positive and statistically significantly different from zero and the slope was not statistically significantly different from zero.

Table 3 contained the calculated slopes of the regression lines and their upper 99% and 95% confidence limits, the range of concentrations used in the calculations, the probability that the slope was zero, and the probability that the intercept was zero. The results were reported only when the slope of the regression line differed significantly from zero. The 95% and 99% upper confidence limits were calculated so that the probabilities that the slope is in fact higher than the upper confidence limits were 5% and 1% respectively.

Figures 1 to 4 contained plots of the regression lines, 95% confidence limits of the regression line, 95% confidence limits for data points around the regression line, and the data points used in the regression calculation.

It was apparent that tumour risks at "high" concentrations of vinyl chloride were not compatible with the linear regression line calculated from the risks observed at "low" concentrations. The following non-linear function was used in order to fit the observed tumour risks over the range of concentrations used in the experiments.

$$R = \begin{cases} K \times D \times A \times e^{-B \times D} & \text{if } A \times e^{-B \times D} \leq 1 \\ K \times D & \text{if } A \times e^{-B \times D} > 1 \end{cases}$$

where R = excess tumour risk

D = concentration of vinyl chloride (ppm)

K = slope of risk function calculated from risks at "low" concentrations of vinyl chloride

A and B were fitted constants and A was subject to the restraint that A must be greater than or equal to 1.

In this non-linear risk function, the factor KxD represents the tumour risk at vinyl chloride concentrations D; the second factor, Axe^{-BxD}, represented the fraction of cells surviving the exposure to vinyl chloride concentration D; the restraint $Axe^{-BxD} > 1$ indicated a range of concentrations at which no significant cell-killing occured.

This risk function increased linearly at "low" concentrations, reached a maximum risk, and as concentration increases further, the risk function decreased.

The function was fitted separately to the excess risk of liver angiosarcoma and to the excess risk of all tumours in Sprague-Dawley rats and in Swiss Mice. The risk of liver angiosarcoma in Sprague-Dawley rats was compatible with the non-linear function. See figure 5. In the other cases, the data and the risk function were not compatible.

Calculation of an Acceptable Air Concentration of Vinyl Chloride

The upper 99% confidence limit of the excess tumour risk factor which was derived from the data observed at the no effect level in Sprague-Dawley rats exposed to vinyl chloride for 52 weeks was used to calculate the acceptable air concentration of vinyl chloride. This particular value was selected because it alone, among all the calculated upper confidence limits of the excess tumour risk factors, was derived from data which represented lifetime tumour risks and also because it was derived by using the more conservative approach which used data observed at the no effect exposure level. The numerical value thus derived was 4.3×10^{-3} excess tumours per animal per ppm of vinyl chloride.

In order to obtain the risk factor for humans, it was necessary to make an assumption. It was assumed that the lifetime tumour risks were the same in man and the Sprague-Dawley rat when the same fractions of each species average lifetime were spent exposed to the same concentration of vinyl chloride in air. In this calculation, the average lifetime of the rat was taken to be 2 years(5). The fraction of the average lifetime spent in exposure by the Sprague-Dawley rat was calculated to be:

$$\frac{4 \text{ hrs/day} \times 5 \text{ days/week} \times 52 \text{ weeks}}{24 \text{ hrs/day} \times 7 \text{ days/week} \times 104 \text{ weeks}} = 6.0 \times 10^{-2}$$

The excess tumour risk factor when the duration of exposure was an average lifetime was calculated to be $\frac{4.3 \times 10^{-3}}{6.0 \times 10^{-2}} = 7.2 \times 10^{-2}$ per ppm of vinyl chloride in air.

The annual exposure duration for a worker was assumed to be 8 hours per day, 5 days per week for 52 weeks and the worker's average lifetime was taken to be 70 years. Hence, the fraction of an average lifetime spent in exposure during the course of one working year was calculated to be

$$\frac{8 \text{ hours/day} \times 5 \text{ days/week} \times 52 \text{ weeks}}{24 \text{ hours/day} \times 7 \text{ days/week} \times 52 \text{ weeks/year} \times 70 \text{ years}} = 3.4 \times 10^{-3}$$

Hence, the lifetime risk when the exposure duration was 3.4×10^{-3} of an average lifetime was calculated to be

$$3.4 \times 10^{-3} \times 7.2 \times 10^{-2} \text{ per ppm} = 2.4 \times 10^{-4} \text{ per ppm}$$

When the workers are exposed year after year to the same concentration of vinyl chloride, the annual risk resulting from the exposure will increase in successive years and approach a maximum value which is equal to the lifetime risk from the exposure accumulated over one working year. Hence, the annual excess tumour risk for persons who are continually in exposure in the workplace to air containing 1 ppm of vinyl chloride will increase towards a maximum value of 2.4×10^{-4} per person or 24 excess tumours per year among 100,000 workers.

The annual acceptable risk for a worker was obtained by using the data of the International Commission on Radiological Protection (4; paragraphs 60 and 104) and was calculated to be 5×10^{-4} or 50 excess deaths per year among 100,000 workers.

Based upon the results of the above calculations and based upon the assumptions made, it was calculated that chronic exposure in the workplace to air containing 2 ppm of vinyl chloride produced an annual excess risk, of at most, of 5×10^{-4} or 50 excess tumours per year among 100,000 workers.

Discussion of Extrapolation Procedures

At the present time, it appears that there is no completely satisfactory method of extrapolating tumour risks from the concentrations used in experiments to lower concentrations (3). The methods used in this report represent the types of approach currently being used to extrapolate experimental data.

In the first approach, the calculation uses the risks observed at the no effect level. The no effect level is the highest concentration at which no excess tumour risk is discernible. The slope of the non-threshold linear function which passes through the upper confidence limit of excess risk at the no excess level is an estimate of the risk factor when the concentration of vinyl chloride is low. The effect of choosing the highest exposure level at which there is no discernible excess risk is to choose the smallest risk factor which is compatible with the data in a single exposure group.

In the second approach, it is also assumed that the risk function is linear. In contrast to the first method, the data in several exposure groups are used in the calculation of the risk factor. In this approach, the hypothesis that there was no threshold could be tested when data from several exposure groups were used. It must be pointed out that many different risk functions would be compatible with the observed data and would provide very different estimates of the risk at low concentrations of vinyl chloride. Hence, the second approach is considered to be less conservative than the previous one. The third approach attempted to show that the data at all the exposure levels were compatible with a single risk function.

When the results of the animal experiments were extrapolated to man, a number of additional assumptions were made: tumour risk increases in proportion to the duration of daily exposure; no adjustment for differences in species size is necessary if the exposure level is measured in terms of concentration in inhaled air; tumour risks are equal in two species when the same fraction of each species lifetime is spent exposed to equivalent exposure levels. In addition, these calculations do not take into account many other aspects of extrapolation between species which may be important (3).

Summary

The calculation of the acceptable concentration of vinyl chloride in air in the workplace was based upon the data observed in the Sprague-Dawley rats which were exposed for 52 weeks because those data alone represented lifetime risks resulting from chronic exposure over a sufficiently long period of time.

The risk factor was calculated by using the data observed in the control animals and in the animals exposed to the highest concentration of vinyl chloride at which there was no discernible excess tumour risk. This approach provided a more conservative estimate of the risk factor than those approaches which used the data from several exposure groups.

In the calculation of the acceptable concentration of vinyl chloride in the workplace, several assumptions were made. It was assumed that lifetime tumour risks were the same in man and in the Sprague-Dawley rat when the same fractions of each species average lifetime were spent exposed to the same concentration of vinyl chloride in air. It was assumed that there was no threshold concentration of vinyl chloride below which there would be no associated risk and that the relationship between air concentration of vinyl chloride and excess tumour risk was linear. The exposure duration for a worker was assumed to be 8 hours a day, 5 days a week, 52 weeks a year for a working lifetime. The acceptable annual risk was taken to be 50 excess tumours among 100,000 workers. Based upon the above assumptions the acceptable concentration of vinyl chloride in the air in the workplace was calculated to be 2 ppm.

Conclusions:

Based upon the calculations made and the assumptions stated, the acceptable concentration of vinyl chloride in air in the workplace is 2 ppm.

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2. Carcinogenicity of Vinyl Chloride and Vinyldine Chloride, C.C. Lee et al, Journal of Toxicology and Environmental Health, 4, 1978.

3. Estimation of Risks of Irreversible Delayed Toxicity, David G. Hoel et al, Journal of Toxicology and Environmental Health, 1, 1975.

4. Recommendations of the International Commission on Radiological Protection, Publication 26, Pergamon Press, 1977.

5. The Rat Reference Tables and Data for the Albino Rat (Mus Norvegicus Albinus) and The Norway Rat (Mus Norvegicus) H. N. Donaldson (editor), Philadelphia (1915).

TABLE 1: Comparison of Tumour Frequencies in Control Animals and in Animals Exposed to Vinyl Chloride in Air

Experimental Animal	Exposure Time(wk)	Observation Time (wk) (1)	Type of Tumour	Probability of No Difference in Tumour Frequency in Exposed(2) Animals and Unexposed Animals
Sprague-Dawley Rat	52	135	Zymbal gland carcinoma	1.07×10^{-2}
			Nephroblastoma	1.75×10^{-2}
			Liver Angiosarcoma	5.33×10^{-4}
			All tumours	8.87×10^{-7}
Sprague-Dawley Rat	17	86	Zymbal gland carcinoma	8.95×10^{-3}
			Brain neuroblastoma	1.38×10^{-2}
			All tumours	1.31×10^{-5}
Swiss Mice	30	61	Liver angiosarcoma	1.88×10^{-8}
			Pulmonary tumours	1.09×10^{-29}
			Mammary carcinoma	2.06×10^{-10}
			Vascular tumours of Other Types or Sites	8.19×10^{-13}
			Epithelial Tumours of the Skin	9.12×10^{-3}
			All tumours	1.42×10^{-36}
Golden Hamster	30	48	All tumours	1.98×10^{-2}

NOTES: (1) Observation time was the same for exposed and unexposed animals.
(2) Exposure levels were 50,250,500,2,500,6,000 and 10,000 ppm of vinyl chloride in air
(3) Results are reported when the probability of no difference between exposed and unexposed animals was less than 0.05.
(4) Probabilities were calculated using the Fisher-Irwin exact probability method.

TABLE 2: Excess Risk Factors for Inhalation of Vinyl Chloride: Results Obtained Using A Single Exposure Group

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Experimental Animal	Exposure Time (wk)	Observation Time(wk)(1)	Type of Tumour	No Effect Level(ppm)	Observed Excess Risk per ppm	Upper Confidence Limit on Excess Risk per ppm 95%	99%
Sprague-Dawley Rat	52	135	Nephroblastoma	50	3.4×10^{-4}	1.6×10^{-3}	2.1×10^{-3}
			Liver Angiosarcoma	50	3.4×10^{-4}	1.6×10^{-3}	2.1×10^{-3}
			All Tumours	50	1.3×10^{-3}	3.4×10^{-3}	4.3×10^{-3}
Sprague-Dawley Rat	17	86	Brain Neuroblastoma	500	0	9.7×10^{-5}	1.5×10^{-4}
			All Tumours	500	4.6×10^{-5}	1.3×10^{-4}	1.6×10^{-4}
Swiss Mice	30	61	PulmonaryTumours	50	-2.2×10^{-4}	5.2×10^{-4}	8.2×10^{-4}
			Mammary Carcinoma	50**	3.5×10^{-3}	5.6×10^{-3}	6.4×10^{-3}
			Liver Angiosarcoma	50	3.5×10^{-4}	1.6×10^{-3}	2.2×10^{-3}
			Angiosarcomas Other than Liver or Other vascular tumours	50**	3.9×10^{-3}	6.0×10^{-3}	6.9×10^{-3}
			Epithelial Tumours of Skin	250	0	2.0×10^{-4}	3.0×10^{-4}
			All Tumours	50**	4.9×10^{-3}	6.9×10^{-3}	7.8×10^{-3}
Golden Hamsters	30	48	All Tumours	50**	2.6×10^{-3}	4.6×10^{-3}	5.5×10^{-3}

NOTES: (1) Observation times for both exposed and unexposed animals were the same.

(2) Results are reported only where there is a statistically significant difference between exposed and unexposed animals (See Table 1). Results concerning Zymbal Gland carcinoma are excluded.

(3) 95% and 99% upper confidence limits are calculated so that the probabilities that the excess risk per ppm is in fact higher than the upper confidence limit are 5% and 1% respectively.

(4) ** indicates that there is a significant difference in tumour frequency between control gr up and lowest exposure group.

3: Risk Factors for Inhalation of Vinyl Chloride: Significant Results of Linear Regression Calculations

perimental mal	Exposure Time(wk)	Observation Time(wk)(1)	Type of Tumour	Range of Concentrations Used in Calculation(ppm)	Slope of Regression Line(Excess Risk per ppm)	Probability that Slope Is Zero	Probability that Intercept is Zero	Upper Confidence Limit of Slope of Regression Line 95%	Upper Confidence Limit of Slope of Regression Line 99%
ague-ley Rat	52	135	Liver Angiocoma	0-500	2.4×10^{-4}	< 0.01	> 0.20	2.7×10^{-4}	3.2×10^{-4}
			Brain Neuroblastoma	0-10,000	1.1×10^{-5}	< 0.02	> 0.50	1.6×10^{-5}	2.0×10^{-5}
			All Tumours	0-500	5.1×10^{-4}	< 0.02	> 0.20	6.9×10^{-4}	9.5×10^{-4}
ague-ley Rat	17	86	Brain Neuroblastoma	0-10,000	9.2×10^{-6}	< 0.001	> 0.50	1.2×10^{-5}	1.3×10^{-5}

(1) Observation time was the same for exposed and unexposed animals.

(2) 95% and 99% upper confidence limits are calculated so that the probabilities that the slope is in fact higher than the upper confidence limits are 5% and 1% respectively.

(3) Results are reported when the slope of the regression line is statistically significantly different from zero ($p < 0.05$).

fig.1:EXCESS RISK OF LIVER ANGIOSARCOMA IN S.D. RATS:52 Wk EXPOSURE
WITH 85% CONFIDENCE LIMITS

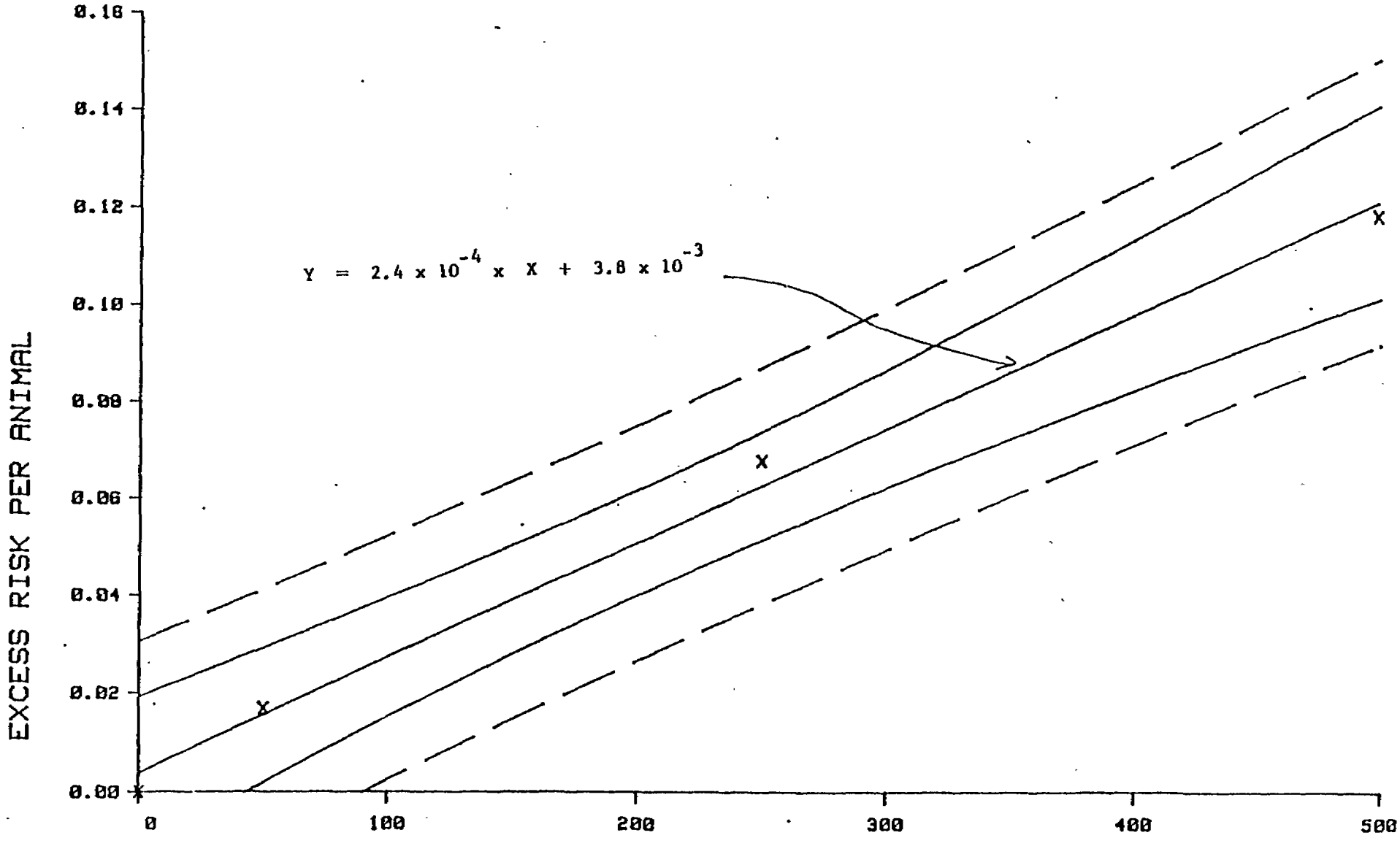

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fig.2:EXCESS RISK OF BRAIN NEUROBLASTOMA IN S.D. RATS:52 Wk EXPOSURE
WITH 95% CONFIDENCE LIMITS

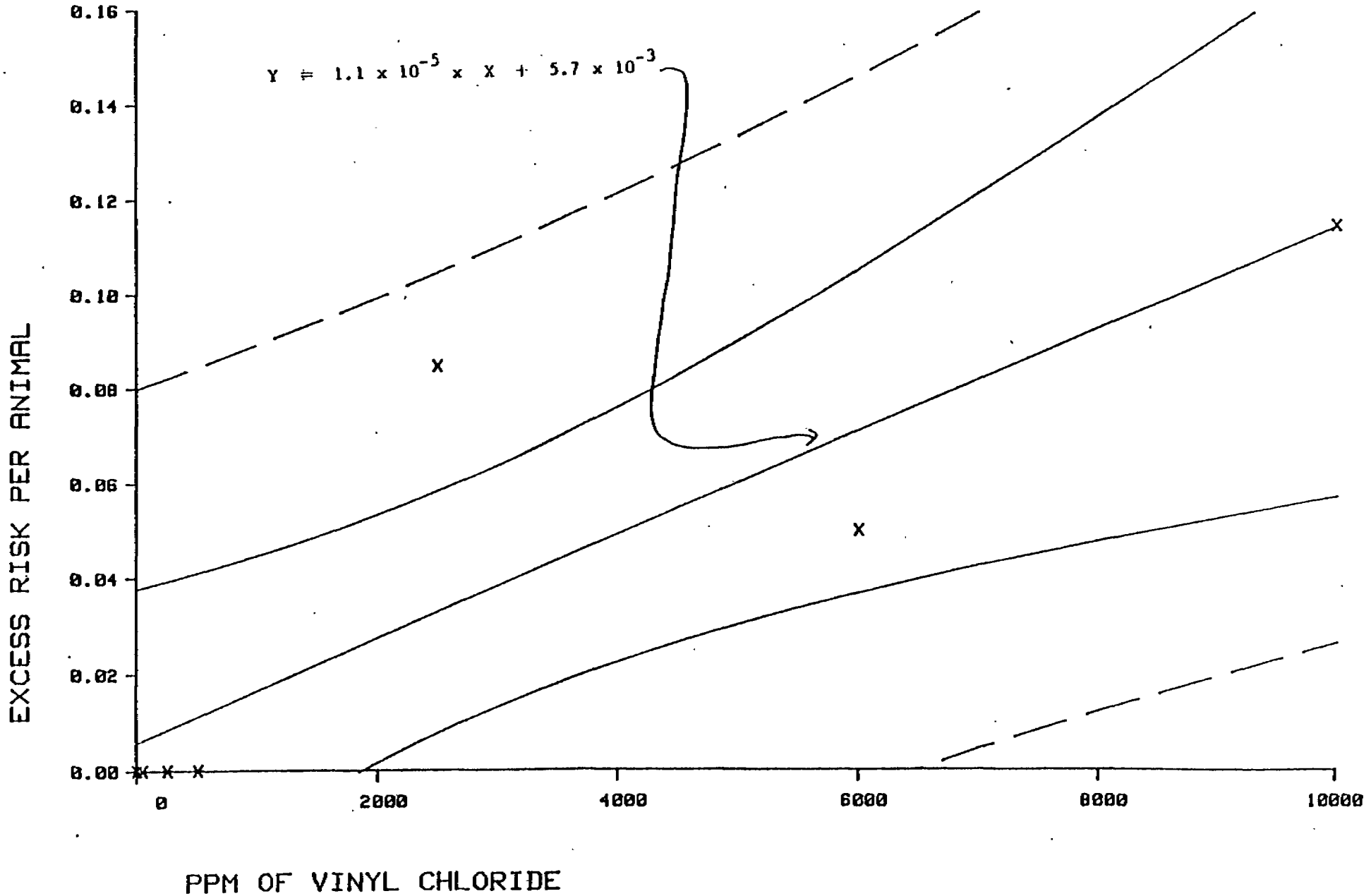

fig.3:EXCESS TUMOUR RISK IN S.D. RATS:52Wk EXPOSURE

WITH 95% CONFIDENCE LIMITS

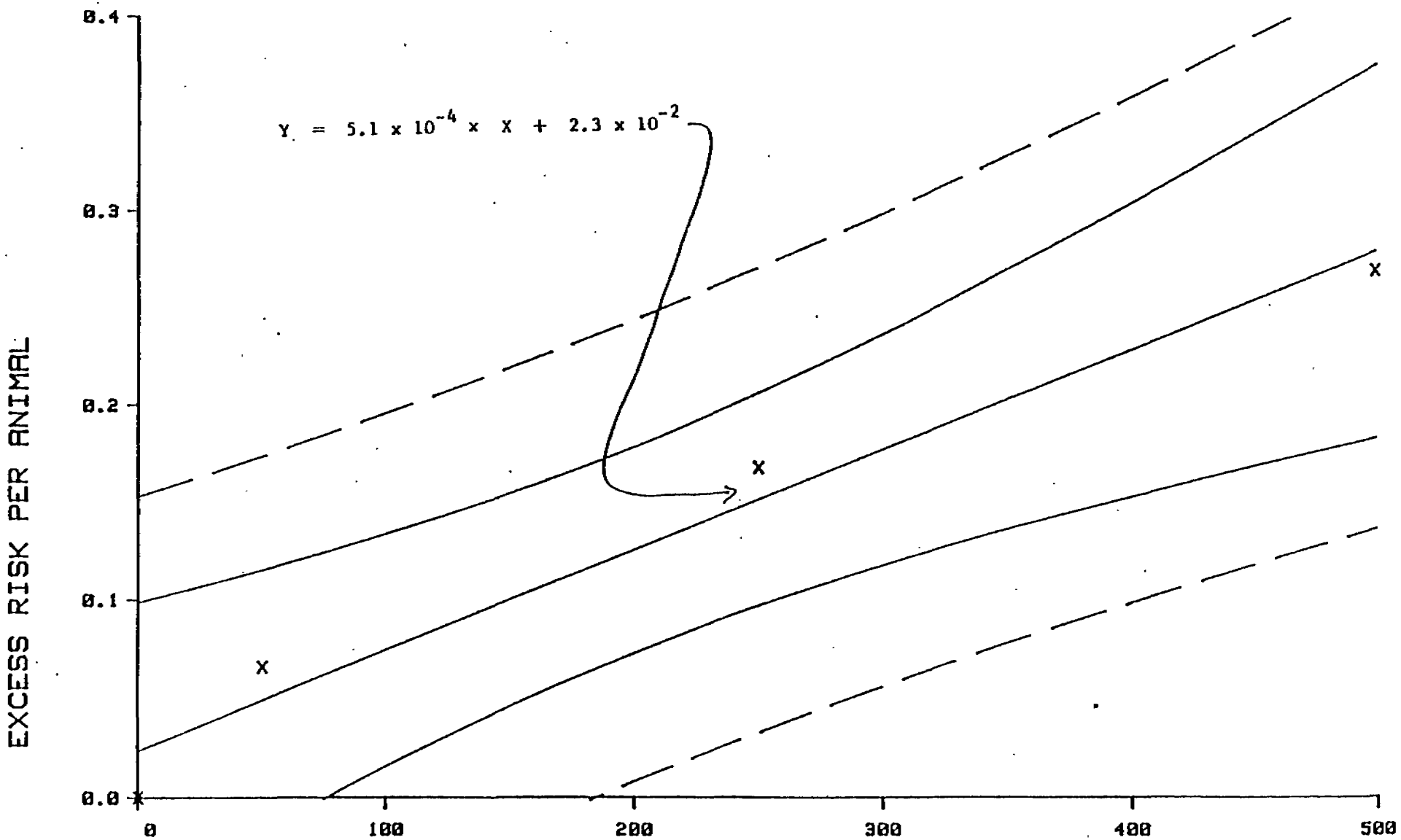

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fig.4:EXCESS RISK OF BRAIN NEUROBLASTOMA IN S.D. RATS:17 Wk EXPOSURE
WITH 95% CONFIDENCE LIMITS

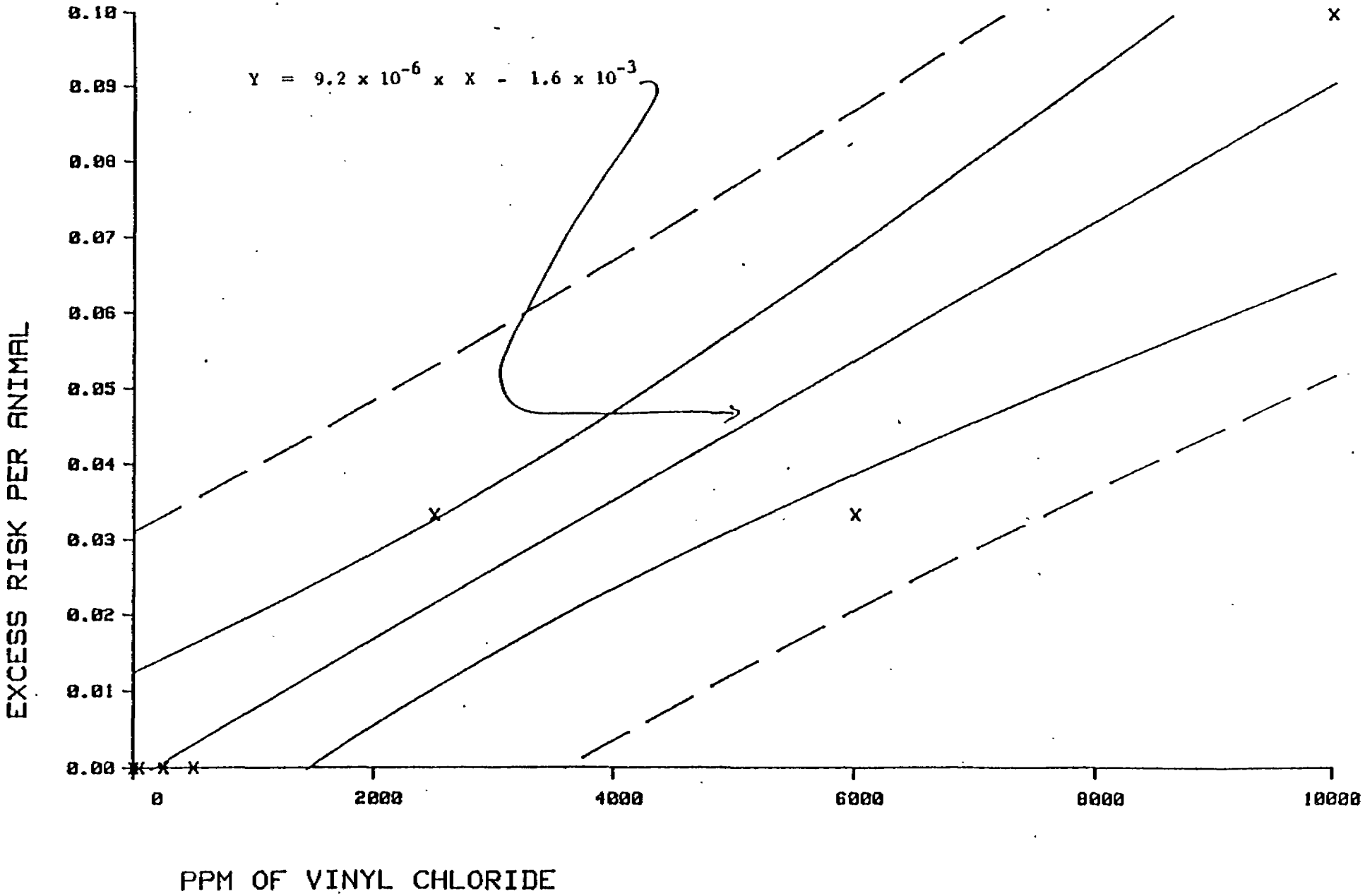
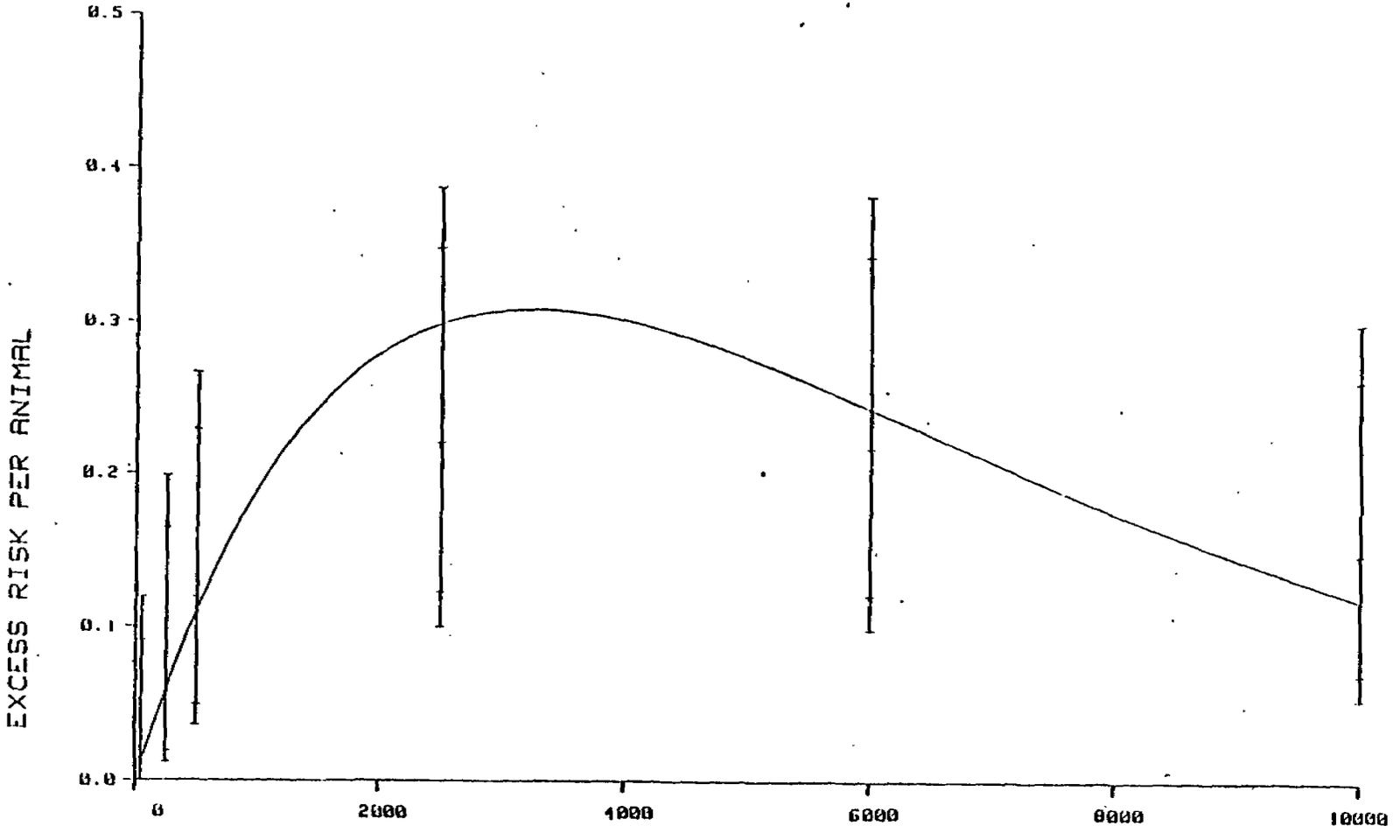


fig.5:EXCESS RISK OF LIVER ANGIOSARCOMA IN S.D. RATS:52 Wk EXPOSURE

WITH 95 & 99% CONFIDENCE LIMITS ON EXCESS RISK



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APPENDIX 2

Table 1. Experiment ST1: Results after 135 weeks (end of the experiment)

Treatment (a)	Animals (Sprague-Dawley rats)		Animals with tumors															
			Zymbal gland carcinomas (c)			Nephroblastomas (e)			Angiosarcomas				Subcutaneous angiomas	Skin carcinomas	Hepatomas	Brain neuroblastomas	Other type and/or site (g)	Total (h)
									Liver (f)			Other sites						
	Total	Corrected number (b)	No.	% (d)	Average latency time (weeks)	No.	% (d)	Average latency time (weeks)	No.	% (d)	Average latency time (weeks)	No.	No.	No.	No.	No.	No.	No.
VC 10000 ppm	69	51	18	35	50	5	9	59	9	18	55	3 (l)	4	3	2	2	7 (a)	38
VC 5000 ppm	72	60	7	12	42	4	7	45	13	22	73	3 (m)	1	1	1	3	8 (a)	31
VC 2500 ppm	74	59	2	3	71	5	10	74	13	22	73	3 (n)	3	1	2	5	4 (a)	32
VC 500 ppm	67	59	4	7	79	4	7	83	7	12	81	2 (l)	1	1	3	—	4 (a)	22
VC 250 ppm	67	59	—	—	—	5	10	80	4	7	79	2 (m)	—	4	—	—	3 (a)	16
VC 50 ppm	64	59	—	—	—	1	2	135	1	2	135	1 (n)	1	1	—	—	3 (a)	10
No treatment	68	58	—	—	—	—	—	—	—	—	—	—	—	—	—	—	10 (a)	6
Total	577	444	29	—	—	28	—	—	47	—	—	14	12	11	7	15	45	165

(a) The animals were treated by inhalation for 4 hours daily, 5 days weekly, for 52 weeks.
(b) Animals alive after 26 weeks, when the first tumor (a Zymbal gland carcinoma) was observed. The percentages are referred to the corrected number.
(c) Metastases to lung.
(d) Percentage of corrected number.
(e) Metastases to liver, lung, spleen and brain.
(f) Metastases to lung.
(g) Several cases of breast fibroadenomas, adrenal and pituitary tumors (generally adenomas) have not been considered, since their distribution in the different groups does not vary.
(h) Several animals with 2 or more tumors.
(i) 1 angiosarcoma of the lips; 1 angiosarcoma of the nose; 1 intra-abdominal angiosarcoma (next to liver).
(j) 1 angiosarcoma in subcutaneous fibrosing angioma; 1 ossifying parauricular angiosarcoma; 1 intra-abdominal angiosarcoma (next to liver).
(k) 2 intra-abdominal angiosarcomas (1 next to spleen and 1 next to ovary); 1 ossifying angiosarcoma of the neck.
(l) 1 pulmonary angiosarcoma; 1 angiosarcoma of the uterus.
(m) 1 intra-abdominal angiosarcoma (next to spleen); 1 intrathoracic ossifying angiosarcoma.
(n) 1 intra-abdominal diffused angiosarcoma.
(o) 2 Zymbal gland adenomas; 3 mammary carcinomas; 1 neurilemmoma; 1 ovarian cystoadenocarcinoma.
(p) 4 Zymbal gland adenomas; 1 salivary gland adenocarcinoma; 2 hepatic and 1 peritoneal angiomas.
(q) 1 Zymbal gland adenoma; 1 mammary carcinoma; 2 ependymomas.
(r) 1 mammary carcinoma; 2 lymphomas; 1 pulmonary fibrosarcoma.
(s) 1 Zymbal gland adenoma; 1 mammary carcinoma; 1 lymphoma.
(t) 1 Zymbal gland adenomas; 2 mammary carcinomas; 1 subcutaneous angiopericitoma; 3 uterine adenocarcinomas (1 with sarcomatous component).
(u) 1 invasive acanthoma of Zymbal gland; 1 subcutaneous fibrosarcoma; 2 peritoneal fibroangiomas, 2 uterine adenocarcinomas (1 with sarcomatous component); 1 uterine leiomyosarcoma; 1 ovarian fibrosarcoma; 1 pulmonary rhabdomyosarcoma; 1 lymphoma.

Table 2. Experiment ST3: Results after 86 weeks

Treatment (a)	Number of animals (Sprague-Dawley rats)		Number of animals with tumors (b)						
			Zymbal gland carcinomas	Nephroblastomas	Angiosarcomas		Brain neuroblastomas	Other type and/or site (c)	Total (d)
	Total	Survivors			Liver	Other sites			
VC 10000 ppm	50	9	8 (16)	— (5)	— (9)	1 (e) (3)	4 (7)	3 (g) (15)	15 (40)
VC 5000 ppm	50	18	4 (7)	— (4)	— (11)	— (3)	2 (3)	7 (h) (9)	10 (27)
VC 2500 ppm	60	33	1 (2)	2 (4)	— (9)	— (3)	3 (2)	— (7)	5 (23)
VC 500 ppm	60	37	— (2)	— (2)	— (3)	— (2)	—	2 (i) (7)	2 (13)
VC 250 ppm	60	15	—	1 (6)	— (2)	— (1)	—	2 (j) (5)	3 (9)
VC 50 ppm	60	18	—	—	—	1 (f)	—	— (3)	1 (3)
No treatment	150	128	—	—	—	—	—	3 (k) (3)	2 (2)
Total	550	256	11 (27)	3 (19)	— (34)	2 (12)	10 (12)	17 (49)	38 (117)

(a) The animals were treated by inhalation 4 hours daily, 5 hours weekly, for 17 weeks.
(b) Between brackets are recorded the tumors found in experiment ST1 after 86 weeks.
(c) Several cases of breast fibroadenomas, adrenal and pituitary tumors (generally adenomas) have not been considered, since their distribution in the different groups does not vary.
(d) Several animals with 2 or more tumors.
(e) 1 subcutaneous angiosarcoma.
(f) 1 orbital angiosarcoma.
(g) 1 parauricular fibrosarcoma; 1 nasal papilloma; 1 renal adenoma.
(h) 1 Zymbal gland fibroangioma; 2 skin carcinomas; 1 subcutaneous angioma; 1 mammary carcinoma; 1 forestomach papilloma; 1 cranial osteoma.
(i) 2 lymphomas.
(j) 1 Zymbal gland adenoma; 1 retrobulbar fibroma.
(k) 1 Zymbal gland adenoma; 2 lymphomas.

Table 3. Experiment ST7: Results after 61 weeks

Treatment (a)	Number of animals (Wistar rats)		Number of animals with tumors (b)						
			Zymbal gland carcinomas	Nephroblastomas	Angiosarcomas		Brain neuroblastomas	Other type and/or site	Total
	Total	Survivors			Liver	Other sites			
VC 10000 ppm	30	8	— (7)	1 (3)	2 (3)	— (1)	1 (2)	2 (c) (7)	5 (18)
VC 5000 ppm	30	10	— (1)	— (1)	— (2)	— (1)	— (1)	— (1)	— (5)
VC 2500 ppm	30	9	— (1)	— (1)	— (1)	— (2)	—	— (1)	— (5)
VC 500 ppm	30	16	— (1)	—	1	—	—	—	1 (1)
VC 250 ppm	30	18	—	—	—	—	—	1 (d)	1
VC 50 ppm	30	22	—	—	—	—	—	—	—
No treatment	40	34	—	—	—	—	—	—	—
Total	220	117	— (10)	1 (3)	3 (6)	— (4)	1 (3)	3 (9)	7 (30)

(a) The animals were treated by inhalation for 4 hours daily, 5 days weekly, for 52 weeks.
(b) Between brackets are recorded the tumors found in male Sprague-Dawley rats of the experiment ST1, after 71 weeks.
(c) 2 Zymbal gland adenomas.
(d) 1 angioma of the caecum.

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