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The Interaction of Ethyl Alcohol and Industrial Chemicals

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A serious, relatively unrecognized, occupational health problem involves the interaction of ethyl alcohol and chemical agents used in industry. Workers who drink alcohol and are exposed to certain chemical agents may experience adverse health effects such as nausea, dizziness, headache, and liver damage. This report reviews the synergistic interactions of ethanol with compounds such as the thiurams, amides, oximes, halogenated hydrocarbons, and metals. Also discussed is the effect of ethanol as a cofactor with vinyl chloride in the etiology of cancer.

Key words: alcohol, ethanol, interaction, synergism, additive effects, combined effects

INTRODUCTION

There is an abundance of information in the literature on the interactions of ethyl alcohol (C_2H_5OH) with foreign chemicals in the human body. Most of these interactions involve pharmacologic agents employed as drugs; however, there is also the problem of adverse reactions arising from ethanol consumption combined with exposure to chemical agents in the workplace. This issue was first addressed by Durie et al [1970], and later by Freundt [1980]. The purpose of this paper is to promote an awareness of this problem among occupational health professionals, and to provide a brief summary of the information available on the subject.

The effects of interactions that occur in the human body between ethyl alcohol (hereafter referred to as ethanol or alcohol) and other foreign chemical agents fall into three main categories: (i) antagonism, where the combined exposure produces a final response that is less than the individual effects; (ii) synergism, where the simultaneous exposure produces a response exceeding the sum of the separate effects exerted by

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either agent alone; and (iii) simple additive effects, where the combined exposure produces a response equal to the sum of the separate effects exerted by either agent alone.

The chronic use of ethanol itself can interfere with an individual's personal health and social and economic functioning. Chronic consumption is known to have various detrimental effects on the body including fatty deposits in the liver, alcoholic hepatitis, and liver cirrhosis. Alcohol intoxication impairs cerebral functions and can cause permanent brain damage. There is also some evidence that alcohol is a factor in the development of cancers at certain sites in the body. There is a significantly higher incidence of cancer of the mouth, throat, and liver among persons who drink heavily [Secretary of HEW, 1974].

It is well known that the use of alcohol can be addictive. Although the precise mechanism of addiction is not known, it is thought to involve the central nervous system. An uncommon form of heart disease, cardiomyopathy, has been reported to occur with increased frequency in problem drinkers and, as might be expected, they have a higher mortality rate than the general population [Secretary of HEW, 1974].

The chronic abuse of alcohol is a major health problem in the United States [National Council on Alcoholism, 1971]. According to the National Council on Alcoholism, 100 million persons aged 15 or over in this country are consumers of ethanol. Of this population, an estimated 10 million, or 10%, suffer from alcoholism [National Council on Alcoholism, 1971]. The onset of this disease varies widely between individuals. It may appear with the first drink or it may take years to develop. A 1975 report [Booz et al, 1975] stated that of the 76 million people in the United States workforce, 3–7.6 million suffered from alcoholism. From this information, it could be estimated that up to 10% of the employees across the industrial population may have an alcoholism problem.

The uptake, distribution, and excretion of ethanol in the body is based on its physiochemical properties. Ethanol is highly soluble in water, rapidly absorbed by the gastrointestinal tract, does not bind to plasma proteins, and is distributed in body water. Elimination of ethanol from the body is accomplished to a small extent through the kidneys and lungs [Mezey, 1976].

Most of the absorbed ethanol (at least 90%) is oxidized in the liver to acetaldehyde by the action of alcohol dehydrogenase and the transfer of hydrogen to nicotinamide adenine dinucleotide (NAD), which forms NADH, as shown in Figure 1.

$$\text{Ethanol} + \text{NAD}^+ \xrightarrow[\text{dehydrogenase}]{\text{alcohol}} \text{Acetaldehyde} + \text{NADH} + \text{H}^+$$

Fig. 1. Reaction of ethanol with NAD.

The NADH must then be reoxidized back to NAD before more ethanol can be oxidized. The resulting increase in NADH affects the NADH/NAD ratio, which produces a change in the ratio of all metabolites that are dependent on NADH/NAD. This shift leads to altered biochemical pathways and a striking metabolic imbalance in the liver. The imbalance is easily established when ethanol is present because it is the preferred fuel of the liver and can displace up to 90% of all other substances normally utilized by the liver and dominates liver metabolism [Lieber, 1980].

Other liver enzymes capable of metabolizing ethanol to acetaldehyde are catalase and the microsomal ethanol oxidizing system (MEOS). However, these enzymes contribute little to the total metabolism of ethanol [Mezey, 1976].

The next step in ethanol metabolism is the conversion of acetaldehyde to acetate by aldehyde dehydrogenase, as shown in Figure 2.

Fig. 2. Ethanol metabolism.

Normally, acetaldehyde levels in the blood are moderately elevated after the ingestion of ethanol. However, if aldehyde dehydrogenase is blocked or inhibited by another substance, acetaldehyde can accumulate in toxic quantities [Lieber, 1980; Graham, 1951; Raby, 1954].

The levels of acetaldehyde measured in the blood by different researchers has not been consistent. Variations between assay methods and the instability of acetaldehyde in vitro may account for these discrepancies [Eriksson, 1980; Eriksson et al, 1979; Stowell et al, 1978a]. In the past several years, a number of analytical procedures have been described that appear to yield more accurate measures of blood acetaldehyde levels [Stowell, 1979; Von Wartburg and Ris, 1979; Stowell et al, 1978b]. Although there is uncertainty concerning the actual level of acetaldehyde in the blood, it is a very reactive compound which exhibits numerous neurotoxic effects and interferes with liver metabolism [Lieber, 1980]. It has been reported that elevated blood levels of acetaldehyde result in tachycardia, decreased diastolic blood pressure, hypertension, increased breathing rate, and symptoms of alcohol intoxication [Lieber, 1980].

In the workplace, compounds such as amides, oximes, thiurams, carbamates, and others have been proven to be effective inhibitors of aldehyde dehydrogenase [Lester and Benson, 1970; DeBruin, 1976]. These agents produce symptoms similar to those seen with elevated acetaldehyde blood levels. The interactions are known by various names such as the "aldehyde syndrome," "antabuse syndrome," or the "disulfiram syndrome." An increased level of acetaldehyde in the body is the primary cause of this syndrome, although it would be an oversimplfication to assume that acetaldehyde is the sole cause. The response to each of these inhibitors is slightly different, a fact that substantiates the involvement of other factors and mechanisms, many of which are still unknown.

INTERACTING AGENTS

Thiuram Disulfides

One widely known synergistic interaction between alcohol and a foreign chemical substance is the disulfiram syndrome. The disulfiram syndrome was observed in laborers of a chemical company that manufactured rubber accelerators for the vulcanization process. Laborers working with tetramethyl thiuram monosulfide (disulfiram) developed flushing of the face and hands, a rapid pulse, a fall in blood pressure, difficulty in breathing, and nausea after drinking a 6-ounce glass of beer [Williams, 1937]. This dis-

covery led to the use of disulfiram, also called antabuse, as a prescription drug to discourage alcohol consumption. Disulfiram greatly decreases a person's tolerance to ethanol. A human therapeutic dose, ranging from 125 to 500 mg per day, will result in symptoms in the presence of even a small quantity of alcohol [Baker, 1974]. The misuse of disulfiram with continued ingestion of ethanol has resulted in at least 13 recorded deaths in humans. In six of these cases, death was the result of circulatory collapse or cerebral hemorrhage [Alha et al, 1957]. Most of the thiuram disulfides have the ability to inhibit aldehyde dehydrogenase. Barnes and Fox [1955] screened thiuram disulfides for antabuse-like activity in rats. The study concluded that the inhibiting action on aldehyde dehydrogenase seemed to stem from linking of the C=S group to the enzyme molecule in competition with the substrate. In addition, they reported that the inhibitor molecule must have an amino group present in order to have a sufficiently high affinity for the enzyme.

Besides their uses in rubber manufacturing, the thiuram disulfides are a component of numerous fungicides, insecticides, seed disinfectants, larvicides, germicidal soaps, lotions, ointments, rubber goods, and fabric finishes [Shelley, 1964; Van Ketel, 1968; Webb et al, 1979; National Occupational Hazard Survey, 1977]. Direct dermal contact with thiuram-containing rubber products and the use of thiuram-containing soaps have induced the antabuse syndrome in several individuals after consumption of alcohol. Contact dermatitis may also develop when rubber products come in contact with the skin [Shelley, 1964; Van Ketel, 1968; Webb et al, 1979].

There are several other substances that induce the disulfiram syndrome upon ethanol ingestion. These include pesticidal dithiocarbamates such as pyrazole [Lester and Benson, 1970], ziram and manam [Van Logten, 1972], hypoglycemic sulphonylureas [Triutt et al, 1962], and the industrial explosive nitroglycol [Yoshitake, 1973].

Since the discovery of the disulfiram-ethanol interaction, numerous other substances have been documented as producing an interaction with ethanol. These chemicals are reviewed below.

Amides

Dimethylformamide. Dimethylformamide (NOC_3H_7) is used widely in a variety of manufacturing processes because of its broad solvent powers for both organic and inorganic chemicals [National Occupational Hazard Survey, 1977; Potter, 1973]. Also referred to as DMF, it is extensively used in the chemical industry as a solvent for acetylene, butadiene, acid gases, and vinyl and acrylic resins [Hawley, 1977]. In the textile industry, DMF is used as a solvent for the spinning of synthetic fiber yarn [Kenkyusha, 1979]. Exposure to DMF in the workplace occurs through two primary routes; skin contact and inhalation of the vapors [Lauwerys et al, 1980]. Intolerance to alcohol has been reported in workers who were exposed to DMF [Tolot et al, 1958; Reinl and Urban, 1965; Tolot et al, 1968; Martelli, 1960]. In several incidents, workers exposed to DMF developed a dermal flushing reaction immediately following the consumption of as little as one-half pint of beer [Chivars, 1978; Lyle, 1979], characterized by a vivid scarlet flushing of the face and neck, and sometimes of the chest, arms, and hands as well. Other symptoms may develop if ethanol is consumed immediately following exposure to DMF. As shown in Figure 3, the probable cause is that the main metabolite of DMF, n-methylformamide (MF), inhibits the metabolism of acetaldehyde to acetic acid.

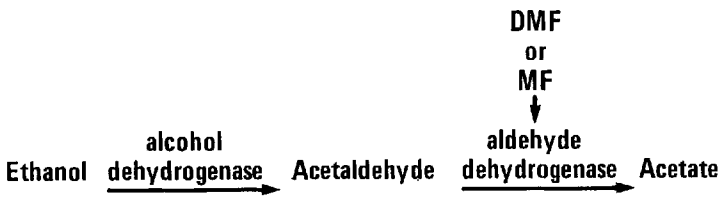

Fig. 3. Action of DMF or MF on ethanol metabolism.

Specifically, MF binds to aldehyde dehydrogenase, resulting in an increased acetaldehyde concentration in the blood stream. Of the two possible inibitors, MF is more likely to be the agent that blocks the action of aldehyde dehydrogenase. This is because DMF is removed from the blood stream within a few hours, which minimizes any possible interaction, whereas elevated MF levels are present up to 48 hours after exposure [Lyle, 1979]; these results are also supported by animal studies [Eben and Kimmerle, 1976; Hanasono et al, 1977].

Cyanamide and calcium cyanamide. Cyanimide (CH_2N_2) and calcium cyanamide ($CaCHN_2$), also known as calcium carbimide, are used principally as fertilizer and as a source of ammonia. They are also used in the synthesis of thiourea, sodium cyanamide, and guanidine compounds [Nevins, 1974; Schwartz et al, 1957; Brien et al, 1979]. Chemical workers and farmers who inhale cyanamide dust may show signs of disulfiram syndrome. These symptoms are markedly exaggerated if ethanol is consumed after exposure.

A number of studies have shown cyanamide to be inhibitors of aldehyde dehydrogenase [Brien et al, 1978, 1979; Pettersson and Kiessling, 1977; Murakami, 1961]. In one study, five male volunteers who were problem drinkers developed symptoms following oral administration of 0.6 mg/kg calcium carbimide followed by as little as 0.125 g/kg ethanol 22 hours later. At a slightly higher dose of 0.25 g/kg ethanol (equivalent to 2 ounces of 80 proof distilled spirits), the blood acetaldehyde levels were increased as much as tenfold over that of the controls [Brien et al, 1978]. Other amides that have been documented as inhibitors of aldehyde dehydrogenase are n-butyramide and isobutyramide [Lester and Benson, 1970].

Oximes

N-Butyraldoxime. The antioxidant N-butyraldoxime has been reported to cause a reaction similar to the antabuse syndrome in workers of a large printing company. Employees complained of flushing of the face, drowsiness, shortness of breath, and rapid pulse. These symptoms sometimes arose within 10 minutes after consumption of as little as 6 ounces of beer. On investigation, it was discovered that the printing ink contained N-butyraldoxime, which was found to be responsible for the reaction. The employees were exposed to this compound by dermal as well as respiratory routes. Increased amounts of blood acetaldehyde were detected in the workers who had ingested ethanol after having been exposed to N-butyraldoxime and ethanol [Lewis and Schwartz, 1956]. In another study, N-butyraldoxime was found to inhibit liver alcohol dehydrogenase in vivo and in vitro. Aldehyde dehydrogenase activity was also found to be decreased in mice pretreated with N-butyraldoxime, but inhibition in vitro has not yet been demonstrated (Koe and Tenen, 1969].

Other oximes that are reported to inhibit the oxidation of ethanol are acetaldoxime, acetoxime, isobutyraldoxime, cyclohexanone oxime, and methyl ethyl ketoxime [Lester and Benson, 1970].

Halogenated Hydrocarbons

Enhancement of the toxicity of several halogenated hydrocarbons by ethanol has been known for some time [Gardner et al, 1925; Bardodej and Vyskocil, 1955]. Carbon tetrachloride was the first to be observed as causing increased toxicity with concurrent ingestion of ethanol. Later, trichloroethylene, chloroform, and methylene chloride showed similar behavior. These compounds are discussed in more detail in this section.

Carbon tetrachloride. Carbon tetrachloride (CCl_4) is used as a solvent for oils, fats, lacquers, varnishes, rubber, waxes, and resins. Other uses are as a fumigant, laboratory solvent, and degreasing agent. Occupational routes of exposure are normally by inhalation and dermal absorption. There are reported cases of accidental oral ingestion [Polacsek et al, 1976].

The consumption of ethanol prior, or during exposure, to carbon tetrachloride vapors may result in increased toxic effects of carbon tetrachloride [Cornish and Adefuin, 1966; Cornish et al, 1977; Maling et al, 1975; Strubelt et al, 1978; Traiger and Plaa, 1972]. There are numerous cases of poisoning and deaths from this combination of exposures [Polacsek et al, 1976]. The initial response is the mutual depressant effect on the central nervous system. This may be followed by pulmonary edema and lesions of the kidney and liver. The toxic reaction may result from either acute or chronic exposure to the two agents, but most reported cases of poisoning involve the chronic use of alcohol. Enhanced toxicity is most apparent when exposure to ethanol precedes exposure to carbon tetrachloride by 16 to 18 hours [Traiger and Plaa, 1971; Cornish and Adefuin, 1967]. Consequently, an employee who drinks after work is most vulnerable to the synergistic effects the following morning when he is again exposed to carbon tetrachloride.

The metabolism of alcohol stimulates the production of various liver enzymes. These enzymes quickly metabolize carbon tetrachloride to the $CCl_3^{\cdot}$ and Cl^- ions that are thought to cause extensive cellular damage [Butler, 1961]. Only a small amount of consumed ethanol can cause liver damage when CCl_4 is present. A 1978 study showed that after rats were administered chronic low-level doses of ethanol and were then injected with carbon tetrachloride (0.1 ml/kg ip), evidence of liver damage and an increase in serum enzyme activities occurred [Strubelt et al, 1978]. When extrapolated to possible conditions of human exposure, a moderate consumption of ethanol (40 to 80 g daily or 2 to 4 beers daily) may increase the hepatotoxic effects of carbon tetrachloride. There is also a report of a fatality involving a worker who consumed only two drinks while being exposed to high concentrations of carbon tetrachloride vapors for 30 minutes [Polacsek et al, 1976]. Clearly, persons who consume alcohol should avoid any exposure to carbon tetrachloride.

Trichloroethylene. Trichloroethylene ($CHCCl_3$) or TCE is used as a degreasing solvent, drycleaning and extracting agent, and as a chemical intermediate in manufacturing. Like carbon tetrachloride, trichloroethylene exposure occurs mostly by inhalation with some dermal exposure [Hawley, 1977; Kenkyusha, 1979; Smith, 1966]. Alcohol intolerance after occupational exposure to TCE has been reported from several sources [Polacsek et al, 1976; Sbertoli and Brambilla, 1962]. When an individual is simultaneously exposed to ethanol and TCE, there is an increase in the concentration

of TCE, chloral hydrate, and trichloroethanol in the blood. The levels of ethanol and acetaldehyde are slightly increased also. This is thought to be the result of inhibition of common enzymatic pathways shared by ethanol and TCE. TCE, chloral hydrate, trichloroethanol, and ethanol all have a strong sedative effect on the central nervous system. Humans who inhaled a concentration of 50 ppm TCE for 6 hours per day for five consecutive days and simultaneously ingested ethanol (blood level 0.6%) showed a 2½-fold increase in blood TCE concentration. Both TCE and ethanol have the ability to permeate membranes, including brain tissue. As a result, the decrease in tolerance to TCE in many may occur when the ethanol-TCE combination approaches the subhypnotic concentration range in the central nervous system [Muller et al, 1975].

One such report [Steward et al, 1974] indicates that a combination of TCE and ethanol exposure causes a phenomenon known as "degreaser's flush." This effect was experienced by workers who were exposed daily for three weeks to TCE vapors at 200 ppm and then consumed as little as one-half pint of beer. The flush is described as a "transient vasodilation of superficial skin vessels producing vivid red blotches in a symmetrical pattern on the face, neck, shoulders, and back." The mechanism responsible for the dermal flushing is not known but it does resemble the symptoms of an acetaldehyde accumulation in the blood. It seems apparent that one or more of the metabolites of TCE are responsible because symptoms usually appear several weeks after initial exposure. TCE is metabolized within 24 hours but the metabolites are cumulative and are detectable weeks after the long-term exposure to the vapors. Dermal flushing ceases when the concentration of metabolites decreases [Steward et al, 1974].

In another study [Windemuller and Ettema, 1978], adult male volunteers who inhaled a constant concentration of 200 ppm TCE for 2½ hours and then ingested 0.35 g/kg ethanol showed a more than additive effect of impairment of mental capacity. The effects of combined exposure to TCE and ethanol do not appear to be of any serious consequence in instances of short-term exposure in young healthy workers. However, it has been suggested that long-term exposure in older workers may result in such effects as an increase in respiratory rate while performing mental tasks [Windemuller and Ettema, 1978].

Chloroform. Chloroform or trichloromethane ($CHCl_3$) is used as a solvent for natural products, as a fumigant, in purifying antibiotics, and in the manufacture of fluorocarbons. The primary route of occupational exposure is by inhalation [Hawley, 1977; Kenkyusha, 1979].

A study conducted on mice showed an increased incidence of abnormal liver function when the mice were pretreated with single or multiple intoxicating doses of ethanol followed by a minimal hepatotoxic (0.08 ml/kg) dose of chloroform. The enhanced toxicity shown was thought to be the result of the increased lipid content of the liver resulting in a prolonged retention of chloroform in the liver, possibly leading to the formation of more toxic metabolites such as free radicals [Cornish et al, 1977].

Methylene chloride. Methylene chloride (MC) or dichloromethane (CH_2Cl_2) is used as a paint and varnish remover, as a fumigant, as a solvent, as a cleanser, in aerosol propellants, and as a blowing agent in foams. Normal routes of occupational exposure are by inhalation and dermal absorption [Hawley, 1977; Kenkyusha, 1979].

There is some indication that for one-time-only exposures or for very short-term exposures to both MC and ethanol, the interaction is antagonistic rather than synergistic or additive. The same author has also shown that, over time, the hepatotoxic effects of MC appear to be enhanced by ethanol. Guinea pigs exposed by inhalation to MC at

500 ppm and ethanol at 26,200 ppm over a 5-day period experienced an increase in hepatic triglyceride levels resulting in fatty livers. This effect and a greater loss in body weight were attributed to MC. The temptation to conclude that ethanol may act as a protective measure against the toxic effects of MC may be improper [Balmer et al, 1976].

Metals

Certain metals are known to interact with ethanol exposure. These include cobalt, mercury, and manganese, which are reviewed below.

Cobalt. Cobalt (Co) is used in metal alloys, carbides, high speed steels, and electroplating. The normal routes of occupational exposure are mainly inhalation with some ingestion of cobalt-containing dusts [Hawley, 1977; Kenkyusha, 1979; Dervillee et al, 1963].

Cobalt was at one time added to some brands of beer in the brewing process to stabilize and improve the appearance of its foam. It has been linked to a rare form of heart disease called "alcoholic perimyocardiopathy" [Kesteloot et al, 1968]. This heart condition developed in chronic drinkers of cobalt-treated beer in Belgium, Canada, and the United States. Symptoms included pericardial effusion, low cardiac output, elevated venous pressure, and some cases of polycythemia. Cobalt was added in some brewing processes from 1959 until 1967, giving the beer a concentration range of 0.5 to 5.5 ppm of cobalt per 12-ounce beer. Since most breweries involved were adding cobalt at a dose of 1 ppm, it has been estimated that beer drinkers were consuming an average of 6 mg of cobalt a day [Kesteloot et al, 1968].

Cobalt given to human volunteers at 75 mg doses per day for six weeks produced no evidence of cardiac toxicity. Each reported case of "alcoholic perimyocardiopathy" in humans has been accompanied by evidence of nutritional deficiency. It seems that an adequate diet may prevent the synergistic effect of cobalt-ethanol exposures [Kesteloot et al, 1968]. Furthermore, cobalt is no longer added to beer, but there are exposures in cobalt mining and the manufacturing of cobalt-containing products that could be hazardous to exposed workers who drink.

In a related study, rats maintained on an adequate nutritional diet were given a combination of cobalt and ethanol in their drinking fluid. The study showed a significant reduction in growth rate and in heart size; the hearts were found to contain more zinc in the test animals than in the controls [Derr et al, 1968].

Manganese. Both ethanol and manganese (Mn) are hepatotoxic. The toxic effects of manganese are enhanced when the metal is administered in combination with ethanol. A study done on rats showed a synergistic effect that was manifested as changes in liver enzyme levels. Ethanol also aids in the absorption of manganese from the intestinal mucosa, which could lead to an increased accumulation of manganese in the liver [Shukla et al, 1978].

Mercury. Mercury (Hg) is used in numerous industrial and agricultural applications [Hawley, 1977]. Hospitals, medical laboratories, and other allied health fields also indicate a wide use of mercury and its compounds [National Occupational Hazard Survey, 1977]. Exposures to mercury occurs by inhalation, ingestion, and dermal absorption, depending on the mercury compound and how it is used.

The toxicity of mercury and its compounds is well documented. Although the interaction of mercury and other chemical compounds is not so well documented, some evidence has been reported for such interaction. The toxicity of methyl mercury chlo-

ride (MMC) was shown to be enhanced when dissolved in 50% ethanol and injected in rats for a 44-day period [Turner et al, 1981]. These animals exhibited more severe hind limb ataxia and a greater weight loss than did animals receiving injections of MMC only.

Methyl mercury acetate (MMA) was reported to increase the rate of absorption of ethanol into the blood compartment of swine exposed to MMA and ethanol simultaneously [Caldwell and Platonow, 1969]. A faster rate of disappearance of ethanol from the blood compartment was also reported. There are several reports of the interaction of mercury and ethanol resulting in an increase in the exhalation rate of mercury from the lungs in both man [Kudsk, 1965] and animals [Dunn et al, 1978; Magos et al, 1973].

Although no direct evidence of the interaction of mercury and ethanol in the work environment has been reported, the likelihood of such interaction should be considered because of its potential hazard.

THE ROLE OF ETHANOL IN THE ETIOLOGY OF CANCER

Ethanol has been linked as a cofactor in the etiology of cancer [Lowenfels, 1979; Schottenfeld, 1979; Lieber et al, 1979; Radike et al, 1977]. It is well recognized that the heavy drinker is more likely to develop cancer than the abstainer or light drinker. A well-documented example is the synergistic interaction from the combined personal use of alcohol and tobacco in the pathogenesis of epithelial cancer of the upper digestive tract [Schottenfeld, 1979].

There are a few reported cases of interaction involving ethanol and industrial chemicals. One such case is a long-term study with vinyl chloride in rats [Radike et al, 1977]. There was an apparent synergistic interaction between ingested ethanol and inhaled vinyl chloride leading to the induction of angiosarcoma in the liver.

Ethanol may act in several ways to promote carcinogenicity. First, one possibility is that ethanol may promote penetration of carcinogens through the mucosal barriers of the body. Second, malnutrition is often associated with alcoholism, which can also lower a person's resistance to cancer. Alcoholic liver injury may also affect important functions of chemical detoxification and biotransformation by the liver, thereby enhancing carcinogenicity [Lowenfels, 1979; Schottenfeld, 1979; Lieber et al, 1979].

CONCLUSION AND RECOMMENDATIONS

The problem of synergistic effects arising from exposure to ethanol in combination with certain chemical agents may be a much greater occupational health problem than is generally recognized. The potentially large scope of the problem results from the drinking habits of the workforce and its occupational exposure to chemicals that have been shown to be, or are suspected of, interacting with ethanol. In addition to the synergistically acting chemicals listed in this paper, there are many others that may also produce synergistic effects as a result of interaction with ethanol. For example, there are many hepatotoxins present in the industrial environment that may interact additively and/or synergistically with consumed alcohol, resulting in increased liver damage. An investigation of the derivatives and compounds that are closely related to the interacting agents presented here may uncover other substances that interact with alcohol.

The responsibility for controlling the problem of synergistic exposures to these chemicals and alcohol lies with both the employer and employee. Each party bears a responsibility to reduce the component of exposure that he is most able. Increased emphasis on the greater toxicity of a substance that interacts synergistically with ethanol should be appreciated by the manufacturers or users of the substance. Where possible, isolation of the process or advanced scheduling of a process or operation where such an exposure is inevitable may be a viable alternative. The notification of employees of this scheduling would forewarn them of the potential risks of consuming alcoholic beverages in conjunction with the scheduled operation so that they could adjust their drinking habits accordingly. It should be noted that the time interval between an occupational exposure and consumption of alcohol required to produce a synergistic or additive effect differs between chemical agents. Some interactions will take place only if the exposures occur within a narrow time period. Other substances such as carbon tetrachloride do not require the occurrence of exposures within a narrow time period, ie, effects can occur 24 hours or more before or after exposure.

In general, there is a greater likelihood of interaction if ethanol consumption precedes exposure to the chemical agent. It should be noted that there may be widely varying responses to these effects among individuals. It is clear that further studies on this subject are needed because of the magnitude of the problem and the current low level of awareness among those who are most directly affected.

In order to modify employees' drinking habits, some form of educational program is necessary. Discussion of the synergistic effects of alcohol consumption and occupational exposures could be part of an ongoing alcohol rehabilitation program, or company safety and health programs. Unions, management, supervisory personnel, and the company's medical staff should be involved. The responsibility for reducing the exposure to synergistic agents lies with the management; however, the ultimate responsibility for controlling alcohol consumption rests with the individual employee.

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