III. BIOLOGIC EFFECTS OF EXPOSURE

Isopropyl alcohol, CH3CHOHCH3 (formula weight 60.09), is a colorless, volatile liquid at room temperature. Its physical and chemical properties are presented in Table XII-1. [1,2]   It is synthesized primarily from propylene, either by indirect hydration (strong-acid process) or by direct catalytic hydration (weak-acid process). [3]   At present, the direct catalytic hydration technique has replaced the older indirect hydration technique in the US. Isopropyl alcohol can be synthesized from acetone. [4]

In the strong-acid process, propylene gas and 88-93% sulfuric acid in an approximate ratio of 1.5:1.0 were fed to a reactor maintained at 25-60 C and containing a mixture of isopropyl sulfates (CS Weil, written communication, September 1975). The reaction time was noted to be "long (hours)." Di-isopropyl sulfate, so formed, was hydrolyzed with hot water to isopropyl alcohol, isopropyl ether, and dilute (approximately 40%) sulfuric acid. The resulting overhead vapors consisted of approximately 90% isopropyl alcohol, 10% isopropyl ether, and 1% steam-distillable polymer oils. The overhead product was condensed, stored in tanks, and diluted to a constant isopropyl alcohol content. On standing, isopropyl ether and the polymer oils separated into a top layer which was removed by decantation. The bottom layer of aqueous isopropyl alcohol was refined in 2 columns and hydrocarbon oils were removed as side streams from both columns. The residue in the initial reactor contained heavier oils (tars) and carbon. Tars were removed from the dilute acid by skimming. The acid was then concentrated and recycled. Isopropyl oil was found to contain

largely polypropylenes composed of 3 and 4 propylene molecules. Less than 1% each of benzene, toluene, alkyl benzenes, polyaromatic rings, hexane, heptane, acetone, ethanol, isopropyl alcohol, and isopropyl ether were present.

In the new weak-acid process, propylene gas is absorbed in, and reacted with, 60% sulfuric acid maintained at 85 C. [4] The reaction time is reported to be "short (seconds)." Isopropyl hydrogen sulfate, so formed, is hydrolyzed to isopropyl alcohol, which is then vaporized in the stripping column. The vapor is neutralized with dilute sodium hydroxide solution and cooled. The condensate consists of isopropyl ether, isopropyl alcohol, acetone, oils, inerts, and water. The condensate is refined in distillation columns. Heavy oils and water are removed as a residue from the column.

From these two descriptions, the following differences are evident: in the old process, the acid used was concentrated (88-93%) and the reaction took place in a mixture of isopropyl sulfates at 25-60 C. The reaction time was long and the polymer oils produced were of high molecular weight. The role of the acid was defined as a reactant. In the current process where weak (60%) sulfuric acid is employed, the reaction takes place in the acid itself and the reaction time is short. The polymer oils produced are of low molecular weight. The role of the acid in the new process is defined as a catalyst. The composition of the oil produced in the weak-acid process has not been reported.

"Rubbing alcohol" is defined as 70% isopropyl alcohol and 30% water in this document. This term is included in the text of the document whenever it was stated by the authors of the papers discussed. It is not

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interchangeable with isopropyl alcohol.

Extent of Exposure

In 1964, almost 1,504 million pounds of isopropyl alcohol were produced in the US. [3] Production was estimated to have increased to about 1,919 million pounds in 1970. [3] More than half of the isopropyl alcohol produced is used in the manufacture of acetone. [3] Other principal uses are in extraction processes and as a solvent, chiefly for oils, perfumes, gums, and synthetic resins. It is also used in liniments, skin lotions, cosmetics, and pharmaceuticals. [5]

NIOSH estimates that approximately 141,000 employees are potentially exposed to isopropyl alcohol in the US.

Historical Reports

In the 1920's, as the pharmaceutical and cosmetic uses of isopropyl alcohol began to expand, interest in its toxicity and human effects increased. In 1922, Pohl [6] stated that before a final decision could be made regarding the possibility of internal use of isopropyl alcohol, the fate of isopropyl alcohol in the animal should be determined. His experiments involved several species of animals. In one experiment, a dog was administered 5 cc of isopropyl alcohol by esophageal catheter. The exhaled air over the next 12 hours was collected and examined for acetone and isopropyl alcohol. Both acetone and isopropyl alcohol were present in the exhaled air. Following the administration of isopropyl alcohol in rabbits, both acetone and isopropyl alcohol were detected in the exhaled

air. The ratio of acetone to isopropyl alcohol was about 88:12. Daily ingestion of 3-5 cc of isopropyl alcohol up to a total of 224 cc by a dog caused no changes in weight gain. Simultaneous administrations in dogs and rabbits of isopropyl alcohol with adrenaline, pituglandol, oxyphenylethylamine, or histamine produced no significant changes. Changes in protein metabolism were measured by the alterations in the total nitrogen content of the urine following isopropyl alcohol administration. Based on these results, Pohl concluded that isopropyl alcohol could be consumed in reasonable amounts.

In 1927, Fuller and Hunter [7] reported the effects of oral doses of 20-30 cc of 50% isopropyl alcohol on 7 healthy subjects. Two subjects received an initial dose of 20 cc, followed about 3 weeks later by 3 consecutive daily doses of 30 cc. Another subject received an initial dose of 10 cc followed about 6 weeks later by 3 consecutive daily doses of 30 cc. A fourth subject was given 30 cc for 3 consecutive days. The final 3 subjects received single doses of 30 cc each. The immediate effect was a lowering of blood pressure, both systolic and diastolic. In 1 subject, the blood pressure was reduced from 132/80 to 124/78 within the first 30 minutes after ingestion of the isopropyl alcohol. The pulse rate varied in all subjects, sometimes rising and sometimes falling, the effect being different on the same subject on different days. The subjective symptoms included a sensation of warmth, dizziness, and headache. These symptoms were severe throughout the first day of the test. On the subsequent days, the effects subsided within 1-3 hours. In 2 cases, drowsiness also occurred on the first day of the test but not thereafter. The authors concluded that tolerance was established. Prior to the ingestion of

isopropyl alcohol, urine examination for acetone was negative in all subjects. During the experiment, acetone was detected in the urine, but neither its amount nor the method of analysis used was specified.

In 1928, Weese [8] compared the anesthetic and lethal concentrations in air of various alcohols including isopropyl alcohol. The lethal concentration was found to be 20 mg/liter while the narcotic concentration was 16-27 mg/liter. The animals were exposed to the narcotic concentrations daily for 3-4.5 hours. Histologic examination of the liver revealed fatty degeneration while the lungs, heart, and kidneys did not show any significant damage.

Other investigators studied the comparative toxicities of various alcohols in animals. [8-12] In 1932, Hufferd [9] demonstrated the narcotic effects in guinea pigs of various alcohols, including isopropyl alcohol, at various oral doses. Narcosis was judged by sluggishness, loss of control of hind and fore limbs, and inability of the animals to be aroused when held by the hind legs and shaken violently. In 1938, Starrek [13] compared the toxicities of various alcohols, including isopropyl alcohol. Isopropyl alcohol ranging from 5 to 10 mg/g was subcutaneously injected into 5 mice. Staggering gait and dyspneic respiration, followed by deep anesthesia at higher doses, were observed. At a dose of 6 mg/g (6 g/kg), the mouse died within 20 hours. The effects of inhalation of isopropyl alcohol vapor were investigated in 14 mice. Isopropyl alcohol on filter paper was placed in bottles and evaporated. Two mice were then placed in each bottle for 100-480 minutes. The animals were observed for 14 days. Walking difficulties, lying on the side, and loss of reflexes were the main signs used for evaluating the effects. The author concluded that isopropyl alcohol was

narcotic, but less so than n-propyl alcohol.

In 1942, Mestre [12] reported that subcutaneous administration of 20% isopropyl alcohol induced narcosis in rabbits. Distribution of isopropyl alcohol in various organs following the ingestion of an aqueous solution of isopropyl alcohol was studied in dogs. It was observed that there was more alcohol in the kidneys and muscles than in the lungs, liver, or brain. Acetone was identified as a possible metabolite and detected in the expired air and in the urine. The author attempted to identify the metabolic pathway of isopropyl alcohol and determined that an alcohol dehydrase enzyme was involved.

In view of the increased use of isopropyl alcohol, Keeser [14] reviewed its toxicity in 1951. He commented that "preparation and processing of isopropyl alcohol in the chemical industry, its use in histological technology, for the production of cosmetics and disinfection of the hands, are not fraught with danger." This comment was based on "experience" but no data or details were given to substantiate it.

Effects on Humans

In 1948, McCord et al [15] reported 3 cases of alcoholics ingesting unspecified amounts of isopropyl alcohol. A profound coma occurred in each case. Acetone was present in the urine of 2 subjects. The treatment included gastric lavage upon admission, fluids, and symptomatic therapy. Recovery was complete within 1-3 days.

In 1962, Adelson [16] reported 5 cases of fatal intoxication following ingestion of various unknown amounts of rubbing alcohol. These involved suicide victims and chronic alcoholics. The ages of the patients

ranged from 31 to 83 years. In 4 cases, death occurred within 3 hours to 14 days after hospital admission and resulted from profound CNS depression and ultimate respiratory failure. One patient was pronounced dead on arrival at the hospital. Autopsy indicated that pulmonary congestion and edema were present in 4 cases. One patient had nephrosclerosis, bronchiectasis, and myocardial fibrosis that were not attributed to isopropyl alcohol. Another patient had "hemoglobinuric nephrosis," characterized by the presence of hemoglobin in the urine, thought to be secondary to shock. Hemorrhagic gastritis probably due to intense vomiting and uremia was also present. Adelson also found that the isopropyl alcohol levels in the blood and the urine were not related to each other. The author surveyed the literature on isopropyl alcohol intoxication and noted that in general there was a narrow range of isopropyl alcohol levels in the blood of comatose patients, ie, 128-200 mg/100 ml. However, he did not explain the fact that 2 of his 5 patients had blood isopropyl alcohol levels of 0 and 20 mg/100 ml, and both were comatose. Moreover, in the case of the patient with no isopropyl alcohol detected in the blood, the only evidence of isopropyl alcohol poisoning was an empty isopropyl alcohol bottle found with him. It is possible that the bottle could have contained something else. King et al [17] reported a patient in coma who had ingested about 1 liter of rubbing alcohol. The patient was an alcoholic with a history of isopropyl alcohol ingestion. The blood isopropyl alcohol level was 440 mg/100 ml, a much higher level than that observed by Adelson. [16] Since the amounts of isopropyl alcohol ingested were not known, blood levels could not be related to the doses. The analytical methods used for determining isopropyl alcohol were not discussed by either Adelson [16] or

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King et al. [17]

Chapin [18] reported that following the ingestion of approximately 1 pint (0.47 liter) of rubbing alcohol a known alcoholic developed edema, oliguria, and nitrogen retention resulting from acute renal insufficiency. Renal insufficiency may have been due to the presence of shock, gastrointestinal bleeding, or even to a preexisting disease from chronic alcoholism. In a similar case reported by Juncos and Taguchi, [19] a chronic alcoholic consumed about 1 pint (0.47 liter) of rubbing alcohol. Kidney damage and acute renal insufficiency followed by hemolysis and myopathy complicated the case. Again, it was not possible to distinguish the direct effects of isopropyl alcohol from preexisting conditions. In both cases, [18,19] the patients survived.

Extracorporeal hemodialysis has been reported to be a successful treatment for the removal of isopropyl alcohol from the blood. [17,20] In 1967, Freireich et al [20] reported that a 59-year-old man who had ingested 1 liter of rubbing alcohol was in deep coma and shock. The blood isopropyl alcohol level was 346 mg/100 ml and was reduced to 212 mg/100 ml before any treatment and to 60 mg/100 ml after 3 hours of hemodialysis. It was further reduced to 3 mg/100 ml, 38.5 hours after the dialysis was discontinued. The recovery was prompt and complete. This is believed to be the first reported case of the use of hemodialysis in isopropyl alcohol poisoning. In 1970, King et al [17] reported using the same treatment on a 28-year-old man who had ingested 1 liter of rubbing alcohol. In this instance, deep coma and shock were also present and the blood isopropyl alcohol was 440 mg/100 ml, 4.5 hours after admission to the hospital. After 5 hours of dialysis, the isopropyl alcohol level in the blood

decreased to 100 mg/100 ml. Again, the patient appeared to recover completely and promptly.

Reports have not been found on intoxication resulting from only inhalation of isopropyl alcohol. However, the effects of combined inhalation and skin absorption have been reported in 4 patients. [21-24] All 4 were sponged with isopropyl alcohol to reduce fever. These were not healthy subjects, and any effects following the sponging might not be attributable to isopropyl alcohol alone. Three of these patients were children who became comatose after the sponging. Garrison [21] reported one child's blood alcohol level to be 128 mg/100 ml, as measured 4.5 hours after admission to the hospital. McFadden and Haddow [22] found another child's serum isopropyl alcohol level to be 40 mg/100 ml, 12 hours after admission. Senz and Goldfarb [24] found that in a third child, blood contained 130 mg of isopropyl alcohol/100 ml, 95 minutes after admission. In this case, [24] inhalation was probably the principal route of entry. In all cases, [21,22,24] recovery occurred within 34 hours. In 1969, Wise [23] reported that immediately following an isopropyl alcohol sponge bath, an elderly man had a blood level of 10 mg isopropyl alcohol/100 ml but the amount of isopropyl alcohol used was not noted. The author did not state in his article that there were any signs of intoxication. Based on these studies, [21,22,24] it appears that high levels of isopropyl alcohol in the blood following the use of isopropyl alcohol for sponge baths may result in coma.

In general, isopropyl alcohol is not a strong dermal irritant, as is evidenced by the small number of cases of irritation reported after application to the skin of this widely used compound. Nixon et al [25]

tested skin irritation by isopropyl alcohol in at least 6 volunteers. Isopropyl alcohol was applied on their backs in about 4-sq cm areas. The sites were evaluated for erythema and edema 4, 24, and 48 hours after the application. There was no tissue destruction observed and the irritancy of isopropyl alcohol was judged to be negligible. Contact dermatitis due to isopropyl alcohol has been reported. [26-28] One of the first of these cases was reported by Wasilewski. [26] A patient developed a pruritic dermatitis around an injection site which had been previously cleaned with 70% isopropyl alcohol. Multiple small blisters appeared on the fingertips which held the alcohol swab against the skin. Closed patch tests for 70% isopropyl alcohol and commercially prepared 70% isopropyl alcohol yielded a pruritic vesicular reaction to each after 48 hours. All dilutions of isopropyl alcohol down to, and including, 5% elicited a vesicular skin response. An almost identical case was reported by McInnes, [27] when a patient developed eczema on the hand at the site of a venipuncture and on the fingers that held a swab saturated with 70% isopropyl alcohol. However, no patch test was used to verify if pure isopropyl alcohol was the cause of the dermatitis.

Richardson et al [28] reported that 5 patients who had developed contact dermatitis from a swab saturated with isopropyl alcohol were given patch tests for various components of a swab. These included the metallic packaging material, the plastic inner lining, the dried fabric of the swab, a dried swab resaturated with 70% isopropyl alcohol, and a moist fresh swab. The authors did not state with what the swabs were moistened. Twenty control subjects were also patch-tested with fresh moist swabs. The results indicated that all 5 patients developed contact dermatitis from the

fresh moist swab but not from the swab saturated with 70% isopropyl alcohol. The patches had to be removed by the end of 24 hours because of intense discomfort. All the control subjects had negative reactions to the swabs after 48 hours. The authors suggested that the skin irritant was some substance in the swab other than 70% isopropyl alcohol.

Fregert et al [29] observed that 2 out of 4 people who were allergic to ethyl alcohol responded positively to a patch test for commercially available isopropyl alcohol. However, the concentrations of the alcohol used for patch tests were not given, and controls were not used. Therefore, in a follow-up study, the same authors [30] tested these 2 patients and 20 control subjects for hypersensitivity to "gas chromatographically pure" isopropyl alcohol and 2-butanol. Both patients but no controls developed strong eczematous reactions to isopropyl alcohol and to 2-butanol.

Therefore, it is possible that some individuals may develop contact dermatitis from isopropyl alcohol. Although the study by Richardson et al [28] demonstrated that some people apparently allergic to isopropyl alcohol were allergic to another substance, Fregert et al [30] clearly showed that some individuals are in fact allergic to isopropyl alcohol.

In 1969, Wills et al [31] investigated the biochemical effects of daily ingestion of diluted isopropyl alcohol on 3 groups consisting of 8 healthy men each. The men in one group drank a daily dose of 2.6 mg/kg (0.003 ml/kg), while those in the second group drank a daily dose of 6.4 mg/kg (0.008 ml/kg). The third group was a control group who drank a placebo. The experiment was conducted for 6 weeks. During this time, various measurements were made on blood, serum, and urine on the first,

third, and seventh day of each week. Serum cholesterol, acid and alkaline phosphatase, and glutamic-oxaloacetic transaminase activities were all normal. Retention of sulfobromophthalein in serum at the end of the experiment did not increase significantly in any group, suggesting that there had been no subacute liver damage. Ophthalmoscopic examinations at the end of the experiment showed no changes from examinations made before initiation of the experiment. Conclusions on chronic effects cannot be deduced from a 6-week study in this instance. The authors noted that there were in general no deleterious effects. Acetone was present in 2% of the urine samples of the subjects receiving 6.4 mg/kg. The analytical method used to detect acetone was not described. In summary, Wills et al [31] did not find any adverse effects of isopropyl alcohol ingestion in doses of 2.6 mg/kg and 6.4 mg/kg.

In 1927, Kemal [32] gave isopropyl alcohol orally, in doses ranging from 0.1-20.0 g, to 4 healthy men. The subjects consumed isopropyl alcohol in single quantities of 0.1-20 g or in 3 repeated quantities of 5 g each at 2-hour intervals (in 1 case at 3-hour intervals). Acute effects, if any, were not reported. Isopropyl alcohol was found to be partially excreted as acetone in the urine and in exhaled air. Following qualitative detection of acetone in the urine by various techniques including iodoform reactions, quantitative determination was made using iodometry. However, Kemal did not report sufficient data to allow the calculation of the percentage of isopropyl alcohol recovered as acetone. Acetone was initially detected in the urine within the first hour and in exhaled air within the first 15 minutes. As much as 100 mg of acetone/hour was detected in the urine. In addition, acetone was detected in the urine after the ingestion of only

0.25 g of isopropyl alcohol, if administered in an abundant quantity of fluid. Hahn [33] reported that a total of 8 mg of acetone was detected in the exhaled air of a man during the first hour following the ingestion of 720 mg of isopropyl alcohol. Complete methodological details of the experiment were not given.

In 1943, Nelson et al [34] attempted to determine the sensory threshold of various compounds, including isopropyl alcohol. This experiment was done as a part of a laboratory course in industrial hygiene. Ten healthy volunteers were exposed for 3-5 minutes to isopropyl alcohol at various estimated concentrations. After every exposure, each person was asked to classify the effect of the vapor on the eyes, nose, and throat, and to give a subjective opinion of whether he could work in such an atmosphere for an 8-hour day. The subjects reported "mild irritation of the eyes, nose and throat" at 400 ppm. At 800 ppm, these effects were "not severe" but this atmosphere was declared "unsuitable" to work in for an 8-hour day by a "majority" of the volunteers. Two hundred ppm was the highest concentration estimated "satisfactory for 8-hour exposure." This study has many drawbacks. The exposure concentrations were estimated and not analytically determined. The validity of an extrapolation from a 3- to 5-minute exposure to an 8-hour workday is questionable.

Two separate reports [35,36] of human experiments indicated the odor threshold for isopropyl alcohol to be 40, 50, and 200 ppm. It appears that isopropyl alcohol vapor can be detected by odor before any irritation occurs, because irritation of the eyes, nose, and throat has been reported to occur at 400 ppm. [34]

In 1958, Scherberger et al [35] reported the design of an air blender in which air-vapor mixtures of known concentrations were formulated. This was a dynamic system and therefore suitable for establishing odor thresholds. The minimum identifiable odor level for isopropyl alcohol was found to be 200 ppm by 3 subjects. Vapor concentrations were determined using a mass spectrometer. Details concerning the experimental design were not given and therefore valid conclusions cannot be drawn from the data presented.

In 1966, May [36] reported that an experiment to measure the odor threshold for various substances, including isopropyl alcohol was devised. A panel of 8 men and 8 women sniffed various concentrations of isopropyl alcohol prepared in 5- to 10-liter bottles. All of the concentrations were determined using gas chromatography. The author reported that the "smallest perceptible" concentration of isopropyl alcohol was 40 ppm. At 50 ppm, the odor was "definitely perceptible." This is a much lower odor threshold than had been previously reported.

In summarizing the effects of isopropyl alcohol on humans, no recorded cases of industrial poisoning by pure isopropyl alcohol by any route of entry were found in the literature. However, there are many case reports of isopropyl alcohol poisoning in chronic alcoholics. [16-19] Such reports are of limited value in assessing the clinical picture of isopropyl alcohol poisoning because of the preexistence of numerous degenerative disorders common in the chronic alcoholic.

Isopropyl alcohol intoxication from ingestion manifests itself in nausea, vomiting, headache, giddiness, and depression. [16] These symptoms are soon followed by coma with or without shock. [16,17] In the absence of

shock, patients usually respond quickly to treatment and make a complete and uncomplicated recovery. [21,22] When shock is present, death may occur within the first 24 hours. [16]

There are a few case reports of combined effects of inhalation and skin absorption. [21-23] These cases suggest that combined skin absorption and inhalation of large amounts of isopropyl alcohol may result in coma. One set of human experiments [34] has shown that isopropyl alcohol vapor is a mild irritant to eyes, nose, and throat. A few cases [26,27,29,30] indicating that some people may develop contact dermatitis from isopropyl alcohol have been reported, but in general isopropyl alcohol produces minimal, if any, adverse skin effects. Although the complete metabolic pathway for isopropyl alcohol is unknown, acetone has been identified in the urine and in exhaled air as a metabolite. [15,32] Ashkar and Miller [37] and Vermeulen [38] cautioned that isopropyl alcohol intoxication may be misdiagnosed as diabetic acidosis due to the presence of acetone in the urine. They suggested that the absence of both acidosis and hyperglycemia should distinguish between the 2 conditions. Except for the presence of isopropyl alcohol in. the blood, and sometimes of acetone in the urine, there appear to be no reported characteristic biochemical abnormalities.

Epidemiologic Studies

Weil et al [39] reported that in the early 1940's the presence of a carcinogen in the isopropyl alcohol-manufacturing area was suspected. In 1950, an epidemiologic investigation was undertaken by Weil et al. [39] The information on cause of death was obtained from insurance records of death claims spanning the 23-year period of 1928-1950. These records

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included all deaths which had occurred among the employees at the plant during that period. However, the records did not include either individuals who might have died but were not employed at the time of their deaths or who had retired and were therefore lost from observation. The only information on the employee population included in the report was for December 31, 1938 and December 31, 1948, at which times 2,261 and 6,165 employees, respectively, were on the payroll.

During the 23-year period, a total of 182 men had worked in the isopropyl alcohol-manufacturing unit. Of these, 71 men had worked in this process for more than 5 years, and in these, 7 neoplasms of the respiratory tract were discovered. Four were malignant tumors of the paranasal sinuses. One was a malignant tumor of the lung, 1 a malignant tumor of the vocal cords, and 1 a nonmalignant tumor (papilloma) of the vocal cords. The nonmalignant papilloma of the vocal cords was removed successfully without recurrence. Four years later, this patient died of accidental causes. At the time of publication (1952), 3 of these 7 individuals had died from the carcinoma. The diagnoses included 1 primary carcinoma of the lung and 2 cancers of the paranasal sinuses. The periods of exposure for the 7 reported cases ranged from 6 to 16 years. In the 3 fatal carcinoma cases, the mean age was 36 years, with a range of 31-41 years.

The results [39] indicated that there were a total of 258 deaths among all plant employees from all causes during the 23-year period. Of this number, 34 (13.2%) employees were reported to have died of some form of cancer. Of the 34 who died of cancer, 5 (14.7%) were reported to have died of cancer of the respiratory tract. In interpreting these results, the authors reported that, according to the United States' vital statistics

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for 1948, cancer caused 13.5% of the deaths from all causes and cancer of the respiratory tract was responsible for 9.6% of all cancer deaths. Weil et al [39] reported further that the upper respiratory and alimentary tracts were found to be the sites of 5.8% of all cancers in a study conducted in Connecticut during the years 1935-1946. Cancers of the paranasal sinuses occurred relatively infrequently, constituting about 0.2% of all human cancers and about 3% of the cancers of the upper respiratory and alimentary tracts. Also, the paranasal sinus cancers were encountered more often in males than in females in the age group 60-70 years. The median age was 54 years.

From 1928-1950, a period of 23 years, 25 men were generally employed in the suspect isopropyl alcohol-production operation at one time. This would be equivalent to 575 (23 x 25) man-years of exposure. Although the age distribution of the population is not known, the expected death rate from all causes in the general poluation is 0.9%. [40] Therefore, 0.9% of 575, or about 5 deaths, would be expected. An expected proportional cancer mortality of 13.5% as stated by Weil [39] for 1948 was 0.68 (0.135 x 5) cancer deaths. Thus if "respiratory" cancer deaths accounted for 9.6% of all cancer deaths, the expected number of respiratory cancer deaths would have been 0.065 (0.096 x 0.68).

Of more importance, if paranasal sinus cancer is responsible for 0.2% of all human cancers, 0.0014 (0.002 x 0.68) paranasal sinus cancers would be expected. Instead, Weil et al [39] reported 4 paranasal sinus cancers, 2 of which were fatal.

The authors [39] concluded that "a high incidence of respiratory cancer was evident when it was considered that the three patients whose

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cancers were fatal plus the two surviving patients with cancers of the
sinuses and one with cancer of the vocal cords for a total of six, were
encountered among only 71 individuals working for more than 5 years in this
unit. In other words, cancer of the respiratory tract developed in 8.4% of
employees exposed for more than five years."

There are several drawbacks to this study. [39] The number of deaths
reported does not represent in any known way the actual causes of death
which occurred in individuals exposed to the process for 5 or more years
during the period 1928-1950, because an unknown number of individuals so
exposed were lost to observation. From the data, there is no way of
determining how many such individuals had died or the causes involved. A
further problem is that the study is not age-adjusted and, therefore,
comparisons to state or national statistics are not necessarily valid. For
example, Weil et al [39] emphasized that among the fatal cases reported in
the paper, 1 died at age 31, 1 at 36, 1 at 41, and the others died while in
their "early 40's." This may suggest an unusually low age at death in the
population, or simply that no one older than the mid-40's worked in the
particular unit of interest for perhaps reasons unrelated to exposure.

Because of the lack of a control population, the authors cited [39]
certain vital statistic data to support the contention that "a high
incidence of respiratory cancer is evident" in a group of 71 employees who
were employed for 5 or more years in the manufacture of isopropyl alcohol.
However, the accuracy of these comparisons cannot be confirmed because
classification according to the International Classification of Diseases
Adapted for Use in the United States (ICDA) were not given. Also, other
possible causative factors, such as smoking, were not considered.

Nevertheless, it can be concluded that there was a very clear excess of paranasal sinus cancers in the population studied [39] and that the apparent mean latency period was 12 years. Thus, an epidemiologic association appears to exist between the manufacture of isopropyl alcohol and paranasal sinus cancer. The significance of 1 lung cancer and 1 vocal cord cancer cannot be established from studies of such a small group, since age distribution and other important factors are unknown.

In 1966, Hueper [41] referred to the work of Nale and Hueper during 1937-1946, in which they found 6 cancers of the respiratory system (4 nasal sinuses, 1 lung, and 1 larynx) in about 75 employees in an isopropyl alcohol plant. This plant had been in operation since 1928. Although the original paper by Nale and Hueper has not been found, according to Weil (written communication, September 1975), these cases of cancers were the same as those reported by Weil earlier. [39] In a written communication, Hueper confirmed that these cancers occurred in the same plant as the one referred to by Weil. [39] Hueper further added that the majority of the afflicted workers were foremen who sustained severe respiratory contact with isopropyl oil fumes during frequent accidents, such as pipe breakage. In addition, minor exposures also occurred during sample withdrawal for quality control tests. Hueper [41] referred further to unpublished observations by Eckardt that the incidence of nasal sinus and laryngeal cancers in men working in an identical isopropyl alcohol-manufacturing plant was 21 times the expected incidence in the general population aged 45-54. Two sinus cancers and 2 larynx cancers occurred in a total of 11 cancers among 779 employees. All the cancer victims had worked in this plant for more than 9 years. Both the above studies [39,41] indicated that

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the latency period of such cancers was 10-12 years.

In yet another report, Hueper [42] stated that 5 additional cases of cancers developed since the 7 reported by Weil. [39] The incidence of cancer of the nasal sinuses and of the larynx for the second group was 134.5/100,000. Based on a normal rate of 6.3, the incidence of these cancers was 21.3 times the expected rate. These appear to include the 4 cases observed by Eckardt. [43] A written communication from CU Dernehl on September 9, 1975, confirmed that 5 additional cancers had developed. This report also added that the last cancer occurred in 1959. All cancers occurred in individuals who had worked in the strong-acid isopropyl alcohol-manufacturing process prior to 1945. Eckardt [43] reported that the differences between the strong-acid process and the weak-acid process, accompanied by better engineering controls in the weak-acid process, have been sufficient to eliminate the cancer hazard. He stated that the production of isopropyl alcohol was transferred to a modern, completely enclosed operation in a different refinery and that no cancers had developed at the new plant in the last 20 years. He also stated that instead of using concentrated sulfuric acid, the new production process used dilute sulfuric acid. However, no studies have been found that furnish information about the incidence of cancers in recent years.

Based on these reports [39,41,43] and written communications, isopropyl alcohol production by the process investigated, ie, the strong-acid process, must be considered to present a cancer hazard. However, there is no evidence that isopropyl alcohol itself is the carcinogen.

In 1974, Bittersohl [44] examined the cancer rate in a factory where propyl and butyl alcohols were manufactured. The author apparently did not

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distinguish between propyl alcohol and isopropyl alcohol. The cancer rate was 8 times higher in a group of workers exposed to propyl alcohol, butyl alcohol, and asbestos, than in a control group exposed to none of these substances. The cancer rate was twice as high in the group exposed to all 3 substances as in a group exposed exclusively to asbestos. Bittersohl concluded that there was no convincing proof of any carcinogenic effect of isopropyl alcohol.

Animal Toxicity

In 1948, Smyth and Carpenter [45] reported that 4 out of 6 rats died within 14 days after a single 8-hour exposure to isopropyl alcohol by inhalation at 16,000 ppm. The concentration of isopropyl alcohol was estimated rather than analytically determined. Carpenter et al [46] reported that inhalation of isopropyl alcohol at an estimated single concentration of 16,000 ppm for a 4-hour period resulted in "2-4" deaths out of 6 rats. Based on these results, the authors placed isopropyl alcohol in a "slight" hazard category. These experiments were range-finding tests. The concentrations used were extremely high and therefore of little value in assessing the effects of inhaling isopropyl alcohol vapor at levels found in the occupational environment.

In 1974, Baikov et al [47] investigated the effects of chronic inhalation of isopropyl alcohol by rats. The animals were exposed to isopropyl alcohol continuously for 24 hours/day for 86 days at concentrations of 20, 2.5, and 0.6 mg/cu m (approximately 8.14, 1.02, and 0.24 ppm). The animals inhaling isopropyl alcohol at 20 mg/cu m (8.14 ppm) showed changes in the latent period of unconditional reaction, increases in

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the retention of BSP, the total leukocyte count, and the number of abnormal fluorescent leukocytes. They also showed a decrease in the blood nucleic acid content, the blood oxidase and catalase activities, and the amount of coproporphyrin in blood. All of these changes were statistically significant. Animals inhaling isopropyl alcohol at 2.5 mg/cu m (1.02 ppm) demonstrated some of the same effects, but none were statistically significant. In animals inhaling isopropyl alcohol at 20 mg/cu m (8.14 ppm), post mortem findings included hyperplasia of the spleen with the development of hemorrhages of the sinuses and erosion of follicular cells, some evidence of liver parenchymal cell dystrophy, hyperplastic ependymal cells, and degenerative changes in the cerebral motor cortex. None of these effects were observed in animals inhaling isopropyl alcohol at 0.6 mg/cu m (0.24 ppm). Based on this continuous exposure study, the authors suggested that 0.6 mg/cu m (0.24 ppm) be adopted as the maximum daily average concentration.

The physiological responses observed in this study, [47] such as the increase in abnormal fluorescent leukocytes, are obscure, and it is therefore difficult to interpret their significance. Additional inadequacies of this study include insufficient experimental details, lack of control animals, lack of data on individual animals, and the lack of details of the statistical analyses. Also, there is no indication of variability. In view of all these deficiencies, conclusions regarding the short-term or long-term effects of the inhalation of isopropyl alcohol cannot be drawn.

In 1927, Fuller and Hunter [7] reported on the oral toxicities of isopropyl and ethyl alcohols for up to 2 weeks in 9 rabbits, 3 dogs, 2

cats, 2 chickens, and 1 monkey. The results of administration of isopropyl alcohol to guinea pigs were unsatisfactory and were not reported by the authors. The alcohols were mixed with an equal volume of water and administered by a catheter. Doses ranged from 5 to 20 cc of the 50% solution. Ethyl alcohol and isopropyl alcohol were given alternately to some animals, but details as to which and how many animals received the alternate doses were not given. The immediate effect of isopropyl alcohol intoxication included inertia and a state of collapse in rabbits and chickens. Cats immediately passed into a stupor from which they recovered several hours later. The effect on the dogs and on the monkey was never as severe as that observed in cats. The dose received by one cat is calculated to be 7.3-9.8 ml/kg and 2.75-5.5 ml/kg for a monkey. Drowsiness, signs of nausea, and vomiting lasting about 24 hours occurred in the monkey. The authors reported that the monkey, rabbits, and chickens acquired tolerance to isopropyl alcohol. This conclusion was based on the observation that the signs following the first dose of isopropyl alcohol diminished in intensity following the ingestion of subsequent doses of isopropyl alcohol. Possible effects resulting from the interaction between isopropyl alcohol and ethyl alcohol were not reported by the authors. This study lacked proper controls; the only control animal used was one rabbit. The effects observed, however, are similar to those observed by others. [48,49]

Morris and Lightbody [50] administered isopropyl alcohol at a dose of 6 cc/kg to 6 young adult rabbits. Acetone was found in all first and second 24-hour urine samples. Five animals continued to excrete acetone in the urine during the third 24-hour period. No acetone was found in the

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fourth 24-hour collection period. In another experiment, they gave isopropyl alcohol in a single dose of 6.5-8.0 cc/kg to 36 rabbits by stomach tube. The alcohol was administered in 25 cc of 0.85% sodium chloride solution. Thirty-four of the 36 rabbits were dead within 80 hours of administration.

In another experiment, the authors [50] gave isopropyl alcohol in a daily dose of 2.5 cc/kg by stomach tube to 10 rabbits for 11 days. Each daily dose produced the same degree of incoordination of movement in every animal. Also, the time required for the animal to recover from narcosis remained the same for the 11-day period of isopropyl alcohol administration. Hence, the authors concluded that tolerance was not established in the rabbits.

Tolerance as defined by these authors [7,50] was very subjective and therefore difficult to evaluate. The reports on tolerance were made during the period 1927-1938. No recent reports were found in the literature, except for the investigation in 1945 by Lehman et al. [49] They reported that 3 dogs acquired a tolerance within 7 months to 4% isopropyl alcohol given in drinking water. Tolerance was manifested by a greater coordination at a given isopropyl alcohol level in blood and an increased rate of removal of the alcohol from the blood. The definitions of tolerance used by all these authors [7,49,50] differed considerably.

In 1944, Lehman and Chase [48] gave 0.5-10.0% isopropyl alcohol solutions to 5 groups of 5 white rats each weighing about 50 g. Consumption was entirely voluntary. Two other groups were given water and served as controls. This experiment was carried out over a period of 27 weeks. The daily dose was estimated to range from 0.75 to 5.28 ml/kg.

Retardation of growth and body weight loss were the general effects observed. Examination of the brain, pituitary and adrenal glands, lungs, heart, liver, spleen, and kidneys showed no evidence of gross or microscopic changes.

In 1960, Wallgren [51] investigated the intoxication produced in rats by several alcohols, including isopropyl alcohol. A group of 15 animals were orally administered 0.043 moles/kg (2.58 g/kg or 3.28 ml/kg) isopropyl alcohol in tap water. As a control, all animals were orally administered 3 mg/g of ethyl alcohol. Six consecutive tests at 20-minute intervals were given. Each animal was placed on a tilted plate with rough surface. The angle of the plate at which the animals slid was the measure of intoxication. The performance before alcohol administration was used as a reference. The lowest performance of animals treated with isopropyl alcohol was 60.4 ± 6.9 percentage of the initial performance without alcohol, and occurred about 80 minutes after the dose administration. Isopropyl alcohol was rated to be about 2-3 times as intoxicating, on a molar basis, as n-propyl alcohol.

In 1971, Kimura et al [52] determined the oral LD50 for isopropyl alcohol to be 5.6, 6.0, and 6.8 ml/kg in 14-day-old, young adult, and older adult white rats, respectively. Munch [53] reported a value of 133 millimoles/kg (10.2 ml/kg) as the oral LD50 for rabbits. The LD50 was determined as that quantity causing death in 1/2 of the rabbits within 24 hours after administration. Hodge and Downs [54] observed that the approximate lethal range of 70% isopropyl alcohol by oral administration was 5-10 ml/kg in rats. The lethal range was defined as the range between the highest dose tolerated by all treated rats and the lowest dose that

killed all treated rats. The animals were observed for a period of at least 2 weeks.

In an experiment with rabbits, Marzulli and Ruggles [55] used 70% isopropyl alcohol as a reference standard in a collaborative study of the Draize eye irritation test. Temporary effects, such as conjunctival redness, corneal opacity, and iritis, were caused by 0.1 ml of 70% isopropyl alcohol.

The acute dermal LD50 in rabbits was determined to be 16.4 ml/kg by Smyth and Carpenter. [45] Isopropyl alcohol was applied to an area on the clipped belly of albino rabbits. Further details of the experiment were not given. Steele and Wilhelm [56] and Macht [10] observed that isopropyl alcohol failed to produce any adverse effects when applied dermally to guinea pigs, dogs, and white rats. Nixon et al [25] reported that isopropyl alcohol did not cause any tissue destruction when applied to intact and abraded skins of rabbits and guinea pigs.

In 1945, Lehman et al [49] studied the isopropyl alcohol blood levels of dogs, cats, rabbits, and pigeons after iv administration. All species, except rats, were divided into 2 groups of 3 animals each, one group receiving 0.987 g/kg and the other 1.974 g/kg of isopropyl alcohol. Rats were divided into 2 groups of 18. They received the same doses. Blood alcohol concentrations were measured at hourly intervals up to 6 hours. It was observed that the rate of disappearance of the alcohol from the blood stream after iv administration of a single dose was dependent on the amount of the dose. The method used to detect isopropyl alcohol in blood was identical to that designed for ethyl alcohol. Metabolite measurements were not made. Furthermore, it was not evident whether the disappearance of

isopropyl alcohol from the blood was due to excretion, metabolism, or diffusion into tissues.

Wax et al [57] studied the absorption and distribution of isopropyl alcohol in groups of 3 dogs each. Thirty minutes after injection of 1.25 cc/ kg of isopropyl alcohol in 10% solution into the stomach and intestinal loop, it was found in all tissues examined, including the brain and liver. The absorption of the alcohol occurred from all portions of the digestive tract, most rapidly from the intestine as a whole, and least rapidly from the stomach. It was observed that ethyl alcohol administered iv might exert some inhibition on the intestinal absorption of isopropyl alcohol. No statistical tests substantiating the significance of the results were reported by the authors. [57] Average absorption from intestinal loops ranged from 67.4 to 91.1%. Average absorption from stomach was only 41.1%. Average milligram percent distribution in various tissues ranged from 25.3 in muscle to 155.7 in spinal fluid. However, there were large variations in isopropyl alcohol levels. For example, the distribution of isopropyl alcohol in the brain ranged from 20 to 100 mg% but was averaged to read 48.3 mg%. Considering the large range of the tissue alcohol levels and the small number of animals used, it is difficult to draw quantitative conclusions from this study.

Ellis [58] studied the metabolic fate of isopropyl alcohol in blood perfused through a rabbit liver in situ. Isopropyl alcohol in quantities of 100 mg or 300 mg/100 ml of perfusing blood produced a progressive rise in acetone concentration in blood. The author noted that the amount of acetone produced was insufficient to account for all the isopropyl alcohol metabolized and suggested that the metabolic transformation of isopropyl

alcohol involved some pathway or pathways other than oxidation to acetone. It was further suggested that conjugation with glucuronic acid might be an alternative mechanism. Kamil et al [59] observed that in rabbits this mechanism appeared to be the alternate metabolic process to oxidation. However, it accounted for only about 10% of the isopropyl alcohol administered.

Nordmann et al [60] examined the enzymes involved in the metabolism of isopropyl alcohol. Groups of 4-10 rats were administered ip pyrazole, an inhibitor of alcohol dehydrogenase and catalase, or 3 amino-1,2,4-triazole, an inhibitor of catalase alone. Isopropyl alcohol was then administered either ip at a dose of 1 g/kg (1.27 ml/kg) or by stomach tube at a dose of 6 g/kg (7.63 ml/kg). The control animals received an equal volume of saline or water. Isopropyl alcohol and acetone levels in the blood were monitored at 0.5, 1.5, 3, 4, 6, 8, and 20 hours after isopropyl alcohol administration. Animals receiving 3-amino-1,2,4-triazole did not show any significant difference in the blood isopropyl alcohol or acetone levels from those found in the animals receiving just isopropyl alcohol. In contrast, pretreatment with pyrazole markedly reduced the blood isopropyl alcohol clearance and delayed the rate of acetone production. The authors concluded that catalase did not play an important role in the oxidation of isopropyl alcohol.

A quantitative relationship between the dose of isopropyl alcohol and the amount of acetone or any other metabolite has not been established. The exact metabolism therefore is not clearly understood. Part of isopropyl alcohol is oxidized to acetone [58] and some probably conjugates with glucuronic acid, [59] but these processes have not accounted for all

of the isopropyl alcohol administered. Since no quantitative relationships were established, a biologic index of exposure cannot be formulated.

Beauge et al [61] administered 6 g/kg (7.63 ml/kg) of isopropyl alcohol to 6 rats by gastric intubation. Six control rats were administered an identical volume of water. Four hours later, the animals were administered labeled palmitate ip. The rats were then decapitated 30 minutes later. Fragments of liver were removed and the lipids were extracted to determine the concentrations of triglycerides and phospholipids. The results indicated that there was an accumulation of triglycerides in the livers of experimental animals. Nordmann et al [62] confirmed these observations. They administered isopropyl alcohol 6 g/kg by stomach tube to 8 rats and decapitated them 8 hours later. The results indicated that liver triglycerides were significantly higher in the experimental animals than in the controls. The dose of the alcohol used was extremely high. Beauge et al [63] administered orally 300 mg/kg of pyrazole, an inhibitor of alcohol dehydrogenase and catalase, to groups of 8 rats each. Isopropyl alcohol at a dose of 3 g/kg (3.82 ml/kg) was administered 23 hours later by stomach tube. The animals were killed 8 hours later and examined for hepatic triglycerides and for the isopropyl alcohol and acetone concentrations in the blood. Compared to the animals receiving isopropyl alcohol alone, the animals receiving both isopropyl alcohol and pyrazole showed an increased blood isopropyl alcohol level accompanied by a decreased blood acetone level. The hepatic triglyceride content of the animals treated with pyrazole and isopropyl alcohol did not differ significantly from that of the controls, but it was elevated in the animals receiving isopropyl alcohol without pyrazole. The authors

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concluded that isopropyl alcohol-induced fatty liver was related to the metabolism of isopropyl alcohol, and that acetone may play a significant role. However, it should be noted that no attempt was made to find any histopathological evidence to support the conclusion that isopropyl alcohol induced fatty liver.

Divincenzo and Krasavage [64] injected guinea pigs ip with 500 mg/kg and 1,000 mg/kg of undiluted isopropyl alcohol. Twenty-four hours later, no increase in serum ornithine carbamyl transferase activity was observed. The authors concluded that liver damage was absent. Microscopic examination revealed that the liver was normal. However, the serum ornithine carbamyl transferase activity is not a frequently used index of early liver damage.

From these reports, [61,64] it can be concluded that isopropyl alcohol increases the concentration of triglycerides in the livers of rats. However, lack of any histological evidence prevents any conclusions regarding induction of fatty liver by isopropyl alcohol.

In 1967, Cornish and Adefuin [65] studied the capacity of various alcohols, including isopropyl alcohol, to potentiate the toxicity of carbon tetrachloride. Isopropyl alcohol at a dose of 2.34 g/kg (2.98 ml/kg) was administered by intubation to 6 rats, 16-18 hours prior to inhalation of carbon tetrachloride. Six control animals and 6 animals receiving only isopropyl alcohol were included in the study. The exposure period to carbon tetrachloride at 1,000 ppm was 2 hours. The serum glutamic-oxaloacetic transaminase (SGOT) activity increased significantly compared to the control animals, indicating that isopropyl alcohol potentiated carbon tetrachloride toxicity at the dosage used. However, as noted by the

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authors, the combined industrial exposures to isopropyl alcohol and carbon tetrachloride would rarely be as high as those used in this experiment.

In 2 separate studies, Traiger and Plaa [66,67] reported that isopropyl alcohol at a dose of 2.5 ml/kg (1.96 g/kg) combined with 0.0075 ml/kg [66] or 0.1 ml/kg [67] of carbon tetrachloride increased serum glutamic-pyruvic transaminase (SGPT) activity. Traiger and Plaa [68] and Plaa et al [69] conducted further experiments to determine whether isopropyl alcohol potentiated the toxicity of other chlorinated hydrocarbons as measured by SGPT activity. Isopropyl alcohol at a dose of 2.5 ml/kg was administered by forced feeding to 106 mice divided into 4 groups. Eighteen hours after isopropyl alcohol administration, each group was injected ip with 1 of the 4 chlorinated hydrocarbons in doses ranging from 0.05 to 2.5 ml/kg. The authors observed that in mice the toxicities of chloroform, 1,1,2-trichloroethane, and trichloroethylene were enhanced by both isopropyl alcohol and acetone. The hepatotoxicity of 1,1,1-trichloroethane was not augmented. Acetone produced greater enhancement of the SGPT-elevating power of 1,1,2-trichloroethane than isopropyl alcohol; isopropyl alcohol had a greater effect on the hepatotoxic actions of chloroform and trichloroethylene than acetone. The authors also undertook preliminary studies, [68] which indicated that administration of isopropyl alcohol or acetone by inhalation-augmented liver injury induced by ip administration of carbon tetrachloride. Moreover, the degree of augmentation observed was related to the hepatotoxicity of the chlorinated hydrocarbon. Therefore, the authors concluded that the likely combination in the occupational environment that might result in a hazardous situation should be predictable on the basis of the hepatotoxicity of the chlorinated

hydrocarbon involved. In 2 separate studies, Traiger and Plaa [70,71] found that acetone was capable of potentiating carbon tetrachloride toxicity. Plaa and Traiger [72] carried out a dose-response study using isopropyl alcohol alone and acetone alone, followed 18 hours later by carbon tetrachloride. SGPT activity was used as a measure of hepatotoxicity. Elevated SGPT activity was evident when isopropyl alcohol was administered in the range of 0.41-4.70 ml/kg or when acetone was administered in the range of 0.35-4.00 ml/kg. The authors noted that the marked potentiation of carbon tetrachloride hepatotoxicty by isopropyl alcohol could have been due to a combined effect of unaltered isopropyl alcohol and acetone which were slowly eliminated. This observation was further supported by the results of a study by Sipes et al, [73] who examined the effect on rat liver microsomes of 2.5 ml/kg of acetone and isopropyl alcohol each. The authors assumed that isopropyl alcohol increases the toxicity of carbon tetrachloride by inducing liver microsomal enzymes. The binding capacity of liver microsomes with some chlorinated hydrocarbons and various other compounds was enhanced by both isopropyl alcohol and acetone.

Cote et al [74] investigated the effect of isopropyl alcohol pretreatment on carbon tetrachloride-induced alteration of hepatic morphology at the ultrastructural level. Isopropyl alcohol at 2.5 ml/kg was administered by mouth 18 hours prior to a threshold dose of carbon tetrachloride at 0.1 ml/kg ip. Alterations of the liver structure comparable to those occurring after the administration of 1.0 ml/kg of carbon tetrachloride alone were observed. The organelle most affected was the endoplasmic reticulum. Also, lysosomal alterations, as measured by an

increase in the ratio of free to total acid phosphatase activity, were present in the animals treated with both substances. The authors concluded that hepatocytes from isopropyl alcohol-treated rats may be more sensitive to the toxic effects of carbon tetrachloride or its metabolite. They also suggested that isopropyl alcohol could stimulate drug-metabolizing enzymes or could act on the endoplasmic reticulum in such a way as to facilitate the attack of carbon tetrachloride on this organelle.

In summarizing the effects of isopropyl alcohol in animals, effects of inhalation, germane to occupational exposure, remain inadequately studied. Most animal experiments involve routes of administration other than inhalation. The few inhalation studies found used isopropyl alcohol either at very high concentrations, such as 16,000 ppm, [45,46] or at very low concentrations, such as less than 10 ppm. [47] Reports on acute or chronic effects of inhalation of isopropyl alcohol at levels usually encountered in the industrial environment, such as up to 400 ppm, have not been found in the literature. Oral intoxication effects include narcosis, [8,9,48] salivation, [48] and vomiting. [48] Conclusive evidence of liver damage has not been reported. However, accumulation of liver triglycerides following isopropyl alcohol administration has been observed. [61,62] Although acetone has been identified as a metabolite, [58] the precise metabolic routes for isopropyl alcohol are unknown. [58] Other animal studies [65-71] showed that when isopropyl alcohol was administered prior to carbon tetrachloride it increased the hepatotoxicty of the latter.

Thus, existing animal studies are not adequate for understanding all the acute and chronic effects of isopropyl alcohol inhalation in humans. Table XII-2 presents a summary of the results of animal experiments.

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Carcinogenicity, Teratogenicity, and Mutagenicity

Subsequent to the discovery of an abnormal incidence of paranasal and sinus cancers in employees involved in isopropyl alcohol manufacture, Weil et al [39] undertook animal studies to identify the carcinogen. The following substances were tested: isopropyl alcohol, isopropyl oil from 2 manufacturing processes, unidentified distillates, and chromatographic fractions of the oils. Inhalation and subcutaneous injection studies were performed on mice. In the inhalation studies, mice were exposed 5 days/week, 3-7 hours/day, for 5-8 months. The undiluted samples were administered subcutaneously in 0.025-ml amounts for 20 - 40 weeks. In some studies, 4-8 mg of the sample dissolved in 1 ml lard were administered in 2-6 biweekly doses. The results of these studies are summarized in Table III-1 and III-2.

As indicated in Table III-1, [39] inhalation of isopropyl alcohol produced no significant numbers of tumors in the species studied. The suspected carcinogen, isopropyl oil from only 1 of the 2 plants was tumorigenic. Tumors were induced in only 3 of 21 groups of mice in the inhalation study and in 1 of 13 groups of mice in the injection study. Lung tumors found in these groups included adenomas and adenocarcinomas. No mammary or sinus tumors were found. The carcinogenic potential of the oil was generally less than that of a well-recognized and studied carcinogen, methylcholanthrene. Although this study is fairly well-designed, it suffers from one major drawback. After examining 74 mice from the first inhalation study for sinus tumors and finding none, Weil et al [39] discontinued the search in subsequent experiments. Since the

TABLE III-1

SUMMARY OF THE RESULTS* OF INHALATION
STUDIES IN 6 STRAINS OF MICE

Substance	Concen-tration	Strain					
		C3H	ABC	CFW	C57	CF1	ABCT
Isopropyl oil, first plant	0.004 ml/liter	12/41**	32/56	-	0/34	-	-
"	0.008 ml/liter	14/41**	37/46	-	0/7	-	-
"	0.002 ml/liter	-	-	13/47	-	62/21	13/46
"	0.004 ml/liter	-	-	14/49	-	72/25	8/38
"	"	-	19/36	22/32	-	35/52	-
Isopropyl oil, second plant	0.002 ml/liter	-	-	13/46	-	63/35	10/39
"	0.004 ml/liter	-	-	16/51	-	44/36	18/34**
Isopropyl alcohol	0.0075*** mg/cu m	6/36	24/41	-	10/47	-	-
Isopropyl sulfate + isopropyl oil	0.00025 mg/cu m	-	17/23	40/20	-	36/52	-
"	0.00425 mg/cu m	-	21/34	39/28	-	38/48	-
Room air (control)		3/69	32/78	-	4/52	-	-
"		-	-	9/56	-	67/21	0/21
"		-	14/42	16/51	-	26/51	-

*   % of mice with tumors/number of mice killed
**   Significantly greater than control values (P values not given)
***   In a communication of Sept 11, 1975, Weil noted there was an error and
the actual metered concentration was 7,700 mg/cu m (3,130 ppm)

From reference 39

TABLE III-2

SUMMARY OF THE RESULTS* OF SUBCUTANEOUS
INJECTION STUDIES IN 6 STRAINS OF MICE

Substance	Strain					
	C3H	ABC	CFW	C57	CF1	ABCT
Undiluted isopropyl oil, first plant	26/46	35/52	–	–	–	–
"	7/43	57/47**	–	4/46	–	–
"	–	32/38	–	–	–	–
"	0/29	11/28	–	–	–	–
"	–	21/38	–	–	–	–
Undiluted isopropyl oil, second plant	6/36	56/36	–	3/38	–	–
"	–	37/38	–	–	–	–
Isopropyl oil in lard distillation residue	3/36	52/40	–	3/37	–	–
"	0/27	38/34	–	3/30	–	–
"	0/21	38/40	–	0/34	–	–
Isopropyl oil in lard chromatographic sample	0/36	41/39	–	0/38	–	–
"	0/28	40/40	–	6/36	–	–
"	3/32	36/39	–	3/34	–	–
"	–	–	0/25	–	29/21	0/21
"	–	–	6/31	–	24/21	4/28
Methyl cholanthrene in lard (control)	–	–	47/19	–	67/3	57/14**
"	–	–	50/12	–	41/56	–
"	–	58/24**	–	–	–	–

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TABLE III-2 (CONTINUED)

SUMMARY OF THE RESULTS* OF SUBCUTANEOUS
INJECTION STUDIES IN 6 STRAINS OF MICE

Substance	Strain					
	C3H	ABC	CFW	C57	CF1	ABCT
No treatment	28/25	32/37	50/12	3/34	41/46	57/14**
"	8/40	37/59	–	11/45	–	–
"	–	26/35	–	–	–	–
"	16/25	68/39	–	0/23	–	–
"	0/29	23/30	–	–	–	–
"	–	–	22/27	–	19/16	17/30
"	–	–	37/30	–	42/31	–
Lard control	36/53	35/51	–	–	–	–
"	24/25	26/50	–	4/44	–	–
"	0/29	38/40	–	4/27	–	–
"	–	–	22/32	–	40/20	7/29
"	–	–	34/35	–	52/29	–
"	–	30/37	–	–	–	–

* % of mice with tumors/number of mice killed (see text for dosage)
** Significantly greater than control values (P values not given)

From reference 39

remaining mice were not examined, sinus tumors may have been present but overlooked.

Weil conducted a second series of experiments to determine the tumorigenic potential of isopropyl oil produced in the present weak-acid process, and to compare it with that of the isopropyl oil from the strong-acid process. Experiments were done with mice and dogs and the results were made available in a communication written on September 11, 1975.

Groups of mice consisting of approximately 40 of each strain received subcutaneous injections of isopropyl oils from each process, a mixture of oils from both processes, or isopropyl alcohol. The strains used were C3H, CFW, CF-1, dba, and A/He. The animals received 20 weekly injections of 0.025 ml each in the inguinal region. Five months after the first injection, when the animals were about 8 months old, they were killed and examined for the presence of pulmonary tumors, especially adenomas. Mice from the untreated control groups of each strain were also examined. The results are presented in Table III-3.

As indicated in Table III-3, the only significant result observed was the 48.1% lung tumor incidence produced when a mixture of isopropyl oils from both the old and the new processes was injected into mice. These results provide little information regarding the difference in the carcinogenic potentials of the isopropyl oils from the 2 processes. It is noteworthy that the incidence of tumors in the animals receiving isopropyl oil obtained from the strong-acid process was not significantly higher than that in the controls. The incidence of tumors in the control animals was extremely high, ranging from 0% in the C3H strain to 41.7% in the A/He strain.

In the skin-painting assay (CS Weil, written communication, September 1975), groups of 30 Rockland all-purpose mice were painted on their clipped backs 3 times/week for 1 year with isopropyl alcohol, isopropyl oil from the strong-acid process, isopropyl oil from the weak-acid process, or distilled water. The positive controls used were catalytically cracked petroleum oil, 0.02% dimethyl benzanthracene (DMBA), and 0.2% methyl cholanthrene (MC). The results are summarized in Table III-4.

TABLE III-3

RESULTS OF SUBCUTANEOUS INJECTIONS
IN MICE

Strain	Process	Substance	No. of Mice Killed	% Tumorous Lungs
C3H (Salk-Mars,Pa)	Strong-acid	Isopropyl oil	23	0.0
"	"	"	22	0.0
"	Weak-acid	"	30	0.0
"	"	"	31	3.2
"	Both	Isopropyl oils	29	3.4
"	"	"	32	3.1
"	—	Isopropyl alcohol	22	4.5
"	—	None	33	0.0
C3H (Rockland)	Weak-acid	Isopropyl oil	20	20.0
"	"	"	35	14.3
"	Both	Isopropyl oils	22	13.6
"	—	None	25	16.0
C3H (Jax)	Weak-acid	Isopropyl oil	37	5.4
"	"	"	42	0.0
"	Both	Isopropyl oils	41	7.3
"	—	None	33	0.0
"	Weak-acid	Isopropyl oil	37	13.5
"	"	"	36	16.7
"	—	None	39	18.0
"	Weak-acid	Isopropyl oil	25	16.0
"	"	"	28	7.1
"	"	"	26	3.8
"	—	None	24	12.5

TABLE III-3 (CONTINUED)

RESULTS OF SUBCUTANEOUS INJECTIONS
IN MICE

Strain	Process	Substance	No. of Mice Killed	% Tumorous Lungs
C3H (Jax + Texas inbred)	Weak-acid	Isopropyl oil	33	9.1
"	"	"	34	8.8
"	"	"	33	3.0
"	-	None	34	11.8
C3H (Cum)	Weak-acid	Isopropyl oil	32	9.4
"	"	"	34	17.6
"	-	None	32	6.2
CFW (Carworth)	"	Isopropyl oil	23	13.0
"	"	"	22	13.6
"	Strong-acid	"	29	24.1
"	Both	Isopropyl oils	25	28.0
"	-	None	25	12.0
CF-1 (Carworth)	Weak-acid	Isopropyl oil	24	37.5
"	"	"	22	22.7
"	Strong-acid	"	28	28.6
"	Both	Isopropyl oils	27	48.1*
"	-	None	30	20.0
"	Weak-acid	Isopropyl oil	34	11.8
"	"	"	30	13.3
"	"	"	34	14.7
"	-	None	28	21.4

TABLE III-3 (CONTINUED)

RESULTS OF SUBCUTANEOUS INJECTIONS
IN MICE

Strain	Process	Substance	No. of Mice Killed	% Tumorous Lungs
dba (Rockland)	Weak-acid	Isopropyl oil	25	16.0
"	"	"	21	19.0
"	Both	Isopropyl oils	14	21.4
"	–	None	21	23.8
dba (Jax)	Weak-acid	Isopropyl oil	36	2.8
"	"	"	40	2.5
"	Both	Isopropyl oils	37	2.7
"	–	None	38	5.3
A/He (Jax)	Weak-acid	Isopropyl oil	33	30.3
"	"	"	36	22.2
"	–	None	36	41.7
A/He (Jax)	Weak-acid	Isopropyl oil	28	28.6
"	"	"	26	38.5
"	"	"	28	35.7
"	–	None	27	25.9
A/He (Cum)	Weak-acid	Isopropyl oil	33	18.2
"	"	"	33	39.4
"	–	None	33	24.2

*P = 0.05, which was reported to be of borderline significance

From Weil (written communication, September 1975)

TABLE III-4

RESULTS OF SKIN APPLICATION
IN GROUPS OF 30 ROCKLAND ALL-PURPOSE MICE

Substance Applied	Process	Number of Mice with Tumors
Isopropyl alcohol	Strong-acid	0
Isopropyl oil	"	3 (all papillomas)
"	Weak-acid	0
Positive control (catalytically cracked petroleum oil)	-	25 (25 with papillomas, 16 with carcinomas)
Negative control (distilled water)	-	2 (all papillomas)
Isopropyl oil	Strong-acid	3 (all papillomas)
"	"	3 (all papillomas)
Positive control 0.02% DMBA	-	4 (4 with papillomas, 1 with carcinoma)
0.2% MC	-	15 (15 with papillomas, 13 with carcinomas)
Negative control (distilled water)	-	1 (1 with both carcinoma and papilloma)

From Weil (written communication, September 1975)

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As indicated in Table III-4, isopropyl alcohol from the strong-acid process and isopropyl oil from the weak-acid process produced no tumors in mice. There was no significant difference between the number of mice with tumors in the groups painted with distilled water or with isopropyl oil obtained from the strong-acid process. In all cases, the positive control animals developed a high tumor incidence. These experiments also failed to bring out the difference between the carcinogenic potentials of the 2 oils in question. In these experiments, isopropyl oil from the strong-acid process failed to produce a significant number of tumors when compared to controls. In all cases, the incidence of tumors in the negative control animals was comparable to that observed in the experimental animals.

In order to determine whether sinus tumors can develop in dogs, 4 groups of 5 mongrel dogs were exposed to aerosols of isopropyl oil obtained from the strong-acid process (CS Weil, written communication, September 1975). The dogs received weekly inhalation exposures for 2 years and then were rested for 14 months. Subsequently, they were exposed every third week for the next 2 years. Another group of 4 dogs received direct sinus instillations of strong acid-produced isopropyl oil, once a month for 48 months. The approximate ages at death ranged from 9 to 12.25 years. X-rays were taken at frequent intervals and were negative. At autopsy, several dogs had tumors that were judged not to be uncommon. No sinus tumors were detected but the incidence of benign thyroid adenomas was found to be increased.

In summary, although the epidemiologic evidence [39] suggests that a carcinogen was present in the strong-acid process, animal experiments (CS

Weil, written communication, September 1975) present little evidence of carcinogenicity of the oils from either the new or the old processes. However, the results do raise a new problem. Isopropyl oil from the old, strong-acid process did not consistently produce a significant number of tumors in the subcutaneous injection assay, in the skin-painting assay, or in the sinus instillation experiment. Therefore, the animal studies are inadequate for determining the identity of the carcinogen in either of the processes. However, there is no evidence that isopropyl alcohol is a carcinogen. Inconclusive results from the animal studies might be associated with the nature of the chemicals being tested, the unusually high tumor incidence in the control animals, or the use of animals that might not be appropriate models for tumorigenic studies. Thus, whether the hazard is present or eliminated in the newer weak-acid process remains unknown.

No evidence of teratogenicity of isopropyl alcohol was found in the literature. McLaughlin et al [75] observed that isopropyl alcohol did not produce teratogenic effects when injected into chicken eggs. However, Walker [76] stated that different modes of administration for the test substance in chicken eggs altered the results and he did not consider chicken egg experiments reliable. In order to ascertain the effect of isopropyl alcohol on reproduction and growth, Lehman et al [49] gave 2.5% isopropyl alcohol in drinking water to 6 female and 3 male rats. The rats were 38-40 days old at the start of the experiment and were mated when they were 120 days old. This was repeated through 2 generations. Forty-four young in the first generation and 66 in the second were produced. Comparison of growth curves showed that 2.5% isopropyl alcohol in drinking

water retarded the very early growth in the first generation. Literature on the mutagenic effects of isopropyl alcohol has not been found.

Correlation of Exposure and Effect

Very few of the reports discussed are germane to the subject of occupational exposure to isopropyl alcohol. The reports in which exposure levels are well documented and established involve primarily routes of administration other than inhalation and skin absorption. [7, 48,50,57] There is only one reported study [39] on the effects on humans of long-term exposures to isopropyl alcohol alone.

A report [34] was found that related the effects of isopropyl alcohol inhalation in humans to the airborne levels. In 1943, Nelson et al [34] exposed 10 human subjects in a chamber to isopropyl alcohol at various concentrations for 3-5 minutes. Exposure to isopropyl alcohol at 400 ppm and 800 ppm caused irritation of eyes, throat, and nose. The subjects believed they would prefer to work for 8 hours in an atmosphere containing 200 ppm or less of isopropyl alcohol. In 1974, Baikov [47] studied the effects of inhalation of isopropyl alcohol in animals but the interpretation of the observed biologic changes is difficult, because experimental design and analysis of data were not described in sufficient detail to allow evaluation of the conclusions. No conclusive comments can be made from the results of the above inhalation studies [34,47] with respect to short-term and long-term effects of the inhalation of isopropyl alcohol.

Marzulli and Ruggles [55] reported that 0.1 ml of 70% isopropyl alcohol caused some conjunctival redness, corneal opacity, and iritis in

rabbits. These effects were temporary, but isopropyl alcohol can be classified as a moderate eye irritant. Acute effects of oral doses of isopropyl alcohol (0.32 ml/kg and 0.14-0.21 ml/kg) include drowsiness, headache, and lowering of blood pressure in man. [7] Several investigators have found that narcosis is a prominent effect of isopropyl alcohol intoxication. [7,8] In 1969, Wills et al [31] reported that low levels of isopropyl alcohol did not cause liver damage in humans.

Weil et al [39] conducted an epidemiologic study which indicated that a carcinogen was present in the isopropyl alcohol-manufacturing process using the strong-acid process. Animal experiments failed to establish or confirm the identity of a carcinogen.