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BIOLOGICAL EFFECTS AND ENVIRONMENTAL ASPECTS OF 1,3-BUTADIENE

(SUMMARY OF THE PUBLISHED LITERATURE)

MAY 1976

FINAL REPORT

ENVIRONMENTAL PROTECTION AGENCY
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This task was initiated because of a reported increased incidence of leukemia among workers in certain styrene-butadiene synthetic rubber manufacturing plants.

16. ABSTRACT

This report is a summary of the literature on the biological effects and environmental aspects of 1,3-butadiene and was prepared from articles and abstracts identified through a search of the technical literature. The report contains information on the effects of 1,3-butadiene in environmental samples and on the reactivity of 1,3-butadiene in environmental media.

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(Summary of the Published Literature)

Final Report

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NOTICE

This report has been reviewed by the Office of Toxic Substances, EPA, and approved for publication. Approval does not signify that the contents necessarily reflect the views and policies of the Environmental Protection Agency, nor does mention of trade names or commercial products constitute endorsement or recommendation for use.

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1.0 Introduction

This literature summary was prepared by Radian Corporation for EPA under task 7 of contract number 68-01-3249, Information Concerning Selected Chemicals. According to the task statement, abstracts concerning biological properties, environmental effects and analytical methods for butadiene were to be collected using several abstracting indices. A narrative summary of literature describing biological and environmental aspects was to be prepared. The literature search and summary were to be completed within a two-week time period.

Literature describing biological aspects of butadiene is summarized in Section 2.0. Plant, laboratory animal, and human studies are described. The majority of published information on biological aspects was written in Russian, and many of the references were unavailable in full text English translations. Information from these sources was obtained from the abstracts. If an abstract rather than a full text article was the source of information, the abstract number was given in the literature citation. If the full text was consulted, the literature citation contains the author's name and the year of publication.

Information on environmental occurrence and reactivity of butadiene is summarized in Section 3.0. Most of the information on this subject was available in full text in English.

References cited in the text are listed in the Bibliography in Section 4.0. Some references were not available in full text in time to be described in the summary. Some abstracts did not contain the information of interest. References in these two categories were not described in the literature summary but are expected to contain useful information. These additional references are listed separately in Section 5.0.

2.0 Biological Effects

This section contains a summary of responses of plants, animals, and humans to 1,3-butadiene and to mixtures of 1,3-butadiene with other substances as reported by various researchers in the technical literature.

2.1 Plant Studies

A summary of the available literature concerning effects of 1,3-butadiene and mixtures of 1,3-butadiene with atmospheric components on plant life is included in this section. Only three reports of plant studies of this type were found.

The effects of hydrocarbon gases representative of the C_1- C_4 range on plant growth and development were individually examined by Heck and Pires (1962). Fumigation with 1000 ppm of 1,3-butadiene produced some indication of injury in cotton, cowpeas, and tomatoes, although the symptoms were too slight to be identified. No effect was reported on coleus, sorghum, and soybean. Further fumigation experiments at 10 and 100 ppm (v/v) gas in air for 3-week periods produced no easily recognizable effect from 1,3-butadiene on cotton, cowpeas, and tomatoes. It was therefore eliminated from further studies. (Heck and Pires, 1962).

Abeles and Gahagan (1968) examined the role of ethylene and ethylene analogs in bean plant abscission acceleration studies. Of the seven test gases studied, 1,3-butadiene was least active in accelerating abscission and only displayed a 10% stimulation at 10,000 ppm exposure for four hours.

Research conducted by Haagen-Smit, *et al*. (1951) in trying to duplicate symptoms induced by smog on plants in the Los Angeles area indicates both typical and atypical injury to plants from exposure to a mixture of butadiene with ozone for five hours. The typical symptoms used for diagnosis were silvering of leaves on spinach, endive, and beet along with speckled necrosis on oats and alfalfa. Atypical damage encountered was wilting, the formation of large necrotic areas, tip burning, chlorosis, bleaching, or minute pitting of leaves. Further experimentation with mixtures of NO_2 and butadiene showed typical smog damage symptoms at 5 ppm butadiene and 7 ppm NO_2 in the absence of sunlight or UV irradiation. Lower concentrations of 0.5 ppm butadiene and 4.5 ppm NO_2 without sunlight or UV irradiation resulted in no symptomatic response. Results of experiments with butadiene, NO_x and UV irradiation or sunlight were not reported. The authors concluded from their work that the plant damaging species were oxidation products of unsaturated hydrocarbons (Haagen-Smit, *et al*, 1952).

The three articles summarized in this section support the hypotheses that 1,3-butadiene itself may have little effect on plants. However, conditions and substances present in the atmosphere may result in the formation of reactive compounds causing plant damage.

2.2 Animal Studies

This section describes the effects of 1,3-butadiene on laboratory animals. Reported observations of the effects on several organs and systems and metabolism are included.

Exposure to 1-3 butadiene either alone or in combination with α-methylstyrene, toluene, N-phenyl-β-naphthylamine, isoprene and toluene was accomplished most often by inhalation of vapors, although a few studies utilized oral administration. The laboratory rat was the most often used animal; guinea pigs, rabbits, mice and cats were also utilized.

2.2.1 Organs and Systems

In an effort to facilitate reading and utilization of reported data concerning effects of 1,3-butadiene and mixtures of 1,3-butadiene with other substances on animals, the information was organized by organ or system. The categories included are the reproductive system; the circulatory system; hematopoietic organs, formed elements, and plasma; liver; kidneys; respiratory system; skin; the nervous system; and the gastrointestinal system.

2.2.1.1 Reproductive System

Female

During the first month of exposure by an unspecified method to 1,3-butadiene and α-methylstyrene, a decrease in the number of primordial cells and maturing follicles is noted. Large numbers of corpora lutea are preserved in the active state. If poisoning by 1,3-butadiene and α-methylstyrene continued for 2-3 months, adaptation occurred (CA75:96902t). Another survey (CA72: 30037w) describing effects of administering butadiene and toluene by inhalation reported prolongation of estrous caused by both chronic and acute poisoning. A normal cycle was reestablished in 50% of the rats within five months after cessation of chronic poisoning.

Male

Chronic vapor inhalation of α-methylstyrene and 1,3-butadiene by rats resulted in inhibited spermatogenesis with dysplastic and necrotic changes noted. Signs of adaptation and restoration of spermatogenesis did occur more than 24 days after cessation of the 60 to 90 day course of poisoning (CA75: 96900r).

2.2.1.2 Circulatory System

Hemodynamic disturbances with increased permeability of vessel walls were the result of chronic exposure of rats to 1,3-butadiene for 81 days at concentrations of 30 mg/m^3 (CA75: 107774f). Chronic vapor inhalation by rats of α-methylstyrene and 1,3-butadiene resulted in disturbed permeability of testicular veins with accumulation of blood proteins in vein walls and testicular stroma (CA75: 96900r). Chronic exposure in another study of the same two substances resulted in vascular dystonia in respiratory structures (CA78: 106680x). During long-term administration of 1,3-butadiene and α-methylstyrene by inhalation, an initial toxic reaction observed was increased permeability of blood vessels in rat lung. Later, sclerotic processes developed in perivascular and peribronchial zones, and blood vessel permeability decreased (CA75: 107749b). Chromotropic compounds accumulated in blood vessel walls of rats subjected to chronic exposure by inhalation of α-methylstyrene and 1,3-butadiene mixtures. After 90 days of poisoning, chromotropic compounds were found in perivascular connective tissue. Again, signs of sclerosis were observed and outlasted the arrest of poisoning (CA75: 96881k). The chronic exposure of rats to 0.03 mg/ℓ 1,3-butadiene for 81 days caused decreased arterial pressure (CA66: 118540s).

Specific histopathology described in one study of rats ingesting 100 mg/kg 1,3-butadiene daily (subacute) for a 2.5 month course were as follows: cytoplasm of the heart showed granular and hydropic dystrophy, cytolysis, neuronophagia, homogenation of vascular walls with permeability disturbance, and lymphohistiocytic infiltration (HEEP/72/03574). Rabbits subjected to chronic exposure to 1,3-butadiene (100 mg/m^3) exhibited fragmentation of muscle fibers in the myocardium (Batkina, 1966).

2.2.1.3. Hematopoietic Organs, Formed Elements, and Plasma

Hematopoietic Organs and Formed Elements

A 120-day test exposing rats to vapors of 5 mg α-methylstyrene/m^3 air and 100 mg 1,3-butadiene/m^3 produced disturbances in the tissues and cells of the bone marrow, lymph glands, and spleen, which began to normalize at 90-120 days. Protein metabolism changes were noted in lymphocytes, normoblasts, and unripe granulocytes during the experiment. The results point to the myelotoxic effect of the combination of the two compounds (CA75:116947s).

A change in the cell distribution in rabbits was observed with the administration, in an unspecified manner, of 200 mg/ℓ of 1,3-butadiene. The ratio of erythroblasts to granulocytes was increased (CA74:97300m).

A separate study using inhalation of 99.8 mg 1,3-butadiene and 5.2 mg of α-methylstyrene per m^3 demonstrated a decreased level of leukocytes in rats (CA78: 106680x). The effect was also reported (CA75: 107786m) with specific reference to decrease in neutrophils. Hypochromic anemia was also observed, indicating inhibited hemopoiesis. Leukopenia was found in mice exposed to fumes from heated butadiene rubber. The fumes contained 0.012 mg/ℓ N-phenyl-β-naphthylamine and 0.339 mg/ℓ 1,3-butadiene (CA71: 41988n). Another study (CA66:118541t) performed on rats exposed by inhalation of butadiene for 81 days also resulted in erythrocytosis and leukocytosis with a neutrophilic shift to the left.

A study of both acute and chronic poisoning of experimental animals was reported by Batkina, 1966. Acute poisoning of rats and rabbits caused leukocytosis with neutropenia and relative lymphocytosis along with changes in protein distribution in the serum. Chronic poisoning of rats with concentrations of 2200 mg/m^3 caused a tendency toward leukopenia along with an increase in the number of pseudoeosinophils and in lymphopenia. In rats and rabbits an inhibition of phagocytic activity of neutrophils developed earlier in the animals subjected to chronic dosages of 2200 mg/m^3 than in those subjected to dosages of 100 mg/m^3. Rabbits subjected to chronic exposure exhibited an increase in erythrocyte sedimentation rate and a decrease in blood hemoglobin content as well as hyperplasia of the spleen pulp (Batkina, 1966).

Chronic exposure of rats to butadiene and α-methylstyrene supressed phagocytic activity of leukocytes (CA78: 106680x), but this activity was increased in macrophages of rats exposed to butadiene (CA75: 107773e).

Additionally, chronic exposure of rats to concentrations of 1,3, and 30 mg of 1,3-butadiene per m^3 of air resulted in structural changes in hematopoetic organs (especially the spleen) and thinning of nuclear endothelium. Also noted was a decrease in the content of nucleic acid of splenic cells and disintegration of red blood cells in the pulp of the spleen (CA75: 107773e).

A study of marrow smears from rats exposed to mixtures of α-methylstyrene and 1,3-butadiene by inhalation was made over a period of 10-120 days. Changes were observed in immature granulocytes and in slightly differentiated cells. SS and SH groups in erythrocytes decreased in the initial period, increased in the intermediate period, and decreased again later. Changes observed in nucleoproteins, amino acids, and functional proteins were a function of dosage (CA73:129116d).

Chronic exposure of rabbits to a combination of toluene and 1,3-butadiene for a 2 month period of time caused an increase in the albumin/globulin ratio of the bone marrow with a decrease in total protein (Faustov and Lobeeva, 1970).

A statistically reliable reduction in hemoglobin concentration in rabbits resulted from oral administration of 40 mg 1,3-butadiene in vegetable oil/kg over a 7-month course (BA52:69712).

Plasma

An increased level of total SH groups in the blood was reported as a result of inhalation of 99.8 mg 1,3-butadiene and 5.2 mg α-methylstyrene/m^3 air in rats (CA78: 106680x). However, another study using oral administration to rabbits of 40 mg/kg 1,3-butadiene in vegetable oil over a 7-month course did not change the number of free SH groups (BA52: 69712).

An increase in cholesterol content in the blood of 84 rats, particularly cholesterol esters, was noted after 120 days of inhalation of 1,3-butadiene and/or α-methylstyrene. An increase from 29.3 to 64.9 mg% was observed (CA75: 96903u).

Exposure to 1,3-butadiene and α-methylstyrene resulted in a decrease in total serum protein, but an increase in the α_2-globulin fraction (CA75:107786m). Changes in the immunological state were observed after an 81-day course of inhalation of 1.0, 3.0, and 30 mg/m^3 1,3-butadiene/m^3 air (CA75:107777j) in experimental animals which can be related to changes in globulin/albumin levels.

2.2.1.4 Liver

Decreased liver metabolism was noted with chronic exposure of rats to 1,3-butadiene and α-methylstyrene by inhalation. Decreased levels of ascorbic acid and thiamine in the liver were found (CA78: 106680x). Also indicated was disturbed metabolism of carbohydrates, fats, and proteins. In another study specific disturbance of lipid and carbohydrate metabolism was observed in rats, especially a decrease in glycogen and accumulation of lipids in hepatic areas after a 60-120 day course of inhalation of a mixture of 0.05 mg 1,3-butadiene and 0.005 mg α-methylstyrene/ℓ. Chronic inhalation of α-methylstyrene and 1,3-butadiene affected lipid metabolism and increased the cholesterol contents of rat livers from 119 to 246.2 mg% (CA75:107720k). Redistribution of total proteins and ribonucleoproteins in liver cells is noted with decreases in protein content in the cytoplasm of vacuolated cells (CA75: 107780e) of rats subjected to chronic exposure by inhalation of butadiene and α-methylstyrene. Hepatic ATP content increased as did the ratio of ATP to ADP with acute inhalation poisoning (Oura and Reiha, 1966).

Chronic inhalation of a mixture of 1,3-butadiene (0.05 mg/ℓ) and α-methylstyrene (0.005 mg/ℓ) caused disturbances in the lipid and carbohydrate metabolism in rats, evidenced by a decrease in glycogen and an increase in lipids in hepatic cells (CA75:107779m).

Chronic exposure of rabbits to 1,3-butadiene (100 mg/m^3) produced granular dystrophy in the liver (Batkina, 1966). Specific histopathologic changes noted in the liver are similar to those previously described for the heart (BA53:5577).

2.2.1.5 Kidneys

Chronic inhalation exposure of rats to mixtures of 1,3-butadiene and α-methylstyrene caused symptoms similar to protein dystrophy (CA75:107797r). During the course of the experiment renin granules disappeared from the epithelioid cells but later reappeared (CA75:107797r). Increased concentrations of urinary hippuric acid are noted in rats exposed to fumes of heated butadiene rubber containing butadiene and N-phenyl-β-naphthylamine (CA71: 41988n).

Other researchers report changes in the urine composition of rats exposed to butadiene and α-methylstyrene by inhalation. Decreased thiamine levels and urinary excretion of riboflavin, coporphyrins, and ascorbic acid were reported (CA78: 106680x).

Morphologic changes in the kidneys are similar to those described for liver and heart (BA53:5577). Small round cell infiltrations and congestion in the kidneys were reported in rabbits chronically exposed to 100 mg/m^3 1,3-butadiene levels (Batkina, 1966).

2.2.1.6 Respiratory System

Chronic exposure of rats to 100 mg/ℓ 1,3-butadiene and 5.27 mg/ℓ α-methylstyrene vapors initially altered bronchial epithelium, caused proliferation of beaker cells, and increased permeability of blood vessels. Later, this significant hyper-secretory state in the connective tissue structures of the lungs resulted in reactive cell production. Toward the end of the experiment, sclerotic processes developed in the perivascular and peribronchial zones with a decrease in the permeability of blood vessels. Irritation of the respiratory tract was noted in mice exposed by inhalation to mixtures of butadiene and N-phenyl-β-naphthylamine. Morphologic changes noted with oral administration of 100 mg/kg 1,3-butadiene daily for 2.5 months included thickening of the interalveolar septa and minor lymphohistiocytic infiltration (BA53:5577).

A study of chronic exposure of rats to butadiene vapor concentrations of 3 mg/m^3 for 81 days caused some changes in the epithelium of the mucous membranes of the lungs and nose (CA69:12741e).

Chronic exposure of rabbits to 1,3-butadiene (100 mg/m^3) resulted in pulmonary vessel congestion, pronounced emphysema, and inflammatory small-cell infiltration around the bronchi. (Batkina, 1966).

2.2.1.7 Skin

Changes in epidermis, connective tissue, hair, glands, and neuron fibers of rat skin caused by inhalation of butadiene and α-methylstyrene disappeared 30-60 days after discontinuation of treatment (CA81: 100372p).

2.2.1.8 Nervous System

Histological changes occurred in rats given 100 mg/kg 1,3-butadiene for 2.5 months. The cytoplasm of the cells of the brain and sympathetic ganglia showed granular and hydropic dystrophy, cytolysis, neuronophagia, homogenation of the vascular walls and disturbances of their permeability (HEEP/72/03574).

A study conducted by Shugaev published in 1969 related toxicity of various hydrocarbons, including butadiene, to brain concentrations in rats, mice, and cats. Acute atmospheric exposure at levels of 270 mg/ℓ for mice and 280 mg/ℓ for rats was the method of administration. In cats the butadiene was found to concentrate in the white nervous tissue. The author recommends that toxicity criteria be based on minimum lethal concentrations in the medulla oblongata. This recommendation is based on the fact that death during acute intoxication is a result of the hydrocarbon concentration in this organ inducing respiratory arrest (Shugaev, 1969). Another study reported by Shugaev (CA69: 50596u) reports higher concentrations of 1,3-butadiene in the medulla oblongata than in the cerebellum or cerebral cortex. Chronic inhalation by laboratory animals of 1,3, and 30 mg/m^3 butadiene in air resulted in functional disturbances of the central nervous system (CA75: 107777j). Rabbits anesthetized repeatedly with 20 to 25% butadiene in air reportedly regained balance and muscular control in about 2 minutes. No tissue changes were noted (Anonymous, 1963).

Chronic exposure by inhalation of 5 mg α-methylstyrene and 100 mg butadiene per m^3 air caused a decrease in cholinesterase activity in experimental animals. Acetylcholinesterase activity in rabbits administered butadiene orally for 7 months at concentrations of 0.4 mg, 4 mg, and 40 mg per kg in vegetable oil was not affected (BA52: 69712).

Acute exposure of mice to 50,000; 100,000; and 200,000 mg 1,3-butadiene per m^3 produced changes in the nervous system. Chronic exposure of rats and rabbits at concentration levels of 2200 mg/m^3 and 100 mg/m^3 also produced nervous system disorders (Batkina, 1966).

2.2.1.9 Gastrointestinal Tract

No alteration of gastric functions was reported. One study (BA53:5577) reported lymphohistiocytic infiltration of the gastrointestinal tract after a 2.5 month course of oral administration of 100 mg 1,3-butadiene/kg daily.

2.2.2 Various Metabolism Disturbances

Disturbances in vitamin metabolism were noted in one study of rats subjected to butadiene (99.8 mg/m^3) and α-methylstyrene (5.2 mg/m^3). The ascorbic acid level in the blood, liver, and brain was low as was the thiamine level in the liver and urine. Urinary excretion of riboflavin and ascorbic acid were noted (CA78: 106680x).

Rabbits given oral doses of 40 mg 1,3-butadiene per kg in vegetable oil showed an increase in fructose 1,6-diphosphate aldolase activities (BA52: 69712).

2.3 Observed Effects on Humans

Industry workers are exposed to mixtures of butadiene, styrene, chloroprene, dimethyl dioxane, α-methyl styrene, catalysts, hydrogen sulfide, carbon monoxide, acrylonitrile, acrolein, aromatic amines, ammonia and/or mixtures of saturated or unsaturated hydrocarbons, through either direct contact or inhalation. Thus, observed effects cannot usually be attributed solely to butadiene. Observed effects on humans are described in terms of organs and organ systems in this section.

2.3.1 Circulatory System

Workers exposed to butadiene, styrene, and ethylbenzene for eight years exhibited dystrophic changes in the myocardium affecting contractile activity, symptoms of hypotension, and changes in capillary resistance (CA81:140347r). A hypotensive effect was also noted in workers exposed to a butadiene-styrene mixture under clinical and subclinical conditions (CA61:1169h).

Persons working with styrene, ethylbenzene, and 1,3-butadiene showed symptons of an increase in capillary permeability and a high resistance to blood flow as compared to control subjects (CA70:80662a). A study of 60 persons employed in the synthetic rubber industry showed that prolonged contact with styrene, butadiene, and ethylbenzene decreased capillary stability. Changes were noted in pictures obtained with a capillaroscope (CA81:67974m). Sixty butyl rubber workers in contact with butadiene, styrene, and ethylbenzene were studied using electrocardiograms and ballistocardiograms. The results were compared with those for a group of persons having no contact with the hydrocarbons. A deviation in the heart contraction function was noted in the rubber workers as compared to those in the

the control group; however, the deviations did not exceed physiological norms. Changes were noted in the phase structure of the systole, but no changes were noted in contraction of the myocardium (CA81:67973k).

Functional disorders of the cardiovascular system resulted from prolonged exposure to α-methylstyrene and butadiene in rubber production workers (CA81:140388e). Sixty petroleum industry employees having prolonged contact with styrene, butadiene, and ethylbenzene were compared to a group having no hydrocarbon contact. Oscillograms were obtained and analyzed to determine hydrocarbon effect on vascular tonus. The tonus of the peripheral vascular system was lower in exposed persons than for the control group and was distinctly unsymmetrical in exposed persons (CA81:67971h).

Batkina studied synthetic rubber workers in the butadiene separation and purification area who had been exposed to more than 100 mg/m^3 of butadiene vapor for prolonged periods. Other unsaturated hydrocarbons were present in insignificant concentrations. One hundred workers were given periodic medical examinations over a 10-15 year period. A tendency toward hypotension was noted (Batkina, 1966).

Three hundred sixty-five persons employed for three years in a chemical factory were exposed to the combined effects of benzene, cyclohexane, and butadiene. The toxicity of the chemicals was studied with attention to the age of the workers. They were described in three age groups: Group 1 was comprised of 67 subjects aged 18 to 21; group 2 had 122 members aged 22 to 25; and group 3 had 176 members aged 26 to 35. Toxic effects were ascribed to the presence of benzene because its MAC was exceeded most frequently. Butadiene concentration was considerably below its MAC. Low blood pressure and changes in vascular tone were noted with a larger percentage of cases being reported among group 1 workers than in other groups (Doskin, 1971).

Angina was prevalent among workers in synthetic rubber production (CA80:63401d).

2.3.2 Hematopoietic Organs, Formed Elements, and Plasma

Workers in a vulcanization plant were exposed to vapors containing 32 to 40 mg/m^3 of butadiene mixed with styrene, oil aerosol, formaldehyde, methanol, sulfur dioxide, acrolein, aromatic amines, ammonia, acrylic acid nitrile, and carbon monoxide. Vulcanization operators performed heavy work under conditions of high air temperature, radiant heat, and noise. Investigation of these workers showed decreases in hemoglobin, red blood cell count, reticulocytes, and thrombocytes in peripheral blood. These changes were ascribed to the presence of styrene and "other components of the mixture" (Volkova and Bagdinov, 1969).

Toxic effects on the blood of chemical plant workers in three age groups described in Section 2.3.1 were studied in detail. Again, the effects were ascribed to benzene rather than to butadiene or cyclohexane which were present in lower concentrations. Blood counts and tests of the functional state of circulating leukocytes and medullary hematopoiesis were performed. Healthy new employees provided hematological data for the control group. Noted hematological disturbances included thrombocytopenia, disturbed erythropoiesis, and normochromic anemia with a tendency toward hyperchromia after one year of employment. When benzene concentrations were reduced to the MAC, normal to high RBC levels occurred.

White blood cell changes included leukocytosis followed by leukopenia, lymphocytocis, and disturbed phagocytic capacity of neutrophils (deterioration in functional capacity of granulocytes).

Investigations of medullary hematopoiesis indicated an intensified proliferation of medullary elements (myelokaryocytes). The content of reticular cells and lymphocytes was high in the marrow tissue. Again, hematological alterations occurred most frequently among group 1 (younger) workers (Doskin, 1971, CA74:57085p).

The butadiene production workers studied by Batkina who were exposed to butadiene concentrations greater than 100 mg/m^3 with insignificant amounts of other hydrocarbons showed blood changes. Leukopenia, an increase in erythrocyte sedimentation rate, and decrease in hemoglobin were reported. Decreases in phagocytic activity of neutrophils were also noted (Batkina, 1966).

The blood of rubber production workers exposed to styrene and butadiene concentrations exceeding the MAC was found to contain increased cholesterol and lecithin. The content of β-proteins was increased while that of α-lipoproteins was decreased. The fraction of globulin was increased, while blood serum albumins were decreased (CA81:67970g, CA80:40675g). A drop in blood albumins and an increase in γ- and β-globulins were also noted in clinical studies with styrene-butadiene mixtures. Styrene-butadiene rubber workers showed changes in peripheral blood including leukopenia, lymphocytosis, thrombocytopenia, and reticulocytosis (CA61:1169h).

The toxic effects of 1,3-butadiene and α-methylstyrene in peripheral blood of 1406 synthetic rubber production workers have been studied. Results were compared with a control group of 200 civil engineering employees having no chemical contact. Noted changes included increased hemoglobin and erythrocytes, decreased color index, leukocytosis, eosinophilia, neutropenia, relative lymphocytosis, monocytosis, both increased and decreased thrombocytes, and a decrease in intracellular content of glycogen, lipids, and peroxidase in leukocytes (CA78:88310v).

2.3.3 Liver

Clinical studies of the chronic effect of a mixture of butadiene and styrene on healthy workers indicated that 35 percent showed liver enlargement and a decrease in functional tests (CA61:1169h). Workers employed in synthetic rubber production showed positive reactions for antihepatic antibodies indicating pathological changes which can be used for diagnoses of early toxic liver disorders (CA80:633902).

The relationship between the excretory function of the liver and the secretory function of the stomach in workers exposed to butadiene and styrene in synthetic rubber production was investigated. While marked suppression of liver function was noted, there was no parallelism between liver test factors and stomach secretory function (CA80:148759b).

Liver and bile duct diseases were observed among workers in synthetic rubber plants where styrene and butadiene concentrations were from 20 to 100 and 85 to 93 mg/m^3, respectively, in 1960. Both concentrations were reduced to below 20 mg/m^3 by 1970 (CA80:136939x). Volkova and Bagdinov reported that styrene and butadiene "have a selective effect" on diseases of the liver and bile duct. The incidence of such diseases was found to be

7.6 cases per 100 workers exposed to vulcanization gases containing butadiene, styrene, and many other impurities (Volkova and Bagdinov, 1969).

2.3.4 Kidneys

Kidney malfunctions were reported to be prevalent in workers involved in monomer production and in isolation of synthetic rubber from reaction products. Catalysts were reported to produce such toxic effects (CA80:63401d).

2.3.5 Respiratory System

Butadiene-styrene mixtures were reported to cause lariyngotrachyitis and sometimes bronchitis among healthy workers studied under clinical conditions (CA61:1169h). Acute catarrh of the upper respiratory tract occurred often among workers in a synthetic rubber plant with chronic exposure to butadiene and styrene (CA80:63401d). Chronic exposure produced increasing tendency toward pathological changes in the upper respiratory tract (CA80:136939x).

An investigation of chemical hazards in the braided hose department of Gates Rubber Company was performed. The study included sampling and analysis of ambient air for 1,3-butadiene. Sampling was conducted on two days, and the concentration of butadiene was below the detection limit of the gas chromatographic method used. Other chemicals in use included styrene, isocyanates, resorcinol, vinyl pyridine, and formaldehyde. Approximately 2200 types of hose are produced in small lots in the work area and 540 chemicals are employed. A medical evaluation of employees included completion of a questionnaire by seventeen persons. A significant number of respondents reported cough, runny nose and sore throat. It was concluded that there was sufficient evidence to indicate a hazard for upper respiratory tract irritation most likely associated with styrene, butadiene, vinyl pyridine, resorcinol or a combination of these (Gunter and Lucas, 1973).

Medical examinations of vulcanization workers exposed to butadiene, styrene and numerous other contaminants were performed. Investigations indicated that 26.6 percent of diseases resulting in absenteeism involved influenza and catarrh of the upper respiratory tract and 10.9 percent involved tonsillitis. Thirty-three percent of the workers examined exhibited subatrophic mucosal changes in the nose, throat and larynx. The extent of such disorders was related to length of employment. Olfactory perception was altered and a high incidence of hyposmia (decreased sensitivity to odors) was noted (Volkova and Bagdinov, 1969).

A statistical treatment of medical records of rubber plant workers indicated a marked rate of increase in respiratory diseases with years of service (CA82:47351y).

2.3.6 Skin

The vulcanization workers described previously (Volkova and Bagdinov, 1969) had abnormally dry palms with superficial cracks. Pyoderma was noted in 15.2 percent of workers due partly to constant friction of skin against rubber articles.

Three cases of urticaria were noted among the workers in the braided hose department of Gates Rubber Company. The incidence was thought to be abnormally high. The possibility that it resulted from chemical substances in the working environment was acknowledged. Nearly half of the employees related problems of subsiding dermatitis (Gunter and Lucas, 1973).

Medical records of 679 workers in a synthetic rubber plant were analyzed in two groups. One group contained workers in contact with styrene, butadiene, butane, butylene, benzene, H_2SO_4, and catalysts. The other group contained workers with no contact with chemicals. Group 1 had 21.7 percent skin diseases and tuberculosis, while the second group had only 3.3 percent (CA82:47350x).

Workers in a synthetic rubber plant exposed to air containing α-methylstyrene, dodecylmercaptan, Neozone D, and butadiene in concentrations exceeding the MAC were affected with dermatosis (CA81:110878x).

2.3.7 Eyes

Sensitivity of the human eye was investigated in studies to determine the upper limit for a single exposure to butadiene. Increased sensitivity was noted at concentrations of 4.0 mg/m^3 but not at 3.6 mg/m^3 (CA69:12741e).

Workers in the braided hose department of Gates Rubber Company are routinely exposed to numerous chemicals, one of which is butadiene. Burning, itching, red eyes were job-related symptoms indicated in employee questionnaires. Viral or allergic conjunctivitis and corneal ulceration were observed, but it is not clear that these problems were caused by exposure to butadiene. Industrial hygienists concluded that a hazard responsible for eye irritation existed in the work area (Gunter and Lucas, 1973).

Conjunctivitis was noted as an effect of exposure to butadiene and styrene mixtures in clinical tests on healthy workers in synthetic rubber production (CA61:1169h).

2.3.8 Nervous System

In a study of vulcanization workers exposed to styrene, butadiene, oil fog, formaldehyde, methanol, hydrogen sulfide, acrolein, aromatic hydrocarbons, ammonia, acrylonitrile, and carbon monoxide, styrene vapor was found to be the product most frequently present in concentrations exceeding the MAC in breathing zones. The increase in time expenditure and the percentage of errors in the execution of tests attested to the effect of the "complex of unfavorable factors" on the state of the central nervous system (the attention function). The effect was more pronounced in the case of workers who had been employed for a longer time. Studies of workers exposed to complex mixtures containing 30-40 mg/m^3 of butadiene and 10-20 mg/m^3 of styrene and working under conditions of high temperature suggested strain on the thermoregulatory system and disturbances in the function of the olfactory analyser. Raised olfactory thresholds and a high incidence of hyposmia were reported. Diseases of the peripheral nervous system inlcuding radiculitis, neuralgia, and lumbago caused 17.6 percent of the cases of absenteeism among the vulcanization operators in 1966 (Volkova and Bagdinov, 1969).

Doskin studied chemical plant workers exposed to benzene levels exceeding the MAC and butadiene and cyclohexane at concentrations below the MAC. He reported that workers in the youngest of three age groups had most frequent complaints of neurological disorders such as asthenovegetative syndrome (Doskin, 1971).

In tests to determine the upper limit for a single exposure of butadiene, the odor threshold value was found to be 4 mg/m^3. Electroencephalograms showed an effect at concentrations of 3 mg/m^3 (CA69:12741e).

Clinical data on 679 synthetic rubber plant workers for a ten-year period were analyzed to determine disease rate. Diseases of the nervous system were found in 44.5 percent of workers exposed to butadiene, styrene, butane, butylene, benzene, H_2SO_4 and catalysts. Only 26.7 percent of plant workers having no contact with the compounds had nervous system diseases (CA82:47350x).

Synthetic rubber production workers exposed to butadiene and styrene, styrene alone, chloroprene, mixtures of saturated and unsaturated hydrocarbons, dimethyl dioxane, and α-methylstyrene manifested symptoms of narcosis on a background of asthenic and neurasthenic reactions (CA61:1169h).

Workers in shops producing latex and in shops recovering SKMS-30 rubber were exposed to 1,3-butadiene and α-methylstyrene. An adverse effect on the nervous system was noted, but the type of effect was not described in the abstract. Workers reacted differently to the action of the gas and some showed asthenia. Changes were observed to be transient (CA78:88318d).

2.3.9 Gastrointestinal Tract

A significantly higher incidence of diseases of the digestive organs was reported in a study of synthetic rubber plant workers in Russia exposed to styrene, butadiene, butane, butylene, benzene, H_2SO_4, and various catalysts when compared to workers not having contact with those substances. The group studied included a total of 679 workers. Digestive system disease occurred in 66.6 percent of the exposed group as opposed to 33.3 percent in the group not exposed (CA82:47350x).

An antacid condition which was resistant to histamine treatment was noted by Russian researchers in 68 of 130 subjects exposed to butadiene and styrene. Five of thirty control subjects exhibited antacid conditions which responded readily to histamine treatment. Significant stomach disorders are attributed to exposure to these hydrocarbon substances (CA74:138804z).

Russian researchers unsuccessfully attempted to relate liver test factors to stomach secretory function in synthetic rubber workers exposed to butadiene and styrene. Hypoacidic, normacidic, and hyperacidic stomach conditions were mentioned with no indication of frequency of occurrence or cause of the conditions (CA80:148759b).

Observations of healthy synthetic rubber plant workers under clinical and subclinical conditions revealed a hypotensive effect causing alterations in the gastrointestinal tract in the form of hypacid and anacid gastritis (CA61:1169h).

2.3.10 Endocrine System

Functional changes in the endocrine glands of 70 workers in the synthetic rubber industry have been attributed both to the prolonged effect of butadiene and styrene and to an upset in the nervous control of endosecretion. Functional changes occurred primarily in the adrenal, thyroid, and pancreas of workers with a history of upsets of the endocrine system (CA73:107692m, CA72:11080p).

3.0 Environmental Aspects

This section summarizes information concerning reported environmental levels of 1,3-butadiene and the chemical behavior of the compound in air and water.

3.1 Occurrence

Table 1 summarizes data on the occurrence and reported levels of butadiene in environmental samples. The abstracts of sources in Russian provided data on butadiene levels in work areas. These were often described in terms of the maximum allowable concentration (MAC) which was 100 mg/m^3 in 1966. However, a study published in that year indicated that 10 mg/m^3 would be a more effective MAC (Batkina, 1966). From Table 1 it is apparent that the butadiene concentration in the air in work areas in Russian factories without emission controls exceeded 100 mg/m^3. Butadiene levels in the air in the braided hose department of the Gates Rubber Company were reported in 1973 to be below 1000 ppm on two occasions on which sampling occurred (Gunter and Lucas, 1973).

Data on levels of butadiene in point source emissions were not found. An abstract describing combustion gases from burning butadiene copolymers did not mention the presence of butadiene. Butadiene is present in cigarette smoke (Osborne, 1956) and gasoline vapors (Stephens and Burleson, 1967). Quantitative data on butadiene concentration in automobile exhaust were not found; however, Altshuller described the rate of butadiene disappearance in irradiated exhaust samples (Altshuller et al, 1962).

Table 1 shows that butadiene levels in urban ambient air are well described in the literature. The concentration

Table 1. REPORTED OCCURRENCE AND LEVELS OF 1,3-BUTADIENE IN THE ENVIRONMENT

Sample Descriptions	Reported Butadiene Concentration	Remarks	Reference
Cigarette Smoke	$0.1\text{-}0.3 \times 10^{-2}$ cc/puff		Osborne, 1956
Stack gases from laboratory combustion of copolymers containing butadiene		Butadiene was not mentioned in the abstract	CA60:69398
Air in factory containing emissions from polymer-modified concrete (SKS-65GP latex)		Butadiene was present	CA77:029900
Air in shoe factories in areas where SKS-30 latex materials are worked		Butadiene was observed	CA78:47439a
Ambient air at sites located 2000 to 8000 meters from synthetic rubber plant	Butadiene concentration exceeded maximum allowable concentration (MAC) by a factor of 5 to 10.	The MAC was not given in the abstract	CA80:40656b
Air in synthetic rubber rubber plants	85-93 mg/m^3 in 1960 5-20 mg/m^3 in 1970		CA80:136939x
Air in dimethyl terephthalate manufacturing facility in winter	0.7 to 1.7 mg/m^3		CA81:175496r
Air in rooms with butadiene-styrene rubber floor covering	The butadiene concentration was found to be above the MAC		CA76:76122f
Butadiene separation and purification facility in synthetic rubber plant	>100 mg/m^3		Batkina, 1966
Ambient air in Santiago, Chile		Butadiene was not present	CA62:15336d
Early morning ambient air in Riverside, California	2-9 ppb		Stephens and Burleson, 1967

Table 1 (Continued). REPORTED OCCURRENCE AND LEVELS OF 1,3-BUTADIENE IN THE ENVIRONMENT

Sample Descriptions	Reported Butadiene Concentration	Remarks	Reference
Ambient air during air pollution episode in afternoon	up to 0.7 ppb		Stephens and Burleson, 1967
Ambient air in Los Angeles, California	0.004 ppm		Glasson and Tuesday, 1970
Air in workshops where polyester resins are used as binders in plastic production		Butadiene concentration was measured but not reported in the abstract	CA81:175460z
Air in vicinity of synthetic rubber plant		Butadiene was monitored. The concentration was not reported in the abstract	CA82:76697w
Air in working premises of plants for production of butadiene-acrylonitrile rubber	0.01 to 0.0009 mg/1		CA55:23883a
Air in working areas at a plant for manufacturing SKMS-30 rubber		Butadiene was measured. Specific results were not given in the abstract. The MAC was exceeded for some compounds in 40% of the samples	CA75:112601b
Air in working areas of butadiene-α-methylstyrene rubber plant	Butadiene concentration exceeded the MAC by a factor of 1.5 to 3.0		CA76:37127s
Ambient air in downtown Los Angeles and Azusa, California	1-2 ppb (avg)		Altshuller, et al, 197
Gasoline vapor	0.001 ppm		Stephens and Burleson 1967

depends on the time of day and is generally below 10 ppb. Butadiene levels in ambient air near a rubber manufacturing plant have been measured (CA80:40656b) but not reported in English.

3.2 Reactivity

At ambient conditions butadiene is a colorless gas. It is easily liquefied and is stored under pressure or at temperatures below 35°F. Butadiene is soluble in organic solvents. The solubility in water is $735 g/10^6 g$ water (McAuliffe, 1966). The compound is highly reactive, and both gas and liquid are highly flammable. Inhibitors must be added to the pure material to prevent polymerization and explosive peroxide formation. Flammable and explosive limits in air are described in the literature (Osugi, et al, 1965; Hawley, 1971). Table 2 gives some physical properties.

Table 2. PHYSICAL PROPERTIES OF 1,3-BUTADIENE

Boiling point	-4.41°C
Specific gravity of liquid at 20°C	0.6211
Vapor pressure at 0°C	17.65 psia

The chemcial behavior of butadiene in the atmosphere is well described in the literature. However, very little data were found describing its presence and reactivity in aqueous waste streams. Recent studies on pollution control in the synthetic rubber industry contained no data on the concentration of butadiene in aqueous waste streams (Sittig, 1975). A high chemical oxygen demand (COD) level was noted for raw waste from the industry, while biochemical oxygen demand (BOD) was reported to be much lower. Organic constituents in the wastewaters were reported to be resistant to biological oxidation (Sittig, 1975).

Wastewaters from the Hüls Chemical Works, at which a variety of chemicals were produced, were reported to contain butadiene and other organics (CA49:11216b). The aqueous wastes could not be treated biologically. Wastes containing butadiene were steam treated and filtered through flue ash in a test program. Color and odor were removed and the permanganate demand was reduced. It was reported that soot contained in the ash promoted butadiene polymerization. The polymerization rate was enhanced by the addition of lime. A butadiene removal method was devised consisting of steam treatment, mixing of the waste with another waste stream containing lime, and addition of soot sludge. Effluent from this treatment method contained no butadiene.

Table 3, which describes waste from a butadiene production plant, contains data on total organic carbon (TOC) and COD. Both of these parameters could be a measure of the level of butadiene in the wastewater. However, butadiene concentrations were not reported.

Table 3. COMPOSITION OF WASTE FROM A BUTADIENE PLANT[a]
(Gloyna and Ford, 1970)

pH	8 - 9
TOD	100 - 200 g/m^3
filtered COD	200 - 375 g/m^3
suspended solids	200 - 500 g/m^3
total solids[b]	3000 - 4000 g/m^3

[a] Flow rate 0.417 m^3/Mg (100 gal/ton of product)
[b] Mostly sulfates and chlorides

Butadiene reactivity in the atmosphere has been studied because hydrocarbons are involved in the production of the strongly oxidizing compounds which are the constituents of photochemical smog. Hydrocarbons react with nitric oxide and oxygen species in photochemical reactions which produce peroxyacetyl nitrates, nitrogen dioxide, ozone, and oxidized forms of the hydrocarbons (EPA, 1975). Hydrocarbons vary in their degree of reactivity in atmospheric oxidation reactions, depending on their chemical structure. Olefins are the most reactive followed by aromatics, paraffins, and naphthenes (CA59:8038f). Olefins are so reactive that their residence time in the atmosphere is short (CA62:15336d; Stephens, 1966). Reaction occurs at the double bond to form oxidation products such as aldehydes. Glasson and Tuesday measured the photooxidation rate of nitric oxide in the presence of various hydrocarbons using long-path infrared spectrophotometry. Mixtures of N_2, O_2, NO, NO_2 and butadiene were irradiated and the rate of NO_2 formation was monitored. The NO photooxidation rate at 79°F in the presence of butadiene was

4.3 ppb/min. Other olefins were more reactive than butadiene (Glasson and Tuesday, 1970b).

In another study published in 1970, Glasson and Tuesday described the effects of NO and butadiene concentration on the rate of NO thermal oxidation at 29°C. The rate constant for NO thermal oxidation in the presence of butadiene was 0.44×10^{-3}/ ppm min. Acrolein and formaldehyde were identified as NO-butadiene reaction products. The reaction of NO_2 and butadiene was also studied. The rate of decrease of NO_2 concentration in a butadiene-air mixture was measured. The rate constant for the NO_2-butadiene reaction was 0.4×10^{-4}/ppm min.

Olefin photooxidation has been studied in laboratory experiments using irradiated automobile exhaust-air mixtures. The rate of decrease of olefin concentration was measured using a wet chemical analysis (Altshuller, 1962). The rates and possible mechanisms of reactions of olefins with oxygen atoms, ozone and nitric oxide have been described (Stephens, 1966a and 1966b).

Stephens and Burleson collected air samples, subjected the samples to irradiation, and measured changes in hydrocarbon concentrations. Samples were acquired in early morning hours before natural photolysis occurred. Table 4 summarizes analytical results for butadiene. The butadiene concentration decreased to zero with UV irradiation of the sample but remained constant in the dark. Samples collected during afternoon pollution episodes contained butadiene concentrations less than 0.7 ppb (Stephens and Burleson, 1967).

Table 4. RESULTS OF UV IRRADIATION OF AMBIENT AIR CONTAINING BUTADIENE

Sample Description	Butadiene Concentration in ppb			
	Original	After 24 hr UV Irradiation	Original	After 24 hr in Dark
Ambient air, 3/10/66, 7:50-8:00 PST, heavy haze, 55-60°F	2.6	0.	2.8	2.6
Ambient air, 12/22/65, 7:40-8:00 PST, light haze, 45-50°F	9.0	0.		
Ambient air, 3/3/66, 8:05-8:25 PST, moderate haze, 40-45°F	2.4	0.	2.0	2.0

Altshuller, et al, described how olefins disappeared more rapidly in ambient air than other hydrocarbons due to their faster rate of photolysis. The butadiene concentration in ambient air was reported to decrease by a factor of three from morning to mid-afternoon (Altshuller, et al, 1971).

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