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AMBIENT WATER QUALITY CRITERIA FOR

ACROLEIN

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FOREWORD

Section 304 (a)(1) of the Clean Water Act of 1977 (P.L. 95-217), requires the Administrator of the Environmental Protection Agency to publish criteria for water quality accurately reflecting the latest scientific knowledge on the kind and extent of all identifiable effects on health and welfare which may be expected from the presence of pollutants in any body of water, including ground water. Proposed water quality criteria for the 65 toxic pollutants listed under section 307 (a)(1) of the Clean Water Act were developed and a notice of their availability was published for public comment on March 15, 1979 (44 FR 15926), July 25, 1979 (44 FR 43660), and October 1, 1979 (44 FR 56628). This document is a revision of those proposed criteria based upon a consideration of comments received from other Federal Agencies, State agencies, special interest groups, and individual scientists. The criteria contained in this document replace any previously published EPA criteria for the 65 pollutants. This criterion document is also published in satisifaction of paragraph 11 of the Settlement Agreement in Natural Resources Defense Council, et. al. vs. Train, 8 ERC 2120 (D.D.C. 1976), modified, 12 ERC 1833 (D.D.C. 1979).

The term "water quality criteria" is used in two sections of the Clean Water Act, section 304 (a)(1) and section 303 (c)(2). The term has a different program impact in each section. In section 304, the term represents a non-regulatory, scientific assessment of ecological effects. The criteria presented in this publication are such scientific assessments. Such water quality criteria associated with specific stream uses when adopted as State water quality standards under section 303 become enforceable maximum acceptable levels of a pollutant in ambient waters. The water quality criteria adopted in the State water quality standards could have the same numerical limits as the criteria developed under section 304. However, in many situations States may want to adjust water quality criteria developed under section 304 to reflect local environmental conditions and human exposure patterns before incorporation into water quality standards. It is not until their adoption as part of the State water quality standards that the criteria become regulatory.

Guidelines to assist the States in the modification of criteria presented in this document, in the development of water quality standards, and in other water-related programs of this Agency, are being developed by EPA.

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ACROLEIN

CRITERIA

Aquatic Life

The available data for acrolein indicate that acute and chronic toxicity to freshwater aquatic life occur at concentrations as low as 68 and 21 µg/l, respectively, and would occur at lower concentrations among species that are more sensitive than those tested.

The available data for acrolein indicate that acute toxicity to saltwater aquatic life occurs at concentrations as low as 55 µg/l and would occur at lower concentrations among species that are more sensitive than those tested. No data are available concerning the chronic toxicity of acrolein to sensitive saltwater aquatic life.

Human Health

For the protection of human health from the toxic properties of acrolein ingested through contaminated aquatic organisms, the ambient water criterion is determined to be 320 µg/l.

For the protection of human health from the toxic properties of acrolein ingested through contaminated aquatic organisms alone, the ambient water criterion is determined to be 780 µg/l.

INTRODUCTION

Acrolein has a wide variety of applications. It is used directly as a biocide for aquatic weed control; for algae, weed, and mollusk control in recirculating process water systems; for slime control in the paper industry; and to protect liquid fuels against microorganisms. Acrolein is also used directly for crosslinking protein collagen in leather tanning and for tissue fixation in histological samples. It is widely used as an intermediate in the chemical industry. Its dimer, which is prepared by a thermal, uncatalyzed reaction, has several applications, including use as an intermediate for crosslinking agents, humectants, plasticizers, polyurethane intermediates, copolymers and homopolymers, and creaseproofing cotton. The monomer is utilized in synthesis via the Diels-Alder reaction as a dienophile or a diene. Acrolein is widely used in copolymerization, but its homopolymers do not appear commercially important. The copolymers of acrolein are used in photography, for textile treatment, in the paper industry, as builders in laundry and dishwasher detergents, and as coatings for aluminum and steel panels, as well as other applications. Hess, et al. (1978) described marketing aspects of acrolein. In 1975, worldwide production was about 59 kilotons. Its largest market was for methionine manufacture. Worldwide capacity was estimated at 102 kilotons/year, of which U.S. capacity was 47.6 kilotons/year.

Acrolein (2-propenal) is a liquid with a structural formula of $CH_2 = CHCHO$ and a molecular weight of 56.07. It melts at -86.95°C, boils at 52.5 to 53.5°C, and has a density of 0.8410 at 20°C (Weast, 1975). The vapor pressure at 20°C is 215 mm Hg, and its water solubility is 20.8 percent by weight at 20°C (Standen, 1967).

A flammable liquid with a pungent odor, acrolein is an unstable compound that undergoes polymerization to the plastic solid disacryl, especially under light or in the presence of alkali or strong acid (Windholz, 1976). It is the simplest member of the class of unsaturated aldehydes, and the extreme reactivity of acrolein is due to the presence of a vinyl group ($H_2C{=}H-$) and an aldehyde group on such a small molecule (Standen, 1967). Additions to the carbon-carbon double bond of acrolein are catalyzed by acids and bases. The addition of halogens to this carbon-carbon double bond proceeds readily (Standen, 1967).

Acrolein can enter the aquatic environment by its use as an aquatic herbicide, from industrial discharge, and from the chlorination of organic compounds in wastewater and drinking water treatment. It is often present in trace amounts in foods and is a component of smog, fuel combustion, wood, and possibly other fire, and cigarette smoke. An evaluation of available data indicates that, while industrial exposure to manufactured acrolein is unlikely, acrolein from nonmanufactured sources is pervasive. Acrolein exposure will occur through food ingestion and inhalation. Exposure through the water or dermal route is less likely. However, analysis of municipal effluents of Dayton, Ohio showed the presence of acrolein in 6 of 11 samples, with concentrations ranging from 20 to 200 µg/l (U.S. EPA, 1977).

Bowmer, et al. (1974) described the loss of acrolein by volatilization and degradation in sealed bottles and tanks of water. The amounts of acrolein dissipated after eight days were 34 percent from the tank and 16 percent from the bottles. The rate of disappearance of acrolein in the tank was 0.83 day^{-1} at a pH of 7.2. The lack of turbulence in the tank reduced acrolein loss by volatilization to 1/20 of what would be expected if volatilization were controlled only by resistance in the gas phase and any dis-

crete surface layers. The authors agree with Geyer (1962), who states that the primary degradation reaction is reversible hydrolysis to β-hydroxypropionaldehyde, which is less volatile than acrolein.

The fate of acrolein in water was observed in buffered solutions and in natural channel waters (Bowmer and Higgins, 1976). An equilibrium between dissipating acrolein and degradation products was reached in the buffered solution following dissipation of 92 percent of the acrolein, but in natural waters there was no indication of an equilibrium, with the dissipating reaction apparently being continued to completion. In natural waters, the accumulation of a reaction (degradation) product was greater at higher initial acrolein concentration, and decay was rapid when acrolein concentrations fell below 2 to 3 mg/l. The initial period of slow decline preceding the rapid dissipation period is thought to be the result of microbiological processes. Unlike earlier works (Bowmer, et al. 1974), there was an 8- to 10-fold increase in the observed dissipation rate as compared to the expected rate in two of four flowing water channels, suggesting major losses in volatilization and absorption.

REFERENCES

Bowmer, K.H. and M.L. Higgins. 1976. Some aspects of the persistence and fate of acrolein herbicide in water. Arch. Environ. Contam. 5: 87.

Bowmer, K.H., et al. 1974. Loss of acrolein from water by volatilization and degradation. Weed Res. 14: 325.

Geyer, B.P. 1962. Reaction with Water. In: C.W. Smith (ed.), Acrolein. John Wiley and Sons, Inc., New York.

Hess, L.B., et al. 1978. Acrolein and Derivatives. In: A. Standen (ed.), Kirk-Othmer Encyclopedia of Chemical Technology. 3rd ed. Interscience Publishers, New York.

Standen, A. (ed.) 1967. Kirk-Othmer Encyclopedia of Chemical Technology. Interscience Publishers, New York.

U.S. EPA. 1977. Survey of two municipal wastewater treatment plants for toxic substances. Wastewater Res. Div. Municipal Environ. Res. Lab., Cincinnati, Ohio.

Weast, R.C. (ed.) 1975. Handbook of Chemistry and Physics. 56th ed. CRC Press, Cleveland, Ohio.

Windholz, M. (ed.) 1976. The Merck Index. 9th ed. Merck and Co., Inc., Rahway, New Jersey.

Aquatic Life Toxicology*

INTRODUCTION

Much of the data concerning the effects of acrolein on freshwater aquatic organisms has been determined using static test conditions with unmeasured concentrations. Consequently, these data may underestimate the toxicity of this volatile, unstable chemical. The study of Bond, et al. (1960) showed acrolein to have a substantially greater acute toxicity to fish than the 14 other herbicides tested. This relationship is also seen in a toxicity bibliography of five herbicides (Folmer, 1977).

Acrolein has been applied directly to the saltwater environment to control fouling organisms in cooling water systems of coastal power plants. The data base for toxicity of acrolein is limited to the results of acute exposures of one fish and three invertebrate species, performed with unmeasured test concentrations.

EFFECTS

Acute Toxicity

The data base for freshwater invertebrate species is limited to two values for Daphnia magna. The reported 48-hour values from static tests with unmeasured concentrations are 57 and 80 µg/l (Table 1).

Three 96-hour LC_{50} values are reported for two freshwater fish species, bluegill and largemouth bass, both in the family Centrarchidae. These results were also obtained from static tests with unmeasured concentrations.

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*The reader is referred to the Guidelines for Deriving Water Quality Criteria for the Protection of Aquatic Life and Its Uses in order to better understand the following discussion and recommendation. The following tables contain the appropriate data that were found in the literature, and at the bottom of each table are calculations for deriving various measures of toxicity as described in the Guidelines.

Ninety-six-hour values of 90 and 100 µg/l for bluegill and 160 µg/l for largemouth bass have been reported (Table 1).

Based on only two fish species, no conclusion can be drawn regarding the relative species sensitivity to acrolein. Also because of a paucity of data, no comparison of relative sensitivity between freshwater invertebrate and fish species can be made.

Among the tested saltwater species, the eastern oyster was most sensitive with a 96-hour EC_{50}, based on decreased shell growth, of 55 µg/l, (Table 1). Tests with other species (Table 5) were conducted for less than the standard testing times for those species or life stages.

Chronic Toxicity

The chronic toxicity data base consists of one value for fish and one for invertebrate species.

Macek, et al. (1976) conducted the only freshwater invertebrate chronic test. Based on the cumulatively reduced survival of Daphnia magna through three generations, a chronic value of 24 µg/l is obtained (Table 2). The acute value for this species by the same investigator is 57 µg/l and this results in an acute-chronic ratio of 2.4. These data show that there is little difference in concentrations between the acute and chronic effects of acrolein on Daphnia magna.

A life cycle test with the fathead minnow, also conducted by Macek, et al. (1976), resulted in a chronic value of 21 µg/l (Table 2). Survival of newly-hatched second generation fathead minnow fry was significantly reduced at 41 µg/l but was not significantly different from control survival at 11 µg/l. A dilutor malfunction killed or severely stressed the fish at an intermediate concentration, 21 µg/l, so no second generation fish were produced. Although no 96-hour LC_{50} for this species is available, a 6-day

incipient LC_{50} for fathead minnows of 84 µg/l was reported by the same authors using a flow-through test with unmeasured concentrations (Table 5). Also, Louder and McCoy (1962) reported a 48-hour LC_{50} of 115 µg/l for fathead minnows.

No saltwater species have been tested to evaluate chronic effects.

Species mean acute and chronic values are summarized in Table 3.

Plant Effects

Although published literature does exist describing the use of acrolein to control aquatic macrophytes and algae, no appropriate plant effect data are available. In some cases, test methods were insufficiently described to evaluate reported results. In others, because of the methods used, no actual exposure concentration under field conditions could be calculated or results were reported as control of the weeds with no quantitative measurements made.

The effects of acrolein on saltwater and freshwater plants have not been studied. Because acrolein is a herbicide, phytoxicity to aquatic species might be expected.

Residues

Bluegills exposed for 28 days to 13 µg/l of ^{14}C-acrolein bioconcentrated acrolein 344 times (Table 4). The half-life was greater than seven days. Thin-layer chromatography was used to verify concentrations.

Miscellaneous

Ninety-eight percent of adult snails and 100 percent of snail embryos died after a 24-hour exposure to 10,000 µg/l (Ferguson, et al. 1961).

Nine short-term exposures with seven fish species yielded acute toxicity values in the range of 46 to 115 µg/l (Table 5). Static tests with unmeasured concentrations were run by Bond, et al. (1960), Louder and McCoy

(1962), and Bridie, et al. (1979). The studies of Burdick, et al. (1964) and Macek, et al. (1976) were performed under flow-through conditions with unmeasured concentrations. That of Bartley and Hattrup (1975) reporting 32 percent mortality of rainbow trout in 48 hours at 48 µg/l was the only flow-through study with measured acrolein concentrations. Because of differences in test methods and the volatility of acrolein, no meaningful comparison of relative sensitivity among the fish species is possible.

The avoidance response of rainbow trout at 100 µg/l is above reported acute levels (Folmar, 1976). Folmar (1980) reported flavor impairment of rainbow trout flesh up to four days after a four-hour exposure to 90 µg/l.

Various species of aquatic weeds were damaged or destroyed following treatment with 500 to 25,000 µg/l of acrolein (Table 5).

The 48-hour LC_{50} values for three saltwater species are in the range from 100 to 2,100 µg/l with the brown shrimp being the most sensitive.

Summary

Appropriate acute freshwater toxicity data for acrolein are limited to LC_{50} values from five tests with one invertebrate and two fish species. The species mean acute values are 68 µg/l for Daphnia magna, 95 µg/l for bluegill, and 160 µg/l for largemouth bass. Because these results were all obtained from static tests with unmeasured concentrations, these data probably underestimate the toxicity of this volatile, unstable chemical.

The chronic values for acrolein, 24 µg/l for Daphnia magna and 21 µg/l for the fathead minnow, reveal similar sensitivity between these species. No 96-hour LC_{50} is available for the fathead minnow but two nonstandard tests showed acute effects at 84 and 115 µg/l. Thus, it appears that there is little difference between acute and chronic toxicity for acrolein.

CRITERIA

The available data for acrolein indicate that acute and chronic toxicity to freshwater aquatic life occur at concentrations as low as 68 and 21 µg/l, respectively, and would occur at lower concentrations among species that are more sensitive than those tested.

The available data for acrolein indicate that acute toxicity to saltwater aquatic life occurs at concentrations as low as 55 µg/l and would occur at lower concentrations among species that are more sensitive than those tested. No data are available concerning the chronic toxicity of acrolein to sensitive saltwater aquatic life.

Table 1. Acute values for acrolein

Species	Method*	LC50/EC50 (µg/l)	Species Mean Acute Value (µg/l)	Reference
		FRESHWATER SPECIES		
Cladoceran, Daphnia magna	S, U	57	-	Macek, et al. 1976
Cladoceran, Daphnia magna	S, U	80	68	U.S. EPA, 1978
Bluegill, Lepomis macrochirus	S, U	100	-	Louder & McCoy, 1962
Bluegill, Lepomis macrochirus	S, U	90	95	U.S. EPA, 1978
Largemouth bass, Micropterus salmoides	S, U	160	160	Louder & McCoy, 1962
		SALTWATER SPECIES		
Eastern oyster Crassostrea virginica	FT, U	55**	55	Butler, 1965

* S = static, FT = flow-through, U = unmeasured

** EC50: 50% decrease in shell growth of oyster.

No Final Acute Values are calculable since the minimum data base requirements are not met.

Table 2. Chronic values for acrolein (Macek, et al. 1976)

Species	Method*	Limits (µg/l)	Species Mean Chronic Value (µg/l)
	FRESHWATER SPECIES		
Cladoceran, Daphnia magna	LC	17-34	24
Fathead minnow, Pimephales promelas	LC	11-42	21

* LC = life cycle or partial life cycle

Acute-Chronic Ratio

Species	Chronic Value (µg/l)	Acute Value (µg/l)	Ratio
Cladoceran, Daphnia magna	24	57	2.4

Table 3. Species mean acute and chronic values for acrolein

Rank*	Species	Species Mean Acute Value (µg/l)	Acute-Chronic Ratio
	FRESHWATER SPECIES		
3	Largemouth bass, *Micropterus salmoides*	160	-
2	Bluegill, *Lepomis macrochirus*	95	-
1	Cladoceran, *Daphnia magna*	68	2.4
	SALTWATER SPECIES		
1	Eastern oyster, *Crassostrea virginica*	55	-

* Ranked from least sensitive to most sensitive based on species mean acute value.

Table 4. Residues for acrolein (U.S. EPA, 1978)

Species	Tissue	Bioconcentration Factor	Duration (days)
	FRESHWATER SPECIES		
Bluegill, *Lepomis macrochirus*	whole body	344	28

Table 5. Other data for acrolein

Species	Duration	Effect	Result (µg/l)	Reference
		FRESHWATER SPECIES		
Aquatic macrophytes, Najas sp., Ceratophyllum sp., and Ipomea sp.	-	Destroyed or badly scorched one week after application	25,000	Ferguson, et al. 1965
Pondweed, Potomogeton crispus	5 hrs	Decayed in 8 days	20,000	Unrau, et al. 1965
Aquatic macrophyte, Elodea densa	24 hrs	Cell deterioration	500	Van Overbeck, et al. 1959
Snail (adult), Australorbis glabratus	24 hrs	98% mortality	10,000	Ferguson, et al. 1961
Snail (embryos) Australorbis glabratus	24 hrs	100% mortality	10,000	Ferguson, et al. 1961
Chinook salmon (fingerling), Oncorhynchus tshawytscha	24 hrs	LC50	80	Bond, et al. 1960
Rainbow trout (fingerling), Salmo gairdneri	24 hrs	LC50	65	Bond, et al. 1960
Rainbow trout (fry), Salmo gairdneri	1 hr	Avoidance	100	Folmar, 1976
Rainbow trout, Salmo gairdneri	48 hrs	32% mortality	48	Bartley & Hattrup, 1975
Rainbow trout, Salmo gairdneri	4 hrs	Tainted flesh at 1 and 4 days post exposure	90	Folmar, 1980
Brown trout (fingerling), Salmo trutta	24 hrs	Mean time to death	46	Burdick, et al. 1964
Goldfish, Carassius auratus	24 hrs	LC50	<80	Bridle, et al. 1979

Table 5. (Continued)

Species	Duration	Effect	Result (µg/l)	Reference
Fathead minnow, *Pimephales promelas*	6 days	Incipient LC50	84	Macek, et al. 1976
Fathead minnow, *Pimephales promelas*	48 hrs	LC50	115	Louder & McCoy, 1962
Bluegill (fingerling), *Lepomis macrochirus*	24 hrs	Mean time to death	79	Burdick, et al. 1964
Mosquitofish, *Gambusia affinis*	48 hrs	LC50	61	Louder & McCoy, 1962
		SALTWATER SPECIES		
Barnacles (adult) *Balanus eburneus*	48 hrs	LC50	2,100	Dahlberg, 1971
Barnacles (adult) *Balanus eburneus*	48 hrs	LC50	1,600	Dahlberg, 1971
Brown shrimp (adult) *Penaeus aztecus*	48 hrs	EC50	100*	Butler, 1965
Longnose killifish (juvenile) *Fundulus similis*	48 hrs	LC50	240	Butler, 1965

* EC50 based on loss of equilibrium.

REFERENCES

Bartley, T.R. and A.R. Hattrup. 1975. Acrolein residues in irrigation water and effects on rainbow trout. Bur. Reclam. Rep. REC-ERC-75-8.

Bond, C.E., et al. 1960. Toxicity to various herbicidal materials to fishes. Biol. Problems in Water Pollut., Trans. 1959 Seminar, U.S. Dept. Health, Edu., and Welfare, PHS Tech. Rep. W60-3; 96-101.

Bridie, A.L., et al. 1979. The acute toxicity of some petro-chemicals to goldfish. Water Res. 13: 623.

Burdick, G.E., et al. 1964. Toxicity of aqualin to fingerling brown trout and bluegills. N.Y. Fish Game Jour. 11: 106.

Butler, P.A. 1965. Commercial fisheries investigations. Effects of pesticides on fish and wildlife, 1964 research findings Fish Wildl. Ser. U.S. Fish Wildl. Ser. Circ.

Dahlberg, M.D. 1971. Toxicity of acrolein to barnacles, Balanus eburneus. Chesapeake Sci. 12: 282.

Ferguson, F.F., et al. 1961. Control of Australorbis glabratus by acrolein in Puerto Rico. Public Health Rep. 76: 461.

Ferguson, F.F., et al. 1965. Preliminary field trials of acrolein in the Sudan. WHO Bull. 32:243.

Folmar, L.C. 1976. Overt avoidance reaction of rainbow trout fry to nine herbicides. Bull. Environ. Contam. Toxicol. 15: 509.

Folmar, L.C. 1977. Acrolein, dalapon, dichlobenil, diquat, and endothall: Bibliography of toxicity to aquatic organisms. U.S. Fish Wildl. Ser., Tech. Paper 88.

Folmar, L.C. 1980. Effects of short-term field applications of acrolein and 2,4-D (DMA) on flavor of the flesh of rainbow trout. Bull. Environ. Contam. Toxicol. 24: 217.

Louder, D.E. and E.G. McCoy. 1962. Preliminary investigations of the use of aqualin for collecting fishes. Proc. 16th Annu. Conf. S.E. Assoc. Game Fish Comm. p. 240.

Macek, K.J., et al. 1976. Toxicity of four pesticides to water fleas and fathead minnows: Acute and chronic toxicity of acrolein, heptachlor, endosulfan, and trifluralin to the water flea (Daphnia magna) and the fathead minnow (Pimephales promelas). U.S. Environ. Prot. Agency, EPA 600/3-76-099.

Unrau, G.O., et al. 1965. Field trials in Egypt with acrolein herbicide-molluscicide. WHO Bull. 32: 249.

U.S. EPA. 1978. In-depth studies on health and environmental impacts of selected water pollutants. U.S. Environ. Prot. Agency, Contract No. 68-01-4646.

Van Overbeck, J., et al. 1959. Acrolein for the control of water weeds and disease-carrying water snails. Science. 129: 335.

Mammalian Toxicology and Human Health Effects

INTRODUCTION

Acrolein, a colorless volatile liquid, is the simplest of the unsaturated aldehydes:

$$CH_2 = CHCHO$$

Table 1 describes its salient physical properties. Since it is a highly reactive organic chemical and capable of self-polymerization, the marketed product contains an inhibitor (0.1 percent hydroquinone) to prevent its degradation. It is extremely reactive at high pH (Hess, et al. 1978; Smith, 1962). Methods for acrolein analysis are summarized in Table 2.

The present technology for acrolein preparation employs catalytic oxidation of propene in the vapor phase. A typical reaction process consists of feeding propylene and air at 300°C to 400°C and 30 to 45 psi over the catalyst (usually of bismuth, molybdenum, or antimony) (Hess, et al. 1978).

An evaluation of available data indicates that, while industrial exposure to manufactured acrolein is unlikely, acrolein from nonmanufactured sources is ubiquitous. Acrolein exposure will occur through food ingestion and through inhalation. Exposure through the water or dermal route is unlikely. Acrolein is often present in trace amounts in foods and is a component of smog, fuel combustion, wood and possibly other fires, and cigarette smoke.

TABLE 1

Physical Properties of Acrolein*

Empirical Formula	C_3H_4O
Molecular Weight	56.06
Melting Point, ^oC	-86.95
Boiling Point, ^oC	52.69
Vapor Pressure at 20^oC, KPa (mmHg)	29.3 (220)
Refractive Index n_D (20^oC)	1.4017
Viscosity at 20^oC, cS	0.393
Solubility in Water (weight %)	20.6
Critical Properties:	
Temperature, ^oK	510
Pressure, atm.	51.58
Volume, cc/g-mole	189

*Source: Smith, 1962; Hess, et al. 1978

Table 2

Methods for Acrolein Measurement*

Analytical Method	Detection Limit	Interferences
NMR (Aldehydic proton)	100 mg/l	few
Colorimetry		
2,4-D	80 µg/l	many
4-Hexylresorcinol	700 µg/l	many
Fluorimetry		
Direct	20 mg/l	very few
J-Acid	20 µg/l	very few
m-Aminophenol derivative	10 µg/l	very few
Differential pulse Polarography	30 µg/l	few
Gas chromatography		
Flame-ionization	500 µg/l	very few
Mass spectral	50 µg/l	very few

*Source: Brady, et al. 1977; Kissel, et al. 1978; Bellar and Sigsby, 1970

EXPOSURE

Ingestion from Water

There is no evidence that acrolein is a contaminant of potable water or water supplies. Available monitoring studies have not noted its presence, and acrolein is not listed in compendia on water monitoring (Junk and Stanley, 1975; Shackelford and Keith, 1978; Abrams, et al. 1975). Investigations on the fate of acrolein in water suggest that it dissipates with a half-life of 4 to 5 hours. Based on these studies and its half-life in water (Table 3), it can be assumed that acrolein is present in water supplies in negligible amounts.

Acrolein is applied to canals as a biocide for the control of harmful organisms and aquatic weeds (Van Overbeek, et al. 1959). This application has prompted studies to delineate the amount of acrolein required to maintain effective pest control (Bowmer and Sainty, 1977; Hopkins and Hattrup, 1974). These studies have examined dilution problems and pathways for loss. Degradation and evaporation appear to be the major pathways for loss, while a smaller amount is lost through absorption and uptake by aquatic organisms and sediments. In a review of the Russian literature, Melnikov (1971) indicates that acrolein is used as a biocide in water reservoirs.

Kissel, et al. (1978) have demonstrated the analytical problems in a study of the effect of pH on the rate of degradation of aqueous acrolein. Their study compared acrolein measurement by 10 analytical techniques in six pH buffer systems (pH 5, 7, and 9).

TABLE 3

First Order Rate Constants of Acrolein Degradation in Laboratory Experiments*

Water[a]	pH	Initial Acrolein ppm	$10^3 k$ hr^{-1}	SE
Supply	7.3	8.0	23.7	2.4
Supply	7.3	6.8	15.9	2.0
Drainage	7.8	6.4	45.1	7.5
Supply	7.2	6.1	13.3	1.9
Supply	7.2	17.5	14.2	2.5
Supply	7.2	50.5	11.4	1.0
Distilled	--	6.4	2.7	0.3

*Source: Bowmer and Higgins, 1976

[a]Water from canal supply, canal drainage, or distilled water

The analytical methods were:

(a) bioassay with an ATPase enzyme system,

(b) bioassay by a plate count method,

(c) bioassay by fish kill (bluegill sunfish),

(d) chemical titration with bromide-bromate solution-iodide-thiosulfate,

(e) colorimetric by the 2,4-dinitrophenylhydrazone (DNP),

(f) fluorometric analysis (m-aminophenol) with excitation at 372 nm and emission at 506 nm,

(g) gas-liquid chromatography (on 6' Poropak Q with injection temperature of 250°C and column at 200°C),

(h) nuclear magnetic resonance using aldehyde proton at 9.44 ppm vs. tetramethylsilane,

(i) polarographic analysis,

(j) direct fluorometric analysis of acrolein with excitation at 276 nm and emission at 370 nm.

Kissel, et al. (1978) separated the analytical techniques into three groups: bioassay, derivatization, and direct measurement. Differences between bioassay methods were less than for any other group. They considered bioassay a good measure of true acrolein concentration. Some titrimetric methods were satisfactory, but others were poor. Among the direct methods, they considered that GLC and direct fluorimetry were poor, but that NMR and polarographic analyses were better methods. Kissel, et al. (1978) did not identify reasons for the large discrepancies. Also, they noted that acrolein rapidly degraded at pH 9.

Bowmer and coworkers (Bowmer and Higgins, 1976; Bowmer and Sainty, 1977; Bowmer, et al. 1974; O'Loughlin and Bowmer, 1975) have measured acrolein degradation rates in laboratory and field studies. They evaluated the possible degradation pathway in buf-

fered, distilled water. At pH 5, the acrolein reacted by a reversible hydrolysis and yielded an equilibrium mixture containing β-hydroxypropionaldehyde:acrolein in a 92:8 ratio.

$$H_2O + CH_2 = CHCHO \longrightarrow HOCH_2CH_2CHO$$

In alkali the primary reaction was consistent with a polycondensation. In natural waters they observed no evidence for an equilibrium. They considered the initial product to be from chemical degradation and suggested, but did not demonstrate, that it further degraded to a carboxylic acid via a microbial pathway. Acrolein was analyzed by colorimetry using the 2,4-DNP method and by bioassay. Results were conflicting, and they concluded that the analytic complication (as described by Kissel, et al. 1978) resulted from the ability of the hydroxypropionaldehyde to form a 2,4-DNP derivative. They resolved the analysis problem by flushing the volatile acrolein from a sample by means of an air stream, which left the nonvolatile hydroxypropionaldehyde in solution. Acrolein concentration was measured as the difference between the sum of absorbances for acrolein and 2,4-DNP in samples before and after air flushing (Bowmer, et al. 1974). Their laboratory studies utilized samples sealed in bottles and maintained at 20.6°C. Table 3 summarizes their results. The authors also examined acrolein loss in field studies, using actual irrigation channels. The apparent dissipation rate, k, was estimated at 0.16 hr^{-1}, which is about an order of magnitude faster than measured in laboratory experiments. They suggested that the difference could result in part from volatization and absorption.

Hopkins and Hattrup (1974) examined acrolein loss in field studies in canals of the Columbia River basin. Their analytical

technique was fluorometric analysis of the m-aminophenol derivative. The work of Kissel, et al. (1978), which is discussed above, suggested that this analytical method could yield higher acrolein concentrations than were actually present. Table 4 describes the acrolein concentration in a flow-plug measured during a 48-hour study period in two canals. Hopkins and Hattrup (1974) suggested that dissipation resulted from acrolein degradation, volatilization, and absorption by weed tissue.

Potable water is normally treated with a chemical oxidant, usually chlorine or less often ozone. These oxidants will react with olefins and are very likely to react with the olefinic portion of acrolein. It is likely that ozone will initially yield a malonozonide. Aqueous chlorine (which exists as HOCl) will probably degrade acrolein as follows (Hess, et al. 1978): $2(CH_2{=}CH{-}CHO) + 2(HOCl) \longrightarrow HOCH_2CHClCHO + ClCH_2CH(OH)CHO$. The relative amounts of the two possible reaction products and their degradation products are not known (Morris, 1975).

Ingestion from Food

Acrolein, at µg/g concentrations, is a common component of food. It is commonly generated during cooking or other processing and is sometimes produced as an unwanted by-product in the fermentation of alcoholic beverages. The information on acrolein in foods has been generated primarily to identify organoleptic properties, so its relevance to exposure levels is limited.

Acrolein can be produced by cooking potatoes in water. El'Ode, et al. (1966) investigated acrolein production in potato extract (Katahdin variety) and synthetic mixtures of the extract.

TABLE 4

Acrolein Dissipation in Two Canals of the Columbia River Basin Over 48 Hours*

Canal	Intended Application ppm	Sampling Point Miles Below Initial Appl. Point	Acrolein ppm
Potholes	0.14	1.0	0.14
		10.0	0.10
		12.5	0.09
	Booster application at 12.6 miles	13.5	0.20
		15.0	0.18
		20.0	0.15
		30.0	0.08
		35.0	0.05
East Low	0.11	1.0	0.09
		5.0	0.10
		10.0	0.10
		20.0	0.08
		30.0	0.06
		40.0	0.02
		64.5	0.03

*Source: Hopkins and Hattrup, 1974

The synthetic mixture contained amino acids (glycine, glutamic acid, lysine, methionine, and phenylalanine) and sugar (glucose, fructose, maltose, and sucrose). Acrolein was identified by gas chromatography (GC) as a product of heating some but not all mixtures of amino acid and sugar. They did not identify acrolein as a product of heating the actual potato extract (30 minutes at 180°C) or of heating the synthetic potato mixture (60 minutes at 100°C).

As reviewed by Izard and Libermann (1978), acrolein is generated when animal or vegetable fats are subjected to high temperatures. In these cases, acrolein is formed primarily from the dehydration of glycerol.

Kishi, et al. (1975) identified acrolein production from cooking potatoes or onions in edible oil. They detected acrolein at concentrations ranging from 2.5 to 30 mg/m^3 in the air 15 cm above the surface of the heated oil. Cooking about 20 g of potatoes or onions in the oil yielded 200 to 400 µg of acrolein. The authors did not determine whether the acrolein came from the oil, the potatoes, the onions, or from all three sources.

Hrdlicka and Kuca (1965) examined aldehydes and ketones in turkey before cooking and in volatiles produced by either boiling (3 kg in 6 l of distilled water for 3 hours) or roasting (3 kg at 170°C to 190°C for 3 hours). Raw turkey was extracted at 2°C with 75 percent ethanol for 72 hours, and volatiles were collected by vacuum distillation. Derivatives were formed from carbonyl fraction with 2,4-DNP, and these were identified by paper chromatography. Acrolein was identified in raw turkey and in the volatile products from both cooking methods.

Love and Bratzler (1966) identified acrolein in wood smoke. Samples (whole smoke and vapor phase) were collected from commercial smokehouses (operated at 48°C to 49.5°C) and from hardwood sawdust (mainly maple) burned on a hot plate (490°C to 500°C). The carbonyl compounds were trapped in 2,4-DNP solution, and the derivatives were identified by GC. Acrolein was identified in all smoke samples but was not quantified.

Levaggi and Feldstein (1970) examined acrolein concentrations in the emissions from a commercial coffee roaster. Acrolein was trapped in Greenberg-Smith impingers containing 1 percent sodium bisulfite solution and was quantified by the 4-hexylresorcinol colorimetric method. At the emission outlet (afterburner abatement device) they measured 0.60 mg/m^3 acrolein, while no acrolein was detected in the inlet air.

Boyd, et al. (1965) measured the unsaturated aldehyde fraction in raw cocoa beans and chocolate liquor. The 2-enols were measured by absorbance (at 373 nm) of its 2,4-DNP derivative. Samples were extracted with hexane and cleaned on Celite® prior to preparation of derivatives. The 2,4-DNP derivatives were separated into fractions prior to measurement. They measured 2-enol concentrations of 0.6 to 2.0 µmol/100 g fat in raw cocoa beans and 1.3 to 5.3 µmol/100 g in the chocolate liquor.

Alcoholic beverages often contain trace amounts of acrolein (Rosenthaler and Vegezzi, 1955). It is sometimes a problem since it causes an organoleptic condition called "pepper" by the alcohol fermentation industry. According to Serjak, et al. (1954), acrolein is detectable in low-proof whiskey at concentrations as low as

10 mg/l. This value probably represents the upper limit for acrolein, since industry has adapted corrective procedures to reduce "pepper" by reducing acrolein concentrations.

The chief point of entry of acrolein into the alcoholic beverages has been reported to be the mash fermentation process (Serjak, et al. 1954; Sobolov and Smiley, 1960; Hirano, et al. 1962), where if glucose levels in the mash are low, some bacterial strains convert glycerol to acrolein.

Avent (1961) investigated the contamination of a wine, which was initially acrolein-free, with 14 µg/g of acrolein. In this case, the possible source was a glycerol-impregnated oak cask.

Hrdlicka, et al. (1968) identified acrolein in the volatile fraction of a hops sample. No quantitative data were available.

Alarcon (1976a) has demonstrated the formation of acrolein from methionine, homoserine, homocysteine, cystathionine, spermine, and spermidine under conditions similar to those used in food processing (neutral pH, 100°C).

The information reviewed herein is insufficient to develop a conclusive measure of acrolein exposure in food, but it indicates that acrolein is a component of many foods and that processing can increase the acrolein content. Volatile fractions collected during cooking suggest that some acrolein would remain in the food.

A bioconcentration factor (BCF) relates the concentration of a chemical in aquatic animals to the concentration in the water in which they live. The steady-state BCFs for a lipid-soluble compound in the tissues of various aquatic animals seem to be proportional to the percent lipid in the tissue. Thus, the per capita

ingestion of a lipid-soluble chemical can be estimated from the per capita consumption of fish and shellfish, the weighted average percent lipids of consumed fish and shellfish, and a steady-state BCF for the chemical.

Data from a recent survey on fish and shellfish consumption in the United States were analyzed by SRI International (U.S. EPA, 1980). These data were used to estimate that the per capita consumption of freshwater and estuarine fish and shellfish in the United States is 6.5 g/day (Stephan, 1980). In addition, these data were used with data on the fat content of the edible portion of the same species to estimate that the weighted average percent lipids for consumed freshwater and estuarine fish and shellfish is 3.0 percent.

A measured steady-state bioconcentration factor of 344 was obtained for acrolein using bluegills (U.S. EPA, 1978). Similar bluegills contained an average of 4.8 percent lipids (Johnson, 1980). An adjustment factor of 3.0/4.8 = 0.625 can be used to adjust the measured BCF from the 4.8 percent lipids of the bluegill to the 3.0 percent lipids that is the weighted average for consumed fish and shellfish. Thus, the weighted average bioconcentration factor for acrolein and the edible portion of all freshwater and estuarine aquatic organisms consumed by Americans is calculated to be 344 x 0.625 = 215.

Inhalation

Acrolein is generated during oxidation of a variety of organic substrates. It has been noted as a combustion product of fuels and

of cellulosic materials (e.g., wood and cigarettes), as an intermediate product in atmospheric oxidation of propylene, and as a component of the volatiles produced by heating organic substrates. Actual exposure will depend on general environmental conditions and specific behavior patterns. Thus, total inspiration is the sum of acrolein inhalations from the ambient air, from local air (e.g., occupational considerations, vehicular considerations, side-stream smoke from cigarettes), and from cigarette smoke.

Acrolein as a component of urban smog has been measured in the atmosphere of Los Angeles (Renzetti and Bryan, 1961; Altshuller and McPherson, 1963). Renzetti and Bryan collected ambient air in 1960 using a series of vapor traps containing SD-3A alcohol and quantified acrolein by absorbance of the 4-hexylresorcinol-mercuric chloride-trichloroacetic acid derivative (605 nm). Altshuller and McPherson (1963) also examined the atmosphere in 1961, but collected samples in bubblers containing the 4-hexylresorcinol reagent; their results were similar to those of Renzetti and Bryan (1961). For 10 days during the period from September through November 1963, Altshuller and McPherson found that acrolein averaged 0.012 mg/m^3 with a peak concentration of 0.025 mg/m^3, whereas Renzetti and Bryan found that acrolein concentrations for seven days of this period in 1961 averaged 0.018 mg/m^3 and peaked at 0.030 mg/m^3. For all of 1961, acrolein averaged 0.016 mg/m^3 and peaked at 0.032 mg/m^3.

Graedel, et al. (1976) developed a mathematical model for photochemical processes in the troposphere. They combined chemical

kinetic measurements and assumed values, time-varying sources of trace contaminants, solar flux variations, bulk air flow, and a geographical matrix of "reaction volumes" for Hudson County, N.J. Their computed peak acrolein concentration was 0.03 mg/m^3. They did not account for other sources of acrolein or for any degradation pathway (McAfee and Gnanadesikan, 1977). That their calculated value favorably compared with the peak values measured in Los Angeles (0.025 to 0.032 mg/m^3) could be due to an artifact.

Trattner, et al. (1977) suggested that enols are present in the air of a subway system. They were measuring airborne particulates by an infrared technique. Samples were collected on a cascade impactor containing a 0.313 μ back-up filter. Potassium bromide pellets were prepared from each sample fraction. Evidence for the presence of unsaturated aldehydes were the weak maxima observed at 1,695 cm^{-1} (6.90 μ) in the pellets prepared from final impactor and backup filter samples. The authors made no quantitative assessment.

Acrolein is a common constituent of vehicle exhaust (National Academy of Sciences (NAS), 1976; Tanimoto and Uehara, 1975). The exact concentration depends upon the type of gasoline, engine, and operating conditions. Acrolein concentrations have been measured by a variety of methods, and the consensus of the studies suggests that the acrolein concentration usually does not exceed 23 mg/m^3. Acrolein has been measured in emissions of diesel engines at 6.7 mg/m^3 and in the emissions of internal combustion engines at 6.0, 22.5, 16.1, 14.7, and about 11.5 mg/m^3 (NAS, 1976). Day, et al. (1971) reported acrolein in exhaust from a 1969 model truck oper-

ated on a dynamometer. Acrolein was measured (by the colorimetric 2,4-DNP method) at 0.05 mg/m^3 at hot idle, 6.4 mg/m^3 at 30 mph, and 4.4 mg/m^3 at 50 mph.

Bellar and Sigsby (1970) developed a GC unit which trapped organic substrates from air directly onto a GC cutter column (10 percent sucrose octaacetate on Gas-Chrom Z) at -55°C and then injected the sample onto the analytical column. Their unit was capable of measuring acrolein in the subpart per million range. The unit was used in measuring diesel exhaust, ambient air in an area of traffic, and ambient air in the open field. Diesel exhaust contained 12.4 mg/m^3 acrolein. No acrolein was detected in the open field sample and, at most, a trace was present in the sample from the traffic area.

Cigarette smoke contains acrolein. While a cigarette smoker inspires acrolein directly, some questions exist on passive exposure of nonsmokers to acrolein in side-stream smoke (Kusama, et al. 1978; Horton and Guerin, 1974; Jermini, et al. 1976; Weber-Tschopp, et al. 1976a).

Horton and Guerin (1974) measured the acrolein content of cigarettes by cryogenically trapping smoke onto a gas chromatography column. A 6-part smoking machine was used with puffs set at 1-minute intervals, 2-second durations, and 35 ml volume. Measured acrolein concentrations for the tested cigarettes are described in Table 5.

Hoffman, et al. (1975) measured acrolein in marijuana and tobacco cigarettes using gas chromatography. Cigarettes were rolled to a length of 85 mm using standard cigarette paper.

TABLE 5

Acrolein Delivery from Some Experimental and Some Commercial Cigarettes*

Cigarette	Acrolein Delivery		
	µg/cig.	µg/puff	µg/g tobacco burned
Kentucky Reference (IRI)	128	12	159
Commercial 85 mm, filtered	102	10	153
Commercial 85 mm, non-filtered	111	12	135
Experimental 85 mm, charcoal filtered	62	7	97
Experimental 85 mm (same as above), no-charcoal	103	12	155
Commercial 85 mm, little cigar	70	8	107
Experimental 85 mm, marijuana	145	14	199

*Source: Horton and Guerin, 1974

Experimental details were incomplete. Hoffman, et al. (1975) stated that smoking machines (1 or 20 channel) were employed and contained 10 or fewer cigarettes. Error was placed at ±4 to 6 percent. They reported acrolein delivery from mainstream smoke was 92 µg from marijuana cigarettes and 85 µg from tobacco cigarettes.

The potential exposure of nonsmokers to side-stream and exhaled cigarette smoke is an unresolved question. Holzer, et al. (1976) suggested that passive exposure to cigarette smoke is not important, while Swiss workers (Weber-Tschopp, et al. 1976b; Jermini, et al. 1976) have offered evidence that passive exposure is an important inhalation route.

Holzer, et al. (1976) developed an absorption tube sampling method to collect organic materials (volatiles and "particulate matter associated"). The tubes (88 mm x 2.5 mm ID) were packed with Tenax GC or Carbopack BHT. These tubes had an uncertain capacity for substances of lower retention than benzene, including acrolein, so their results were only qualitative for acrolein. The samples were desorbed and analyzed by GC-MS (mass spectral detection) using a glass capillary column. The authors compared the GC chromatograms of a sample of urban air (3.5 l samples at 220 ml/min), a standard cigarette (IRI, University of Kentucky) (3 ml of smoke taken during a puff of 2-second duration and 35 ml volume), and air where a cigarette had been smoked under standard conditions (same sampling conditions as for urban air). They suggested that the volatiles in both air samples were associated with gasoline vapor and that cigarette smoking did not appreciably add to these volatiles. The journal editor disagreed and in a footnote

stated that the chromatograms suggested that "a person breathing in a room where one cigarette was smoked inspires the equivalent of a 3.5 ml puff of cigarette smoke".

The Swiss team (Jermini, et al. 1976; Weber-Tschopp, et al. 1976b) measured acrolein concentration from cigarettes (U.S.) in side-stream smoke in a nearly air-tight, 30-m^3 climatic room and in a 272-liter plexiglass chamber. Acrolein was measured by gas chromatography. They reported acrolein concentrations as follows: in the 30-m^3 room, 0.11 mg/m^3 and 0.87 mg/m^3 with 5 and 30 cigarettes, respectively; and in the chamber, 0.85 mg/m^3 for one cigarette. These results suggested that inhalation of significant quantities of acrolein can result from passive exposure to side-stream smoke.

Acrolein has been identified as a component of smoke from wood burning. Its detection in wood smoke at commercial smoke houses (Love and Bratzler, 1966) was discussed in the Ingestion from Food section. Bellar and Sigsby (1970) studied volatile organics by GC (see above) in emissions from a trench incinerator burning wood. They published chromatograms for the wood smoke emissions but did not present quantitative data. An acrolein peak was present in the chromatogram for wood smoke from the incinerator without forced air. With forced air, the chromatogram did not contain a peak for acrolein, and the peaks for carbonyl compounds were lower than those for alcohols.

Hartstein and Forshey (1974) measured combustion products from burning four classes of materials: polyvinyl chloride (PVC), neoprene, rigid urethane foams, and treated wood. The materials were

burned by two techniques: a sealed system (approximately 370°C) and a stagnation burner (approximately 400°C). Condensible products were collected in a liquid nitrogen trap and analyzed by GC (thermal conductivity detection). They noted that the acrolein concentrations measured were less than the actual amount present since the tars and condensed water retain some acrolein. They never observed acrolein in emissions from the PVC, neoprene, or urethane foam samples. Acrolein was present in emissions from all wood samples, as summarized in Table 6.

Dermal

Based upon the physical properties and known distribution of acrolein in the environment, dermal exposure is judged to be negligible.

PHARMACOKINETICS

Absorption

Egle (1972) has measured the retention of inhaled acrolein as well as formaldehyde and propionaldehyde in mongrel dogs anesthetized with sodium pentobarbital. In this study, dogs were exposed to acrolein concentrations from 0.4 mg to 0.6 mg/l for 1 to 3 minutes, and retention was calculated using the amount inhaled and the amount recovered. In measurements of total respiratory tract rentention at ventilatory rates between 6 and 20/min., 81 to 84 percent of inhaled acrolein was retained. An increase in tidal volume (from 100 ml to 160 ml) resulted in a significant ($p \leq 0.001$) decrease in acrolein retention (from 86 to 77 percent). This was consistent with findings that acrolein was taken up more readily by the upper than the lower respiratory tract.

TABLE 6

Acrolein Produced by Burning Standard Southern Pine*

Wood Treatment	Acrolein Produced (mg/g wood burned)	
	Sealed Tube	Stagnation Burner
None	0.67	0.21
None	0.62	--
Pentachlorophenol	1.21	0.70
Creosote	0.43	0.59
Koppers fire retardent Type C®	unknown	0.22
Koppers waterborne preservative CCA®	0.47	0.68

*Source: Hartstein and Forshey, 1974

Distribution

Studies that were directly relevant to the distribution of acrolein upon oral administration were not found. Munsch, et al. (1974b) have examined the incorporation of tritiated acrolein in rats. Rats were injected (i.p.) with acrolein at 3.36 mg/kg 70 hours after partial hepatectomy. At 24 hours after injection, 88.66, 3.13, 1.72, 0.94, and 0.36 percentages of the recovered radioactivity were found in the acid-soluble, lipid, protein, RNA, and DNA fractions of the liver, respectively. Based on measurements taken 10 minutes to 24 hours after dosing, the extent of RNA and DNA binding remained relatively constant, while protein binding increased by about 70 percent. In vitro studies on the binding of acrolein to nucleic acids are discussed in the Acute, Subacute, and Chronic Toxicity section.

Metabolism

In terms of the potential toxicologic effects of acrolein in drinking water, the instability of acrolein at acid pHs (see Ingestion from Water section) may be highly significant. As discussed by Izard and Libermann (1978) and detailed in the Effects section of this report, several of the toxic effects of acrolein are related to the high reactivity of the carbon-carbon double bond. However, the low pHs encountered in the upper portions of the gastrointestinal tract would probably rapidly convert acrolein to saturated alcohol compounds. The primary breakdown product would probably be beta-propionaldehyde (see Ingestion from Water section). If this is the case, the toxic effects of acrolein given by oral administration would differ markedly from the effects observed

following other routes of administration. No information is available on the toxic effects of the acrolein breakdown products. However, an analysis of subchronic and chronic studies suggests that acrolein is markedly less toxic when given by oral administration than when inhaled (see Basis and Derivation of Criterion section).

Relatively little direct information is available on the metabolism of acrolein. Smith and Packer (1972) found that preparations of rat liver mitochrondria were capable of oxidizing several saturated aldehydes but not unsaturated aldehydes, such as acrolein, crotonaldehyde, and cinnamaldehyde. In vitro, acrolein can serve as a substrate for alcohol dehydrogenases from human liver, horse liver, and yeast with equilibrium constants of 6.5×10^{-11}, 8.3×10^{-11}, and 16.7×10^{-11}, respectively (Pietruszko, et al. 1973). In vivo studies in rats indicate that a portion of subcutaneously administered acrolein is converted to 3-hydroxypropylmercapturic acid (Kaye and Young, 1972; Kaye, 1973). Acrolein has also been shown to undergo both spontaneous and enzymatically catalyzed conjugation with glutathione (Boyland and Chasseaud, 1967; Esterbauer, et al. 1975).

Alarcon (1964, 1970) has demonstrated that acrolein is formed during the degradation of oxidized spermine and spermidine. Serafini-Cessi (1972) has shown that acrolein is a probable metabolite of allyl alcohol. Several investigators have demonstrated that acrolein is a metabolite of the anti-tumor agent cyclophosphamide (Alarcon, 1976b; Alarcon and Meienhofer, 1971; Alaroon and Melendez, 1974; Alarcon, et al. 1972; Connors, et al. 1974; Cox, et al. 1976a,b; Farmer and Cox, 1975; Gurtoo, et al. 1978; Hohorst, et al. 1976; Thomson and Colvin, 1974).

Excretion

In rats given single subcutaneous injections of acrolein, 10.5 percent of the administered dose was recovered in the urine as 3-hydroxypropylmercapturic acid after 24 hours (Kaye and Young, 1972; Kaye, 1973).

EFFECTS

Acute, Subacute, and Chronic Toxicity

Acute Effects on Experimental Systems: Several investigators have described the toxic effects of acute lethal exposure to acrolein on experimental mammals (Boyland, 1940; Carl, et al. 1939; Carpenter, et al. 1949; Skog, 1950; Smyth, et al. 1951; Pattle and Cullumbine, 1956; Philippin, et al. 1969; Salem and Cullumbine, 1960). Albin (1962) has summarized some of these earlier studies as well as unpublished reports (Table 7). Skog (1950) compared the pathological effects of acute lethal subcutaneous and inhalation exposures to acrolein in rats. After inhalation exposures, the rats evidenced pathological changes only in the lungs. These changes included edema, hyperemia, hemorrhages, and possible degenerative changes in the bronchial epithelium. Similar changes have been noted in mice, guinea pigs, and rabbits (Pattle and Cullumbine, 1956; Salem and Cullumbine, 1960). After administering lethal subcutaneous doses of acrolein to rats, Skog (1950) noted less severe lung damage (edema without significant hemorrhaging) but also found pathological changes in the liver (hyperemia and fatty degeneration) and kidneys (focal inflammatory changes).

Given the probable instability of acrolein on oral administration, a quantitative comparison of oral exposure with other routes

TABLE 7

Acute Lethal Toxicity of Acrolein*

Species	Route	Lethal Dose	Exposure Time	Remarks
Mouse	Inhalation	LC_{50}-875 ppm	1 min	Approximate value
Mouse	Inhalation	LC_{50}-175 ppm	10 min	Approximate value
Dog	Inhalation	LC_{50}-150 ppm	30 min	Approximate value
Rat	Inhalation	LC_{50}-8 ppm	4 hr	Approximate value
Rat	Oral	LD_{50}-46 mg/kg	...	Approximate value
Rat	Oral	LD_{50}-42 mg/kg	...	
Mouse	Oral	LD_{50}-28 mg/kg	...	
Rabbit	Percutaneous	LD_{50}-200 mg/kg	...	
Rabbit	Percutaneous	LD_{50}-562 mg/kg	...	Undiluted acrolein
Rabbit	Percutaneous	LD_{50}-335 mg/kg	...	20% acrolein in water
Rabbit	Percutaneous	LD_{50}-1022 mg/kg	...	10% acrolein in water
Rabbit	Percutaneous	LD_{50}-164 mg/kg	...	20% acrolein in mineral spirits
Rabbit	Percutaneous	LD_{50}-238 mg/kg	...	10% acrolein in mineral spirits

*Source: Albin, 1962

would be of particular interest. In a study by Carl, et al. (1939), rats given intraperitoneal injections of acrolein at 2.5 mg/kg/day died on the second day. Single doses of 10 mg/kg given to two rats by stomach tube killed both within 24 hours. However, six rats tolerated doses of 5 mg/kg/day given by stomach tube for nine days. Although firm conclusions cannot be made from this limited data, these results suggest that acrolein has a greater acute lethal potency when administered intraperitoneally than when given orally.

The sublethal effects of acute acrolein exposure on the liver have received considerable investigation. In adult male rats, inhalation exposures to acrolein or intraperitoneal injections of acrolein cause increases in hepatic alkaline phosphatase activity as well as increases in liver and adrenal weights. These effects, however, occurred only in exposures causing dyspnea and nasal irritation (e.g., 4.8 mg/m^3 x 40 hours). Other hepatic enzyme activities, acetylcholine esterase and glutamic-oxalacetic transaminase, were not affected. Since similar patterns were seen with other respiratory irritants, the alkaline phosphatase response was attributed to an alarm reaction rather than specific acrolein-induced liver damage (Murphy, et al. 1964). In subsequent studies (Murphy, 1965; Murphy and Porter, 1966), the effect of acrolein on liver enzymes was linked to stimulation of the pituitary-adrenal system resulting in hypersecretion of glucocorticoids and increased liver enzyme synthesis. Although these results do not suggest that acrolein is a direct liver toxin, Butterworth, et al. (1978) have shown that intravenous infusions of acrolein at doses of 0.85 and 1.70 mg/kg induce periportal necrosis in rats. In further studies

on the adrenocortical response of rats to acrolein, Szot and Murphy (1970) demonstrated increased plasma and adrenal corticosterone levels in rats given intraperitoneal injections of acrolein. Unlike similar effects caused by DDT and parathion, the effect of acrolein was not blocked by subanesthetic doses of phenobarbital but was blocked by dexamethasone only at lower doses of acrolein. The degree of increased corticosterone levels is dependent on the state of the adrenocortical secretory cycle in which acrolein as well as other toxins are administered (Szot and Murphy, 1971).

Since acrolein is a component of cigarette smoke, the sublethal effects of acrolein on the respiratory system have been examined in some detail. Murphy, et al. (1963) found that, in guinea pigs, inhalation of acrolein at concentrations from 0.92 to 2.3 mg/m^3 for periods of up to 12 hours caused dose-related increases in respiratory resistance, along with prolonged and deepened respiratory cycles. In tests on guinea pigs exposed to whole cigarette smoke from various types of cigarettes, Rylander (1973) associated concentrations of acrolein and acetaldehyde with decreases in the number of free macrophages. In mice exposed to acrolein in air at concentrations from 2.3 to 4.6 mg/m^3 for 24 hours there was evidence of decreased pulmonary killing of Staphylococcus aureus and Proteus mirabilis. This decrease in intrapulmonary bacterial killing was further suppressed in mice with viral pneumonia (Jakab, 1977). Kilburn and McKenzie (1978) have shown that acrolein (13.8 mg/m^3 x 4 hours) by inhalation is cytotoxic to the airway cells of hamsters, causing both immediate and delayed exfoliation. When administered either with or adsorbed onto carbon particles, acro-

lein induced leukocyte recruitment to the airways, mimicking the effect of whole cigarette smoke. In a single 10-minute inhalation exposure of mice, acrolein caused dose-related decreases in respiration attributed to sensory irritation, with an EC_{50} of 3.9 mg/m^3 (Kane and Alarie, 1977). Formaldehyde caused the same effect and exhibited competitive agonism in combination with acrolein (Kane and Alarie, 1978).

Acrolein has been shown to exert pronounced ciliastatic activity in a variety of aquatic invertebrates (see review by Izard and Libermann, 1978). As discussed by Wynder, et al. (1965), impairment of ciliary function in the respiratory tract of mammals may be involved in the pathogenesis of several respiratory diseases, including cancer. Of several respiratory irritants examined by Carson, et al. (1966), acrolein was the most effective in reducing mucus flow rates in cats after short-term inhalation exposures. In in vivo assays of chicken trachea ciliary activity, acrolein and hydrogen cyanide were found to be among the most potent ciliatoxic components of cigarette smoke (Battista and Kensler, 1970). Similarly, in tests on various types of cigarette smoke, Dalhamn (1972) associated ciliastasis in cats with variations in the concentrations of acrolein and tar.

In in vitro studies on the effects of cigarette smoke components on rabbit lung alveolar macrophages, acrolein has been shown to inhibit phagocytosis, adhesiveness, and calcium-dependent ATPase activity (Low, et al. 1977) and to inhibit the uptake of cycloleucine and α-aminoisobutyrate but not 3-O-methylglucose (Low and

Bulman, 1977). However, acrolein has been shown to inhibit the uptake of glucose by rabbit erythrocytes (Riddick, et al. 1968).

Egle and Hudgins (1974) noted that low doses (0.05 mg/kg) of acrolein administered by intravenous injection to rats caused an increase in blood pressure, but higher doses (0.5 to 5.0 mg/kg) caused marked decreases in blood pressure and bradycardia. The pressor response was attributed to increased catecholamine release from sympathetic nerve endings and the adrenal medulla, while the depressor response was attributed to vagal stimulation. Depressor effects were noted after 1-minute inhalation exposures to acrolein at 2.5 and 5.0 mg/l. Acrolein elicited significant cardiovascular effects at concentrations below those encountered in cigarette smoke. Basu, et al. (1971) have also examined the effects of acrolein on heart rate in rats. Tachycardia was induced in animals under general (sodium pentobarbital) anesthesia, while bradycardia was induced in animals receiving both general anesthesia and local ocular anesthesia (2 percent tetracain hydrochloride) prior to acrolein exposure. Pretreatment with atropine (0.5 mg/kg, i.v.) along with local and general anesthesia blocked the bradycardia response. Tachycardia was attributed to increased sympathetic discharge caused by eye irritation. Since the bradycardia response was blocked by atropine, parasympathetic involvement was suggested.

Several groups of investigators have examined the general cytotoxic effects of acrolein. Alarcon (1964) determined the inhibitory activities of spermine, spermidine, and acrolein to S-180 cell cultures. The concentrations of these compounds causing 50 percent inhibition were 1.4 to 1.5 x 10^{-5} mmol/ml for spermine,

2.8 to 3.1 x 10^{-5} mmol/ml for spermidine, and 2.6 to 3.5 x 10^{-5} mmol/ml for acrolein. Since the inhibitory potencies of these compounds were similar and since only the two amines required amine oxidase in exerting the inhibitory effect, Alarcon (1964) proposed that the inhibitory activity of the two amines was due to the in vitro formation of acrolein. Two groups of investigators have examined the role of acrolein in the viricidal effects of oxidized spermine (Bachrach, et al. 1971; Bachrach and Rosenkovitch, 1972; Nishimura, et al. 1971, 1972). Both groups determined that the antiviral potency of acrolein was substantially less than that of oxidized spermine and that the antiviral effects of oxidized spermine are not attributable to the generation of acrolein.

Koerker, et al. (1976) have examined the cytotoxicity of acrolein and related short-chain aldehydes and alcohols to cultured neuroblastoma cells. Aldehydes were consistently more toxic than the corresponding alcohols. Based on viability of harvested cells and increase in the number of sloughed cells after exposure, acrolein was more potent than formaldehyde and much more potent than acetaldehyde or propionaldehyde. Based on decreases in neurite formation and viability of sloughed cells, formaldehyde was somewhat more potent than acrolein and substantially more potent than either acetaldehyde or propionaldehyde. In in vitro tests on Ehrlich-Landschutz diploid ascites tumor cells, Holmberg and Malmfors (1974) found acrolein to be substantially more toxic than formaldehyde over incubation periods of 1 to 5 hours. Both of these aldehydes, however, were among the more toxic organic solvents assayed in this study. Similarly, in in vitro tests of tobacco

smoke constituents on mouse ascites sarcoma BP8 cells (48-hour exposure periods), Pilotti, et al. (1975) found aldehydes to be among the most toxic group of compounds studied. At a concentration of 100 µM, acrolein caused substantially greater inhibition (94 percent) than formaldehyde (15 percent).

Several of the cytotoxicity studies on acrolein have addressed the role of acrolein in the antineoplastic effects of cyclophosphamide. Sladek (1973) determined the cytotoxicity of cyclophosphamide and various cyclophosphamide metabolities, including acrolein, to Walker 256 ascites cells. In this study, ascites cells were exposed to the various compounds in vitro for one hour, then injected into host rats. The proportion of viable ascites cells was estimated from survival times of the rats. Based on this assay, acrolein was found to be only marginally cytotoxic (LC_{90} of 8.75 µM) and did not account for a substantial proportion of the cytotoxicity of cyclophosphamide metabolites generated in vivo. Cyclophosphamide itself was virtually nontoxic (LC_{90} of $>$ 100 µM). Similar results on the cytotoxicity of acrolein to Walker ascites cells was obtained by Phillips (1974) using an in vitro test system in which cells were exposed to cytotoxic agents for one hour, then transferred to fresh culture medium. Cytotoxicity was expressed as a 72-hour IC_{50} -- the exposure concentration causing a 50 percent decrease in cell number compared to untreated cells 72 hours after treatment. The IC_{50} for acrolein was 1.0 µg/ml (approximately 18 µM) and the IC_{50} for cyclophosphamide was 6,000 µg/ml. Lelieveld and Van Putten (1976) measured the cytotoxic effects of cyclophosphamide and six possible metabolites, including acrolein, to normal

hematopoietic stem cells of mice, osteosarcoma cells, and L1210 leukemia cells. Acrolein was inactive against normal hematopoietic stem cells and osteosarcoma cells, and less active than cyclophosphamide against leukemia cells. Similarly, Brock (1976) has found that acrolein is less active than cyclophosphamide against Yoshida ascitic sarcoma of the rat.

The cytotoxic effects of acrolein may be attributed, at least in part, to direct damage of nucleic acids or impaired nucleic acid or protein synthesis. Using primary cultures of mouse-kidney tissue exposed to a total of 70 µg acrolein, Leuchtenberger, et al. (1968) noted a progressive decrease in the uptake of tritiated uridine, decreased RNA, and pycnosis of cell nuclei. Similarly, in cultures of polyoma-transformed cells from cell lines of Chinese hamsters exposed to acrolein at concentrations of 0.8 to 2.5 x 10^{-5} M for one hour, Alarcon (1972) found concentration-related decreases in the uptake of tritiated uridine, tritiated thymidine, and tritiated leucine. Using similar methods, Kimes and Morris (1971) have also demonstrated inhibition of DNA, RNA, and protein synthesis by acrolein in Escherichia coli.

In in vitro studies on the kinetics of acrolein inhibition of rat liver and E. coli RNA-polymerases, Moule, et al. (1971) found that inhibition was unaffected by the amount of DNA in the medium but was partially offset by increased levels of RNA-polymerase, suggesting that acrolein acts on RNA-polymerase rather than DNA. In parallel studies on rat liver and E. coli DNA-polymerase, Munsch, et al. (1973) noted that acrolein inhibited rat liver DNA-polymerase but stimulated E. coli DNA-polymerase. Since the active

site of rat liver DNA-polymerase is associated with a functional sulfhydryl group but E. coli DNA-polymerase is not and since acrolein's inhibitory effect on rat liver DNA-polymerase could be antagonized by 2-mercaptoethanol (see Synergism and/or Antagonism section), these investigators concluded that acrolein acts on rat liver DNA-polymerase by reacting with the sulfhydryl group. Subsequently, Munsch, et al. (1974a) demonstrated that tritiated acrolein binds 20 to 30 times more to rat liver DNA-polymerase than to E. coli DNA-polymerase. In partially hepatectomized rats given intraperitoneal injections of acrolein at doses of 0.1 to 2.7 mg/kg, DNA and RNA synthesis was inhibited in both the liver and lungs (Munsch and Frayssinet, 1971).

Subacute Toxicity to Experimental Mammals: Most studies on the subacute toxicity of acrolein have involved inhalation exposures. In 1-month inhalation exposures of rats to acrolein at 1.2 mg/m^3, Bouley (1973) noted decreases in growth rates and in the levels of oxidation-reduction coenzymes in the liver (additional details not given). Rats continously exposed to acrolein in the air at 1.27 mg/m^3 for up to 77 days evidenced decreased food intake accompanied by decreased body weight gain. Between days 7 and 21 of exposure, animals evidenced nasal irritation. Changes in relative lung and liver weights, as well as serum acid phosphatase activity, are summarized in Table 8. Respiratory tract irritation, a decrease in the number of alveolar macrophages, and increased susceptibility to respiratory infection by Salmonella enteritidis were noted only during the first three weeks of exposure (Bouley, et al. 1975, 1976). Philippin, et al. (1969) also noted decreased

TABLE 8

Relative Weights of Lungs and Liver, and Serum Level of Acid Phosphatases*

Parameters	Time	Control rats	Test Rats	Statistical Analysis
Lungs weight x 100 / Body weight	15th and 32nd days	no significant difference between 2 x 10 control and 2 x 10 test rats		
	77th day	n = 10 m = 0.489 s.d. = 0.087	n = 15 m = 0.588 s.d. = 0.111	t = 2.67 0.02>P>0.01
Liver weight x 100 / body weight	15th day	n = 10 m = 5.00 s.d. = 0.14	n = 10 m = 4.55 s.d. = 0.14	t = 7.12 0.001>P
	32nd and 77th days	no significant difference between 10 and 15 control, and 10 and 15 test rats		
mU of acid phosphatases per ml of serum	15th day	n = 10 m = 77.87 s.d. = 10.59	n = 10 m = 62.11 s.d. = 6.72	t = 3.91 P = 0.001
	32nd and 77th days	no significant differences between 10 and 11 control, and 10 and 11 test rats		

*Source: Bouley, et al. 1976
n = number of rats; m = mean value; s.d. = standard deviation

body weight in mice exposed to airborne acrolein at 13.8 mg/m^3 and 34.5 mg/m^3, six hours per day, five days per week, for six weeks. Although the decreased body weight was significant (p 0.01), the extent of the decrease was neither substantial (approximately 6 percent) nor dose-related.

Lyon, et al. (1970) exposed rats, guinea pigs, monkeys, and dogs to acrolein concentrations of 1.6 and 8.5 mg/m^3 in the air for eight hours per day, five days per week, for six weeks. In addition, continuous exposures were conducted at 0.48, 0.53, 2.3, and 4.1 mg/m^3 for 90 days using the same animals. The following biological endpoints were used to assess the effects of exposure: mortality, toxic signs, whole body weight changes, hematologic changes (hemoglobin concentration, hematocrit, and total leukocytes), biochemical changes (blood urea nitrogen, alanine and aspartate aminotransferase activities), and pathological changes in heart, lung, liver, spleen, and kidney. Gross effects were not noted in the continuous exposures to acrolein at 0.48 and 0.53 mg/m^3 or in the repeated exposures to 1.6 mg/m^3. In continuous exposures to 2.3 and 4.1 mg/m^3 and in repeated exposures to 8.5 mg/m^3, dogs and monkeys displayed signs of eye and respiratory tract irritation and rats evidenced decreased weight gain. All animals exposed repeatedly to acrolein at 1.6 mg/m^3 developed chronic inflammatory changes of the lung. These changes were more pronounced in dogs and monkeys than in rats and guinea pigs. At 8.5 mg/m^3 squamous metaplasia and basal cell hyperplasia of the tracheas of dogs and monkeys were attributed to acrolein exposure. In addition, this exposure induced necrotizing bronchitis and bron-

chiolitis with squamous metaplasia in the lungs of 7 of 9 monkeys. Similar pathological results were noted in continuous exposures of rats, guinea pigs, dogs, and monkeys to 2.3 and 4.1 mg/m^3.

Feron, et al. (1978) exposed hamsters, rats, and rabbits to acrolein vapor at 0.4, 3.2, and 11.3 mg/m^3 six hours per day, five days per week, for 13 weeks. At the highest concentration, all animals displayed signs of eye irritation, decreased food consumption, and decreased weight gain. In rats and rabbits, no abnormal hematological changes were noted. Female guinea pigs at the highest dose, however, showed statistically significant increases in the number of erythrocytes, packed cell volume, hemoglobin concentration, number of lymphocytes, and a decrease in the number of neutrophilic leukocytes. Additional changes noted in this study are summarized in Table 9.

Watanabe and Aviado (1974) have demonstrated that repeated inhalation exposures of mice to acrolein (100 mg/m^3 for 30 minutes, twice a day for five weeks) cause a reduction in pulmonary compliance.

The subacute oral toxicity of acrolein has been examined in less detail. Albin (1962) found that rats exposed to acrolein in drinking water at concentrations up to 200 mg/l for 90 days evidenced only slight weight reduction at the highest level tested. This was attributed to unpalatability of the drinking water. Similar results have been reported by Newell (1958) (summarized in NAS, 1977). In one study, acrolein was added to the drinking water of male and female rats at 5, 13, 32, 80, and 200 mg/l for 90 days. No hematologic, organ-weight, or pathologic changes could be attributed to acrolein ingestion. At the highest concentration, water

TABLE 9

Summary of Treatment-Related Effects in Hamsters, Rats and Rabbits Repeatedly Exposed to Acrolein for 13 Weeks*

Criteria Affected	Effects[a]								
	Hamsters Acrolein (ppm)			Rats Acrolein (ppm)			Rabbits Acrolein (ppm)		
	0.4	1.4	4.9	0.4	1.4	4.9	0.4	1.4	4.9
Symptomatology	0	x	xxx	0	x	xx	0	x	xxx
Mortality	0	0	0	0	0	+++	0	0	0
Growth	0	0	--	-	--	---	0	-	--
Food intake	NE	NE	NE	0	-	--	0	-	--
Haematology	0	0	x	0	0	0	0	0	0
Urinary amorphous material	0	0	+	0	0	+	0	0	+
Urinary crystals	0	0	-	0	0	-	0	0	0
Organ weights									
Lungs	0	0	++	0	0	++	0	0	++
Heart	0	0	+	0	0	+	0	0	0
Kidneys	0	0	+	0	0	+	0	0	0
Adrenals	0	0	0	0	0	+++	0	0	0
Gross pathology									
Lungs	0	0	0	0	0	x	0	0	0
Histopathology									
Nasal cavity	0	x	xxx	x	xx	xxx	0	0	xx
Larynx	0	0	x	0	0	xx	NE	NE	NE
Trachea	0	0	xx	0	0	xxx	0	0	x
Bronchi + lungs	0	0	0	0	0	xxx	0	0	xx

*Source: Feron, et al. 1978

[a]0 = not affected; x = slightly affected; xx = moderately affected; xxx = severely affected; + = slightly increased; ++ = moderately increased; +++ = markedly increased; - = slightly decreased;-- = moderately decreased; --- = markedly decreased; NE = not examined

consumption was reduced by one-third for the first three weeks. By the 12th week, the rats had apparently adapted to the odor and taste of acrolein. In a subsequent study, acrolein was added to the drinking water of male rats at concentrations of 600, 1,200, and 1,800 mg/l for 60 days. All animals died at the two higher concentrations, and 1 of 5 animals died at 600 mg/l concentration. Death was apparently due to lack of water intake. Tissues from the animals surviving 600 mg/l did not show any gross or micropathologic abnormalities.

Chronic Toxicity to Experimental Mammals: The only published chronic toxicity study on acrolein is that presented by Feron and Kruysse (1977). In this study, male and female Syrian golden hamsters were exposed to acrolein at 9.2 mg/m^3 in the air, seven hours per day, five days per week, for 52 weeks. During the first week of exposure, animals evidenced signs of eye irritation, salivated, had nasal discharge, and were very restless. These signs disappeared during the second week of exposure. During the exposure period, males and females had reduced body weight gains compared to the control animals but the survival rate was unaffected. Hematological changes, i.e., slight but statistically significant increased hemoglobin content and packed cell volume, occurred only in females. Similarly, significant ($p<0.05$) decreases in relative liver weights (16 percent) and increases in lung weights (32 percent) occurred only in females. In both sexes, pathologic effects included inflammation and epithelial metaplasia in the nasal cavity. No other pathological changes in the respiratory tract were attributable to acrolein.

Effects on Humans: As summarized in Table 10, considerable information is available on the irritant properties of acrolein to humans. In studies on photochemical smog, Altshuller (1978) has estimated that acrolein could cause 35 to 75 percent as much irritation as formaldehyde. Schuck and Renzetti (1960) indicated that acrolein and formaldehyde account for most of the eye irritation caused by the photooxidation of various hydrocarbons. Acrolein is also involved in the irritant effect of cigarette smoke (Weber-Tschopp, et al. 1976a,b, 1977).

Relatively little information, however, is available on the toxic effects of acrolein in humans. Henderson and Haggard (1943) state that vapor concentrations of 23 mg/m^3 are lethal in a short time.

In a study on irritant dermatitis induced by diallylglycol carbonate monomer, Lacroix, et al. (1976) conducted patch tests on humans with acrolein. In these tests, acrolein solutions in ethanol caused no irritation at concentrations (v/v) of 0.01 to 0.1 percent. At a concentration of 1 percent, 6 of 48 subjects showed a positive response (two erythemas and four serious edemas with bullae). At a concentration of 10 percent, all eight subjects had positive responses. Histological findings of a second series of tests with 10 percent acrolein are summarized in Table 11.

Kaye and Young (1974) have detected 3-hydroxypropylmercapturic in the urine of patients receiving cyclophosphamide orally (50 mg twice or three times daily) but not in the urine of untreated humans. Based on analogies to the metabolic patterns of

TABLE 10

Irritant Properties of Acrolein to Humans

Exposure	Effect	Reference
0.58 mg/m^3 x 5 min.	moderate irritation of sensory organs	Albin, 1962
2.3 mg/m^3 x 1 min.	slight nasal irritation	
2.3 mg/m^3 x 2 to 3 min.	slight nasal and moderate eye irritation	
2.3 mg/m^3 x 4 to 5 min.	moderate nasal irritation and practically intolerable eye irritation	
4.1 mg/m^3 x 30 sec.	odor detectable	
4.1 mg/m^3 x 1.0 min.	slight eye irritation	
4.1 mg/m^3 x 3 to 4 min.	profuse lachrymation; practically intolerable	
12.7 mg/m^3 x 5 sec.	slight odor; moderate nasal and eye irritation	
12.7 mg/m^3 x 20 sec.	painful eye and nasal irritation	
12.7 mg/m^3 x 1 min.	marked lachrymation; vapor practically intolerable	
50.1 mg/m^3 x 1 sec.	intolerable	
0.48 mg/m^3	odor threshold	Reist and Rex, 1977
2.3 mg/m^3	highly irritating	Pattle and Cullumbine, 1956
9.2 mg/m^3	lacrimation	
1.8 mg/m^3 x 10 min.	lacrimation within 20 seconds, irritation to exposed mucosal surfaces	Sim and Pattle, 1957
2.8 mg/m^3 x 5 min.	lacrimation within 5 seconds, irritation to exposed mucosal surfaces	

TABLE 11

Patch Tests with Ten Percent Acrolein in Ethanol on Control Subjects (Biopsied at 48 Hours)*

No. of Biopsy	Polymorph. Infiltrate	Papillary Edema	Epidermis	Result
CM 375	+++	++	0	Irritation
CM 376	+	++	Necrosis	Irritation
CN 74	++	++	0	Irritation
CN 88	++	++	Necrosis	Irritation
CN 89	+	+	0	Irritation
CN 90	+	+	Necrosis	Irritation
CN 91	++	+	0	Irritation
CN 178	+	+	Necrosis	Irritation
CN 179	+	+	Necrosis	Irritation
CN 346	0	+	Bullae	Irritation
CN 347	+++	+	0	Irritation
CN 348	++	++	Bullae	Irritation

*Source: Lacroix, et al. 1976

cyclophosphamide in rats, these investigators concluded that acrolein is probably a metabolite of cyclophosphamide in man.

In studies on human polymorphonuclear leukocytes (PMNs), Bridges, et al. (1977) found that acrolein was a potent in vitro inhibitor of PMN chemotaxis (EC_{50} of 15 µm) but had no significant effect on PMN integrity (measured by beta-glucuronidase release, lactic acid dehydrogenase release, and cell viability) or glucose metabolism (measured by glucose utilization, lactic acid production, and hexose monophosphate activity). Cysteine, at a concentration of 10 mM, completely blocked the inhibitory effect of 160 µm acrolein on PMN chemotaxis. These results are consistent with the assumption that acrolein inhibits chemotaxis by reacting with one or more essential thiol groups on cellular proteins involved in chemotaxis. These proteins, however, do not appear to be involved in glucose metabolism.

Schabort (1967) demonstrated that acrolein inhibits human lung lactate dehydrogenase. Inhibition appeared to be noncompetitive with respect to both NADH and pyruvate.

Little information is available on the chronic effects of acrolein on humans. An abstract of a Russian study indicates that occupational exposure to acrolein (0.8 to 8.2 mg/m^3), methylmercaptan (0.003 to 5.6 mg/m^3), methylmercaptopropionaldehyde (0.1 to 6.0 mg/m^3), formaldehyde (0.05 to 8.1 mg/m^3), and acetaldehyde (0.48 to 22 mg/m^3) was associated with irritation of the mucous membranes. This effect was most frequent in women working for less than one year and greater than seven years (Kantemirova, 1975).

Synergism and/or Antagonism

Acrolein is highly reactive toward thiol groups. Acrolein rapidly conjugates with both glutathione and cysteine (Esterbauer, et al. 1975, 1976). Cysteine has been shown to antagonize the cytotoxic effects of acrolein on ascites tumor cells of mice (Tillian, et al. 1976). Cysteine also antagonizes the inhibition of acrolein on rabbit alveolar macrophage calcium-dependent ATPase, phagocytosis, and adhesiveness (Low, et al. 1977). Both cysteine and ascorbic acid have been shown to antagonize the acute lethal effects of orally administered acrolein in male rats (Sprince, et al. 1978). Munsch, et al. (1973, 1974a) have demonstrated that 2-mercaptoethanol antagonizes the inhibitory effect of acrolein on rat liver DNA-polymerase. The irritant effects of acrolein injected into the footpad of rats were blocked by N-acetyl-cysteine, penicillamide, glutathione, γ-mercaptopropionylglycine, 2-mercaptoethanol, and β,β-dimethylcysteamine (Whitehouse and Beck, 1975).

The effects of acrolein, unlike those of DDT and parathion, on the adrenocortical response of rats is not inhibited by pretreatment with phenobarbital and is only partially inhibited by dexamethasone (Szot and Murphy, 1970).

Pretreatment of rats with acrolein (3 mg/kg, i.p.) significantly prolongs hexobarbital and pentobarbital sleeping times (Jaeger and Murphy, 1973).

Teratogenicity

Reports have not been encountered on the potential teratogenicity of acrolein.

Bouley, et al. (1976) exposed male and female rats to acrolein vapor at 1.3 mg/m^3 for 26 days and found no significant differences either in the number of pregnant animals or in the number and mean weight of fetuses.

Mutagenicity

In the dominant-lethal assay for mutagenicity in ICR/Ha Swiss mice, acrolein did not cause a significant increase in early fetal deaths or pre-implantation losses at doses of 1.5 and 2.2 mg/kg given in single intraperitoneal injections to male mice prior to an 8-week mating period (Epstein, et al. 1972).

As summarized by Izard and Libermann (1978), Rapoport (1948) assayed several olefinic aldehydes for their ability to induce sex-linked mutations in Drosophila melanogaster. Acrolein had the highest activity, causing 2.23 percent mutations (15 mutations among 671 chromosomes).

Using a strain of DNA-polymerase deficient Escherichia coli, Bilimoria (1975) detected mutagenic activity in acrolein as well as cigar, cigarette, and pipe smoke. In a strain of E. coli used for detecting forward mutations (from gal R^s to gal^+ and from 5-methyl-tryptophan sensitivity to 5-methyltryptophan resistance) and reverse mutations (from arg^- to arg^+), acrolein demonstrated no mutagenic activity with or without activation by mouse liver homogenates (Ellenberger and Mohn, 1976, 1977).

Bignami, et al. (1977) found that acrolein induced mutagenic effects in Salmonella typhimurium strains TA1538 and TA98 (insertions and deletions), but showed no activity in strains TA1535 or TA100 (base-pair substitutions). Anderson, et al. (1972) were

unable to induce point mutations in eight histidine-requiring mutants of S. typhimurium. This system also gave negative results for 109 other herbicides but was positive for three known mutagens: diethyl sulfate, N-methyl-N'-nitro-N-nitrosoguanidine, and ICR-191®.

Izard (1973) determined the mutagenic effects of acrolein on three strains of Saccharomyces cerevisiae. In strain N123, a histidine auxotroph, acrolein at 320 mg/l induced twice the control incidence of respiratory-deficient mutants. In two methionine auxotroph haploid strains used to assay for frameshift mutations and base-pair substitutions, acrolein was inactive. As discussed by Izard and Libermann (1978), these results suggest that acrolein is not a strong inducer of respiratory deficient mutants and does not appear to induce frameshift mutations or base-pair substitutions in S. cerevisiae. However, this lack of activity could be due to the high toxicity or instability of acrolein or to the inability of these strains to convert acrolein to some other active molecule.

Carcinogenicity

Ellenberger and Mohn (1976) indicated that acrolein is "known as (a) cytotoxic and carcinogenic compound." The carcinogenicity of acrolein has not been confirmed in this review of the literature. In the chronic inhalation study by Feron and Kruysse (1977) acrolein gave no indication of carcinogenic activity, had no effect on the carcinogenic activity of diethylnitrosamine (DENA), and had a minimal effect on the carcinogenic activity of benzo(α)pyrene (BP). Detailed tumor pathology from this study is presented in

Table 12. Based on these results, Feron and Kruysse (1977) concluded that "...the study produced insufficient evidence to enable acrolein to be regarded as an evident cofactor in respiratory tract carcinogenesis." Similar results have been obtained in a not-yet-published bioassay sponsored by the National Cancer Institute (Sharon Feeney, personal communication). In this study, hamsters were exposed to acrolein vapor at 11.5 mg/m^3, six hours per day, five days per week, throughout their life span. Evidence was not found that acrolein was a carcinogen or a cocarcinogen with either benzo(a)pyrene or ferric oxide. DiMacco (1955) summarizes a study by Savoretti (1954) indicating that acrolein resulted in an increase in the incidence of benzopyrene-induced neoplasms. This summary does not provide information on the species tested, doses, routes of administration, or the significance of the observed increase.

Boyland (1940) found that acrolein, at daily oral doses of 0.25 mg/mouse, had a marginal ($p \leq 0.1$) inhibitory effect on the growth of spontaneous skin carcinomas and a significant ($p \leq 0.05$) inhibitory effect on the growth of grafted sarcomas.

TABLE 12

Site, Type, and Incidence of Respiratory Tract Tumors in Hamsters Exposed to Air or Acrolein Vapor and Treated Intratracheally with BP or Subcutaneously with DENA[a]

Site and Type of Tumors	Incidence of Tumors							
	Inhalation of Air				Inhalation of Acrolein			
	[a] 0.9% NaCl[b]	BP[c] (18.2 mg)	BP[d] (36.4 mg)	DENA[e]	[a] 0.9% NaCl[b]	BP[c] (18.2 mg)	BP[d] (36.4 mg)	DENA[e]
	Females							
No of animals examined[f]	14 14 / 28	27	24	27	14 13 / 27	29	30	28
Larynx								
Papilloma	0	1	0	3	0	0	0	5
Trachea								
Polyp	0	0	0	0	0	1	0	0
Papilloma	0	0	1	8	1	3	6	8
Squamous cell carcinoma	0	0	2	0	0	0	2	0
Bronchi								
Polyp	0	0	0	0	0	0	0	1
Papilloma	0	1	0	2	0	0	0	1
Adenocarcinoma	0	0	1	0	0	0	0	0
Squamous cell carcinoma	0	0	0	0	0	0	1	0
Lungs								
Papillary adenoma	0	0	1	0	0	2	4	0
Acinar adenoma	0	0	2	0	0	2	5	0
Adenosquamous adenoma	0	1	0	0	0	0	2	0
Squamous cell carcinoma	0	0	0	0	0	0	1	0
Oat cell-like carcinoma	0	0	0	0	0	0	1	0

TABLE 12 (continued)

Site and Type of Tumors	Incidence of Tumors							
	Inhalation of Air				Inhalation of Acrolein			
	[a] 0.9% NaCl[b]	BP[c] (18.2 mg)	BP[d] (36.4 mg)	DENA[e]	[a] 0.9% NaCl[b]	BP[c] (18.2 mg)	BP[d] (36.4 mg)	DENA[e]
	Males							
No of animals examined[f]	15 15 / 30	29	30	29	15 15 / 30	30	29	30
Nasal cavity								
Polyp	0	0	0	1	0	0	0	0
Papilloma	0	0	0	0	0	0	0	1
Adenocarcinoma	0	0	0	1	0	0	0	0
Larynx								
Papilloma	0	0	1	7	0	0	1	4
Trachea								
Polyp	0	0	0	2	0	1	2	1
Papilloma	0	2	5	1	0	1	3	5
Squamous cell carcinoma	0	0	1	0	0	0	3	0
Anaplastic carcinoma	0	0	1	0	0	0	2	0
Sarcoma	0	0	1	0	0	1	1	0
Bronchi								
Polyp	0	0	0	1	0	0	2	0
Papilloma	0	1	2	2	0	1	0	0
Adenoma	0	0	0	0	0	0	1	0
Adenocarcinoma	0	0	1	0	0	0	2	0
Lungs								
Papillary adenoma	0	0	6	0	0	0	4	0
Acinar adenoma	0	1	1	0	0	1	1	0
Adenosquamous adenoma	0	1	2	0	0	1	1	0
Adenocarcinoma	0	0	2	0	0	0	0	0

TABLE 12 (continued)

Site and Type of Tumors	Incidence of Tumors							
	Inhalation of Air				Inhalation of Acrolein			
	[a] 0.9% NaCl[b]	BP[c] (18.2 mg)	BP[d] (36.4 mg)	DENA[e]	[a] 0.9% NaCl[b]	BP[c] (18.2 mg)	BP[d] (36.4 mg)	DENA[e]
Adenosquamous carcinoma	0	0	0	0	0	0	1	0
Squamous cell carcinoma	0	0	1	0	0	1	1	0
Oat cell-like carcinoma	0	0	0	0	0	0	1	0
Anaplastic carcinoma	0	0	1	0	0	0	0	0

*Source: Feron and Kruysse, 1977

[a]No further treatment

[b]Given intratracheally (0.2 ml) weekly during 52 wk

[c]Given intratracheally in 52 weekly doses of 0.35 mg

[d]Given intratracheally in 52 weekly doses of 0.70 mg

[e]Given subcutaneously in 17 three-weekly doses of 0.125 ul

[f]A few hamsters were lost through cannibalism or autolysis

CRITERION FORMULATION

Existing Guidelines and Standards

The current time-weighted average threshold limit value (TLV) for acrolein established by the American Conference of Governmental Industrial Hygienists (ACGIH, 1977) is 0.1 ppm (0.25 mg/m^3). The same value is enforced by the Occupational Safety and Health Administration (39 FR 23540). The ACGIH standard was designed to "minimize, but not entirely prevent, irritation to all exposed individuals" (ACGIH, 1974). Kane and Alarie (1977) have reviewed the basis for this TLV in terms of both additional data on human irritation and their own work on the irritant effects of acrolein to mice (summarized in the Acute, Subacute, and Chronic Toxicity section). These investigators concluded that "the 0.1 ppm TLV for acrolein is acceptable but is close to the highest value of the acceptable 0.02 to 0.2 ppm range predicted by this animal model" (Kane and Alarie, 1977).

The Food and Drug Administration permits the use of acrolein as a slime-control substance in the manufacture of paper and paperboard for use in food packaging (27 FR 46) and in the treatment of food starch at not more than 0.6 percent acrolein (28 FR 2676).

In the Soviet Union, the maximum permissible daily concentration of acrolein in the atmosphere is 0.1 mg/m^3 (Gusev, et al. 1966). This study did not specify whether this level is intended as an occupational or ambient air quality standard.

Current Levels of Exposure

As detailed in the Exposure section, quantitative estimates of current levels of human exposure cannot be made based on the available data. Acrolein has not been monitored in ambient raw or finished waters.

Special Groups at Risk

Since acrolein is a component of tobacco and marijuana smoke, people exposed to these smokes are a group at increased risk from inhaled acrolein. In addition, acrolein is generated by the thermal decomposition of fat, so cooks are probably also at additional risk (see Exposure section). Since acrolein has been shown to suppress pulmonary antibacterial defenses, individuals with or prone to pulmonary infections may also be at greater risk (Jakab, 1977).

Basis and Derivation of Criterion

Although acrolein is mutagenic in some test systems (see Mutagenicity section) and can bind to mammalian DNA (see Acute Effects on Experimental Systems section), current information indicates that acrolein is not a carcinogen or cocarcinogen (see Carcinogenicity section). Water quality criteria for acrolein could be derived from the TLV, chronic inhalation studies, or subacute oral studies using noncarcinogenic biological responses.

Stokinger and Woodward (1958) have described a method for calculating water quality criteria from TLVs. Essentially, this method consists of deriving an acceptable daily intake (ADI) for man from the TLV by making assumptions on breathing rate and absorption. The ADI is then partitioned into permissible amounts from drinking water and other sources. However, because the TLV is based on the prevention of the irritant effects of acrolein on inhalation exposures, such a criterion would have little, if any, validity.

A criterion could also be estimated based on chronic inhalation data. Female hamsters exposed to acrolein at 9.2 mg/m^3 in the

air, seven hours per day, five days per week, for 52 weeks evidenced slight hematologic changes, significant decreases in liver weight, and significant increases in lung weights (Feron and Kruysse, 1977). By making assumptions of respiratory volume and retention, the exposure data from this study can be converted to a mg/kg dose and an "equivalent" water exposure level can be calculated. The average body weight for the hamsters at the end of the exposure was about 100 g. Assuming a mean minute volume (amount of air exchanged per minute) of 33 ml for a 100 g hamster (Robinson, 1968) and a retention of 0.75, the average daily dose is estimated at 68.3 µg/animal (9.2 mg acrolein/m^3 x 0.033 l/min x 1 m^3/1,000 liters x 60-min/hour x 7 hours/day x 5 days/7 days x 0.75) or 683 µg/kg. Using an uncertainty factor of 1,000 (NAS, 1977), an estimated "unacceptable" daily dose for man is 0.683 µg/kg or 47.8 µg/man, assuming a 70 kg body weight.

A criterion based on this daily dose level would be unsatisfactory for two reasons. First, the dose data used to derive the standard are not based on a no-observed-effect level (NOEL). In this respect, the derived criterion could represent an undesirably high level in water. Secondly, the estimation is based on an inhalation study. Given the probable instability of acrolein in the gastrointestinal tract, the use of inhalation data may not be suitable for deriving a criterion.

In Drinking Water and Human Health, the National Academy of Sciences (NAS, 1977) summarized the study by Newell (1958) in which acrolein was added to the drinking water of rats at concentrations of 5, 13, 32, 80, and 200 mg/l for 90 days without apparent adverse

effects (see Acute, Subacute, and Chronic Toxicity section). Assuming a daily water consumption of 35 ml/day and a body weight of 450 g (ARS Sprague-Dawley, 1974), the chronic no-effect dose for rats based on 200 mg/l in water is estimated at 15.6 mg/kg. This value may be converted into an ADI for man by applying an uncertainty factor. Since the study involved only 90-day exposures, an uncertainty factor of 1,000 is recommended (NAS, 1977). Thus, the estimated ADI for man is 15.6 µg/kg or 1.09 mg/man, assuming a 70 kg body weight. Therefore, consumption of 2 liters of water daily and 6.5 grams of fish having a bioconcentration factor of 215 would result in, assuming 100 percent gastrointestinal absorption of acrolein, a maximum permissible concentration of 0.32 µg/l for the ingested water:

$$\frac{1.09 \text{ mg}}{2 \text{ l} + (215 \times 0.0065) \times 1.0} = 0.321 \text{ mg/l}$$

This calculation assumes that 100 percent of man's exposure is contributed by ingesting water and contaminated fish/shellfish products. Although it is desirable to develop a criterion based on total exposure analysis, the data for other exposure are not sufficient to support a factoring of the ADI level.

In summary, based on the use of acute toxicologic data for rats and an uncertainty factor of 1,000, the criterion level corresponding to the calculated acceptable daily intake of 15.6 µg/kg is 0.32 mg/l. Drinking water contributes 12 percent of the assumed exposure while eating contaminated fish products accounts for 88 percent. The criterion level for acrolein can alternatively be expressed as 0.78 mg/l if exposure is assumed to be from the consumption of fish and shellfish products alone.

REFERENCES

Abrams, E.F., et al. 1975. Identification of organic compounds in effluents from industrial sources. EPA-560/3-75-002. PB 241-641. Natl. Tech. Inf. Serv., Springfield, Virginia.

Alarcon, R.A. 1964. Isolation of acrolein from incubated mixtures of spermine with calf serum and its effects on mammalian cells. Arch. Biochem. Biophys. 106: 240.

Alarcon, R.A. 1970. Acrolein. IV. Evidence for the formation of the cytotoxic aldehyde acrolein from enzymically oxidized spermine or spermidine. Arch. Biochem. Biophys. 137: 365.

Alarcon, R.A. 1972. Acrolein, a component of a universal cell-growth regulatory system. Jour. Theor. Biol. 37: 159.

Alarcon, R.A. 1976a. Formation of acrolein from various amino-acids and polyamines under degradation at 100°C. Environ. Res. 12: 317.

Alarcon, R.A. 1976b. Studies on the in vivo formation of acrolein. 3-Hydroxypropylmercapturic acid as an index of cyclophosphamide (NSC-26271) activation. Cancer Treat. Rep. 60: 327.

Alarcon, R.A. and J. Meienhofer. 1971. Formation of the cytotoxic aldehyde acrolein during in vitro degradation of cyclophosphamide. Nature. 233: 250.

Alarcon, R.A. and L.V. Melendez. 1974. Acrolein formation in aerobic interactions of methionine or spermine with ribose and from related compounds. Fed. Proc. 33: 681.

Alarcon, R.A., et al. 1972. Isophosphamide as a new acrolein producing antineoplastic isomer of cyclophosphamide. Cancer Res. 32: 2519.

Albin, T.B. 1962. Handling and Toxicology. In: C.W. Smith (ed.), Acrolein. John Wiley and Sons, Inc., New York. p. 234.

Altshuller, A.P. 1978. Assessment of the contribution of chemical species to the eye irritation potential of photochemical smog. Jour. Air Pollut. Control Assoc. 28: 594.

Altshuller, A.R. and S.P. McPherson. 1963. Spectrophotometric analysis of aldehydes in the Los Angeles atmosphere. Jour. Air Pollut. Control Assoc. 13: 109.

American Conference of Governmental Industrial Hygienists. 1974. Documentation of the Threshold Limit Value. 3rd ed. Am. Conf. Govt. Indus. Hyg. Cincinnati, Ohio.

American Conference of Governmental Industrial Hygienists. 1977. Threshold Limit Values for Chemical Substances in Workroom Air. Cincinnati, Ohio.

Anderson, K.J., et al. 1972. Evaluation of herbicides for possible mutagenic properties. Jour. Agric. Food Chem. 20: 649.

ARS Sprague-Dawley. 1974. Ordering manual.

Avent, A.G. 1961. Presence of acrolein in a Rhine wine. Liebfraumilch 1959. Analyst. 86: 479.

Bachrach, U. and E. Rosenkovitch. 1972. Effect of oxidized spermine and other aldehydes on the infectivity of vaccinia virus. Appl. Microbiol. 23: 232.

Bachrach, U., et al. 1971. Antivirus action of acrolein, glutaraldehyde, and oxidized spermine. Jour. Gen. Virol. 13: 415.

Basu, P.K., et al. 1971. Effect of air pollutants on the eye. II. Their effect on the oculocardiac reflex. Can. Jour. Ophthalmol. 6: 136.

Battista, S.P. and C.J. Kensler. 1970. Mucus production and ciliary transport activity. *In vivo* studies using the chicken. Arch. Environ. Health. 20: 326.

Bellar, T.A. and J.E. Sigsby. 1970. Direct gas chromatographic analysis of low molecular weight substituted organic compounds in emissions. Environ. Sci. Technol. 4: 150.

Bignami, M., et al. 1977. Relationship between chemical structure and mutagenic activity in some pesticides: The use of Salmonella typhimurium and Aspergillus nidulans. Mutat. Res. 46: 243.

Bilimoria, M.H. 1975. Detection of mutagenic activity of chemicals and tobacco smoke in bacterial system. Mutat. Res. 31: 328.

Bouley, G. 1973. Effects of atmospheric pollutants on health. Econ. Med. Anim. 14: 97.

Bouley, G., et al. 1975. Effects of a small dose of acrolein constantly inhaled by rats. Eur. Jour. Toxicol. Environ. Hyg. 8: 291.

Bouley, G., et al. 1976. Phenomena of adaptation in rats continuously exposed to low concentrations of acrolein. Ann. Occup. Hyg. 19: 27.

Bowmer, K.H. and M.L. Higgins. 1976. Some aspects of the persistence and fate of acrolein herbicide in water. Arch. Environ. Contam. Toxicol. 5: 87.

Bowmer, K.H. and G.R. Sainty. 1977. Management of aquatic plants with acrolein. Jour. Aquatic Plant Manage. 15: 40.

Bowmer, K.H., et al. 1974. Loss of acrolein from water by volatilization and degradation. Weed. Res. 14: 325.

Boyd, E.N., et al. 1965. Measurement of monocarbonyl classes in cocoa beans and chocolate liquor with special reference to flavor. Jour. Food Sci. 30: 854.

Boyland, E. 1940. Experiments on the chemotherapy of cancer: Further experiments with aldehydes and their derivatives. Biochem. Jour. 34: 1196.

Boyland, E. and L.F. Chasseaud. 1967. Enzyme-catalyzed conjugations of glutathione with unsaturated compounds. Biochem. Jour. 104: 95.

Brady, J.L., et al. 1977. Determination of acrolein in aqueous systems. Spec. Tech. Publ. STP 641, 89. Am. Soc. Test. Matter.

Bridges, R.B., et al. 1977. Effects of cigarette smoke components on in vitro chemotaxis of human polymorpho-nuclear leukocytes. Infect. Immun. 16: 240.

Brock, N. 1976. Comparative pharmacologic study *in vitro* and *in vivo* with cyclophosphamide (NSC-26271), cyclophosphamide metabolites, and plain nitrogen mustard compounds. Cancer Treat. Rep. 60: 301.

Butterworth, K.R., et al. 1978. The production of periportal necrosis by allyl alcohol in the rat. Br. Jour. Pharmacol. 63: 353.

Carl, M., et al. 1939. Physiological effects of garlic and derived substances. Am. Jour. Hyg. 29: 32.

Carpenter, C.P., et al. 1949. The assay of acute vapor toxicity, and the grading and interpretation of results on 96 chemical compounds. Jour. Ind. Hyg. Toxicol. 31: 343.

Carson, S., et al. 1966. Characterization of physical, chemical, and biological properties of mucus in the intact animal. Ann. N.Y. Acad. Sci. 130: 935.

Connors, T.A., et al. 1974. Active intermediates formed in the microsomal metabolism of cyclophosphamide and isophosphamide. Biochem. Pharmacol. 23: 115.

Cox, P.J., et al. 1976a. Studies on the selective action of cyclophosphamide (NSC-26271). Inactivation of the hydroxylated metabolite by tissue-soluble enzymes. Cancer Treat. Rep. 60: 321.

Cox, P.J., et al. 1976b. The use of deuterated analogs in qualitative and quantitative investigations of the metabolism of cyclophosphamide (NSC-26271). Cancer Treat. Rep. 60: 483.

Dalhamn, T. 1972. Factors influencing the respiratory toxicity of cigarette smoke. Jour. Natl. Cancer Inst. 48: 1821.

Day, A.G., et al. 1971. Improved instrumentation for determination of exhaust gas oxygenate content. NTIS-PB 210 251.

DiMacco, G. 1955. Acroleinosis. Sci. Med. Ital. 4: 100.

Egle, J.L., Jr. 1972. Retention of inhaled formaldehyde, propionaldehyde, and acrolein in the dog. Arch. Environ. Health. 25: 119.

Egle, J.L. and P.M. Hudgins. 1974. Dose-dependent sympathomimetric and cardioninhibitory effects of acrolein and formaldehyde in the anesthetized rat. Toxicol. Appl. Pharmacol. 28: 358.

Ellenberger, J. and G.R. Mohn. 1976. Comparative mutagenicity testing of cyclophosphamide and some of its metabolites. Mutat. Res. 38: 120.

Ellenberger, J. and G.R. Mohn. 1977. Mutagenic activity of major mammalian metabolites of cyclophosphamide toward several genes of Escherichia coli. Jour. Toxicol. Environ. Health. 3: 637.

El'Ode, K.E., et al. 1966. Effects of pH and temperature on the carbonyls and aromas produced in heated amino acid-sugar mixtures. Jour. Food Sci. 31: 351.

Epstein, S.S., et al. 1972. Detection of chemical mutagens by the dominant lethal assay in the mouse. Toxicol. Appl. Pharmacol. 23: 288.

Esterbauer, H., et al. 1975. Reaction of glutathione with conjugated carbonyls. Z. Naturforsch. C: Biosci. 30c: 466.

Esterbauer, H., et al. 1976. The reaction of cysteine with α-unsaturated aldehydes. Tetrahedron. 32: 285.

Farmer, P.B. and P.J. Cox. 1975. Synthesis and antitumor activity of 6-trifluoromethylcyclophosphamide and related compounds. Jour. Med. Chem. 18: 1106.

Feron, V.J. and A. Kruysse. 1977. Effects of exposure to acrolein vapor in hamsters simultaneously treated with benzo(a)pyrene or diethylnitrosamine. Jour. Toxicol. Environ. Health. 3: 379.

Feron, V.J., et al. 1978. Repeated exposure to acrolein vapor: Subacute studies in hamsters, rats and rabbits. Toxicology. 9: 47.

Graedel, T.E., et al. 1976. Kinetic studies of the photochemistry of the urban troposphere. Atmos. Environ. 10: 1095.

Gurtoo, H.L., et al. 1978. Studies on the binding of (3H-chloroethyl)-cyclophosphamide and 14(C-4)-cyclophosphamide to hepatic microsomes and native calf thymus DNA. Life Sci. 22: 45.

Gusev, M.I., et al. 1966. Substantiation of the daily average maximum permissible concentration of acrolein in the atmosphere. Hyg. i Sanit. 31: 3.

Hartstein, A.M. and D.R. Forshey. 1974. Coal mine combustion products. Neoprenes, polyvinyl chloride compositions, urethane foam, and wood. PB Rep. No. 240211. Natl. Tech. Inf. Serv., Springfield, Virginia.

Henderson, Y. and H.W. Haggard. 1943. Noxious Gases. Reinhold Publishing Co., New York.

Hess, L.G., et al. 1978. Acrolein and Derivatives. Kirk-Othmer Encyclopedia of Chemical Technology. 3rd ed. 1: 277.

Hirano, S., et al. 1962. Formation of acrolein by Clostridium perfringens. Acta. Med. Univ. Kagoshima. 4: 239.

Hoffmann, D., et al. 1975. On the carcinogenicity of marijuana smoke. Recent Adv. Phytochem. 9: 63.

Hohorst, H.J., et al. 1976. The problem of oncostatis specificity of cyclophosphamide (NSC-26271): Studies on reactions that control the alkylating and cytotoxic activity. Cancer Treat. Rep. 60: 309.

Holmberg, B. and T. Malmfors. 1974. Cytotoxicity of some organic solvents. Environ. Res. 7: 183.

Holzer, G., et al. 1976. Gas chromatographic-mass spectrometric evaluation of exhaled tobacco smoke. Jour. Chromatogr. 126: 771.

Hopkins, D.M. and A.R. Hattrup. 1974. Field evaluation of a method to detect acrolein in irrigation canals. NTIS-PB 234 926. Natl. Tech. Inf. Serv., Springfield, Virginia.

Horton, A.D. and M.R. Guerin. 1974. Determination of acetaldehydes and acrolein in the gas phase of cigarette smoke using cryothermal gas chromatography. Tob. Sci. 18: 19.

Hrdlicka, J. and J. Kuca. 1965. The changes of carbonyl compounds in the heat-processing of meat. Poultry Sci. 44: 27.

Hrdlicka, J., et al. 1968. Volatile carbonyl compounds isolated from hops. Sb. Vys. Sk. Chem. Technol, Praze, Potraviny. E23: 23.

Izard, C. 1973. Recherches sur les effets mutagenes de l'acroleine et des ses deux epoxydes: Le glycidol et le glycidal, sur Saecharomyces cerevisiae. C.R. Acad. Sci. Ser. D. 276: 3037. (Fre.)

Izard, C. and C. Libermann. 1978. Acrolein. Mutat. Res. 47: 115.

Jaeger, R.J. and S.D. Murphy. 1973. Alterations of barbiturate action following 1,1-dichloroethylene, corticosterone, or acrolein. Arch. Int. Pharmacodyn. Ther. 205: 281.

Jakab, G.J. 1977. Adverse effect of a cigarette smoke component, acrolein, on pulmonary antibacterial defenses and on viral-bacterial interactions in the lung. Am. Rev. Respir. Dis. 115: 33.

Jermini, D., et al. 1976. Quantitative determination of various gas-phase components of the side-stream smoke of cigarettes in the room air as a contribution to the problem of passive-smoking. Int. Arch. Occup. Environ. Health. 36: 169.

Johnson, K. 1980. Memorandum to D.W. Kuell. U.S. EPA. March 10.

Junk, G.A. and S.E. Stanley. 1975. Organics in drinking water: Part I-listing of identified chemicals. Rep. IS-3671. Energy Res. Div. Admin.

Kane, L.E. and Y. Alarie. 1977. Sensory irritation to formaldehyde and acrolein during single and repeated exposures in mice. Jour. Am. Ind. Hyg. Assoc. 38: 509.

Kane, L.E. and Y. Alarie. 1978. Evaluation of sensory irritation from acrolein-formaldehyde mixtures. Jour. Am. Ind. Hyg. Assoc. 39: 270.

Kantemirova, A.E. 1975. Illness with temporary work disability in workers engaged in acrolein and methylmercaptopropionaldehyde (MMP) production. Tr. Volgogr. Gos. Med. Inst. 26: 79. Chem. Abst. 88: 109868g.

Kaye, C.M. 1973. Biosynthesis of mercapturic acids from allyl alcohol, allyl esters, and acrolein. Biochem. Jour. 134: 1093.

Kaye, C.M. and L. Young. 1972. Synthesis of mercapturic acids from allyl compounds in the rat. Biochem. Jour. 127: 87.

Kaye, C.M. and L. Young. 1974. Acrolein as a possible metabolite of cyclophosphamide in man. Biochem. Soc. Trans. 2: 308.

Kilburn, K.H. and W.N. McKenzie. 1978. Leukocyte recruitment to airways by aldehyde-carbon combinations that mimic cigarette smoke. Lab. Invest. 38: 134.

Kimes, B.W. and D.R. Morris. 1971. Inhibition of nucleic acid and protein synthesis in Escherichia coli by oxidized polyamines and acrolein. Biochem. Biophys. Acta. 228: 235.

Kishi, M., et al. 1975. Effects of inhalation of the vapor from heated edible oil on the circulatory and respiratory systems in rabbits. Shokuhin Eiseigaku Zasshi. 16: 318.

Kissel, C.L., et al. 1978. Analysis of acrolein in aged aqueous media. Comparison of various analytical methods with bioassays. Jour. Agric. Food Chem. 26: 1338.

Koerker, R.L., et al. 1976. The cytotoxicity of short-chain alcohols and aldehydes in cultured neuroblastoma cells. Toxicol. Appl. Pharmacol. 37: 281.

Kusama, M., et al. 1978. Studies on cellulose cigarette smoke. Part V. Low boiling compounds in cellulose cigarette smoke. Agric. Biol. Chem. 42: 479.

Lacroix, M., et al. 1976. Irritant dermatitis from diallylglycol carbonate monomer in the optical industry. Contact Dermat. 2: 183.

Lelieveld, P. and L.M. Van Putten. 1976. Biologic activity of two derivatives and six possible metabolites of cyclophosphamide (NSC-26271). Cancer Treat. Rep. 60: 373.

Leuchtenberger, C., et al. 1968. Further cytological and cytochemical studies on the biological significance of the gas phase of fresh cigarette smoke. Z. Prav. Med. 13: 130.

Levaggi, D.A. and M. Feldstein. 1970. Determination of formaldehyde, acrolein, and low-molecular-weight aldehydes in industrial emissions on a single collection sample. Jour. Air Pollut. Control Assoc. 20: 312.

Love, S. and L.J. Bratzler. 1966. Tentative identification of carbonyl compounds in wood smoke by gas chromatography. Jour. Food Sci. 31: 218.

Low, E.S., et al. 1977. Correlated effects of cigarette smoke components on alveolar macrophage adenosine triphosphatase activity and phagocytosis. Am. Rev. Respir. Dis. 115: 963.

Low, R.B. and C.A. Bulman. 1977. Substrate transport by the pulmonary alveolar macrophage: Effects of smoke components. Am. Rev. Respir. Dis. 116: 423.

Lyon, J.P., et al. 1970. Repeated and continuous exposure of laboratory animals to acrolein. Toxicol. Appl. Pharmacol. 17: 726.

McAfee, K.B., Jr. and R. Ghanadesikan. 1977. A chemical and statistical formulation of the New Jersey/New York atmosphere. AICHE Symp. Ser. 73: 50.

Melnikov, N.N. 1971. Chemistry of Pesticides. Springer-Verlag, New York.

Morris, J.C. 1975. Formation of halogenated organics by the clorination of water supplies. EPA-600/1-75-002. U.S. Environ. Prot. Agency, Cincinnati, Ohio.

Moule, Y., et al. 1971. Effects of acrolein on transcription in vitro. Fed. Eur. Biochem. Soc. Lett. 16: 216.

Munsch, N. and C. Frayssinet. 1971. Action of acrolein on nucleic acid synthesis in vivo. Biochim. 53: 243.

Munsch, N., et al. 1973. Effects of acrolein on DNA synthesis in vitro. Fed. Eur. Biochem. Soc. Lett. 30: 286.

Munsch, N., et al. 1974a. In vitro binding of tritium-labeled acrolein to regenerating rat liver DNA polymerase. Experientia. 30: 1234.

Munsch, N., et al. 1974b. Incorporation of tritium-labeled acrolein in rat liver and in Dunaliella bioculata. Biochim. 56: 1433.

Murphy, S.D. 1965. Mechanism of the effect of acrolein on rat liver enzymes. Toxicol. Appl. Pharmacol. 7: 833.

Murphy, S.D. and S. Porter. 1966. Effects of toxic chemicals on some adaptive liver enzymes, liver glycogen, and blood glucose in fasted rats. Biochem. Pharmacol. 15: 1665.

Murphy, S.D., et al. 1963. Respiratory response of guinea pigs during acrolein inhalation and its modification by drugs. Jour. Pharmacol. Exp. Ther. 141: 79.

Murphy, S.D., et al. 1964. Biochemical effects in rats from irritating air contaminants. Toxicol. Appl. Pharmacol. 6: 520.

National Academy of Sciences. 1976. Vapor-phase organic pollutants: Volatile hydrocarbons and oxidation products. Washington, D.C.

National Academy of Sciences. 1977. Drinking Water and Human Health. Washington, D.C.

Newell, G.W. 1958. Acute and subacute toxicity of acrolein. Stanford Res. Ins., SRI Project No. 5-868-2. Summarized in Natl. Acad. Sci., 1977.

Nishimura, K., et al. 1971. Phagocidal effects of acrolein. Biochem. Biophys. Acta. 247: 153.

Nishimura, K., et al. 1972. Effects of oxidized spermine and acrolein on the transforming activity of T4 DNA. Biochem. Biophys. Acta. 262: 24.

O'Loughlin, E.M. and K.H. Bowmer. 1975. Dilution and decay of aquatic herbicides in flowing channels. Jour. Hydrol. 26: 217.

Pattle, R.E. and H. Cullumbine. 1956. Toxicity of some atmospheric pollutants. Brit. Med. Jour. 2: 913.

Philippin, C.L., et al. 1969. Physiological effect of acrolein on the mouse. Praeventivmedizin. 14: 317.

Phillips, B.J. 1974. Simple, small scale cytotoxicity test, and its uses in drug metabolism studies. Biochem. Pharmacol. 23: 131.

Pietruszko, R., et al. 1973. Comparison of substrate specificity of alcohol dehydrogenases from human liver, horse liver, and yeast towards saturated and 2-enoic alcohols and aldehydes. Arch. Biochem. Biophys. 159: 50.

Pilotti, A., et al. 1975. Effects of tobacco and tobacco smoke constituents on cell multiplication in vitro. Toxicology. 5: 49.

Rapoport, I.A. 1948. Mutations under the influence of unsaturated aldehydes. Dokl. Akad. Nauk. (USSR) 61: 713. Summarized in Izard and Libermann, 1978.

Reist, P.C. and F. Rex. 1977. Odor detection and respirator cartridge replacement. Jour. Am. Ind. Hyg. Assoc. 38: 563.

Renzetti, N.A. and R.J. Bryan. 1961. Atmospheric sampling for aldehydes and eye irritation in Los Angeles smog - 1960. Jour. Air Pollut. Control Assoc. 11: 421.

Riddick, J.H., Jr., et al. 1968. Effects of aldehydes on glucose metabolism in rabbit erythrocytes. Am. Chem. Soc. Div. Water Air Waste Chem. Gen. Pap. 8: 148.

Robinson, P.F. 1968. General Aspects of Physiology. In: R.A. Hoffman, et al. (eds.), The Golden Hamster: Its Biology and Use in Medical Research. Iowa State University Press, Ames. p. 111.

Rosenthaler, L. and G. Vegezzi. 1955. Acrolein in alcoholic liquors. Z. Lebensm. Untersuch. u. Forsch. 102: 117.

Rylander, R. 1973. Toxicity of cigarette smoke components. Free lung cell response in acute exposures. Am. Rev. Respir. Dis. 108: 1279.

Salem, H. and H. Cullumbine. 1960. Inhalation toxicities of some aldehydes. Toxicol. Appl. Pharmacol. 2: 183.

Savoretti, G. 1954. Dieta, acroleina e benzopirene. Neoplasie. 6: 185.

Schabort, J.C. 1967. Lactic dehydrogenase from human lung. Inhibition by certain water-soluble cilia-static components of tobacco smoke. Jour. S. African Chem. Inst. 20: 103.

Schuck, E.A. and N.A. Renzetti. 1960. Eye irritants formed during photo-oxidation of hydro-carbons in the presence of oxides of nitrogen. Jour. Air Pollut. Control Assoc. 10: 389.

Serafini-Cessi, F. 1972. Conversion of allyl alcohol into acrolein by rat liver. Biochem. Jour. 128: 1103.

Serjak, W.C., et al. 1954. Acrolein production by bacteria found in distillery grain mashes. Appl. Microbiol. 2: 14.

Shackelford, W.M. and L.H. Keith. 1978. Evolution of the Priority Pollutant List from the Consent Decree. In: Proc. Second Open Forum on Management of Petroleum Refinery Wastewater. EPA-600/2-78-058. p. 103.

Sim, V.M. and R.E. Pattle. 1957. Effect of possible smog irritants on human subjects. Jour. Am. Med. Assoc. 165: 1908.

Skog, E. 19 J. A toxicological investigation of lower aliphatic aldehydes. I. Toxicity of formaldehyde, acetaldehyde, propionaldehyde, and butyraldehyde; as well as of acrolein and crotonaldehyde. Acta Pharmacol. Toxicol. 6: 299.

Sladek, N.E. 1973. Cyclophosphamide metabolism. 5. Bioassay and relative cytotoxic potency of cyclophosphamide metabolites generated in vitro and in vivo. Cancer Res. 33: 1150.

Smith, C.W. 1962. Acrolein. John Wiley and Sons, Inc., New York.

Smith, L. and L. Packer. 1972. Aldehyde oxidation in rat liver mitochondia. Arch. Biochem. Biophys. 148: 270.

Smyth, H.F., et al. 1951. Range-finding toxicity data: List IV. AMA Arch. Ind. Health. 4: 119.

Sobolov, M. and K.L. Smiley. 1960. Metabolism of glycerol by an acrolein-forming lactobacillus. Biochem. Jour. 79: 261.

Sprince, H., et al. 1978. Ascorbic-acid and cysteine protection against aldehyde toxicants of cigarette smoke. Fed. Proc. 37: 247.

Stephan, C.E. 1980. Memorandum to J. Stara. U.S. EPA. July 3.

Stokinger, H.E. and R.L. Woodward. 1958. Toxicologic methods for establishing drinking water standards. Jour. Am. Water Works Assoc. 50: 515.

Szot, R.J. and S.D. Murphy. 1970. Phenobarbital and dexamethasone inhibition of the adrenocortical response of rats to toxic chemicals and other stresses. Toxicol. Appl. Pharmacol. 17: 761.

Szot, R.J. and S.D. Murphy. 1971. Relations between cyclic variations in adrenocortical secretory activity in rats and the adrenocortical response to toxic chemical stress. Environ. Res. 4: 530.

Tanimoto, M. and H. Uehara. 1975. Detection of acrolein in engine exhaust with microwave cavity spectrometer of stark voltage sweep type. Environ. Sci. Technol. 9: 153.

Thomson, M. and M. Colvin. 1974. Chemical oxidation of cyclophosphamide and 4-methylcyclophosphamide. Cancer Res. 34: 981.

Tillian, H.M., et al. 1976. Therapeutic effects of cysteine adducts of alpha, beta-unsaturated aldehydes on ehrlich ascites tumor of mice. Eur. Jour. Cancer. 12: 989.

Trattner, R.B., et al. 1977. Infrared analysis of the chemical composition of particulates in subway air. Spectrosc. Lett. 10: 699.

U.S. EPA. 1978. In- -pth studies on health and environmental impacts of selected water pollutants. Contract No. 68-01-4646. U.S. Environ. Prot. Agency.

U.S. EPA. 1980. Seafood consumption data analysis. Stanford Research Institute International, Menlo Park, California. Final rep., Task II, Contract No. 68-01-3887.

Van Overbeek, J., et al. 1959. Acrolein for control of water weeds and disease-carrying water snails. Science. 129: 335.

Watanabe, T. and D.M. Aviado. 1974. Functional and biochemical effects on the lung following inhalation of cigarette smoke and constituents. II. Skatole, acrolein, and acetaldehyde. Toxicol. Appl. Pharmacol. 30: 201.

Weber-Tschopp, A., et al. 1976a. Air pollution and irritation due to cigarette smoke. Soz.-Praeventivmed. 21: 101.

Weber-Tschopp, A., et al. 1976b. Objective and subjective physiological effects of passive smoking. Int. Arch. Occup. Environ. Health. 37: 277.

Weber-Tschopp, A., et al. 1977. Experimental irritating effects of acrolein on man. Int. Arch. Occup. Environ. Health. 40: 117.

Whitehouse, M.W. and F.W.J. Beck. 1975. Irritancy of cyclophosphamide-derived aldehydes (acrolein, chloracetaldehyde) and their effect on lymphocyte distribution in vivo: Protective effect of thiols and bisulfite ions. Agents Actions. 5: 541.

Wynder, E.L., et al. 1965. Ciliatoxic components in cigarette smoke. II. Carboxylic acids and aldehydes. Cancer. 18: 505.

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