ACROLEIN

Ambient Water Quality Criteria

Criteria and Standards Division
Office of Water Planning and Standards
U.S. Environmental Protection Agency
Washington, D.C.

CRITERION DOCUMENT

ACROLEIN

CRITERIA

Aquatic Life

For acrolein the criterion to protect freshwater aquatic life as derived using the Guidelines is 1.2 ug/l as a 24-hour average and the concentration whould not exceed 2.7 ug/l at any time.

The data base for saltwater aquatic life is insufficient to allow use of the Guidelines. The following recommendation is inferred from toxicity data for freshwater organisms.

For acrolein the criterion to protect saltwater aquatic life as derived using procedures other than the Guidelines is 0.88 ug/l as a 24-hour average and the concentration should not exceed 2.0 ug/l at any time.

Human Health

For the protection of human health from the adverse effects of acroelin ingested through the consumption of water and contaminated aquatic organisms a criterion of 6.5 ug/l is suggested.

Introduction

Acrolein has a wide variety of applications. It is directly used as a biocide for aquatic weed control; for algae, weed and mollusk control in re-circulating 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, 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 ($H_2C=\overset{H}{C}-$) and an aldehyde group ($-\overset{O}{\overset{\|}{C}}-H$) 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).

Freshwater acute toxicity values as low as 61 µg/l have been reported. A chronic fish value of 21.8 µg/l has been demonstrated. Acrolein has been found to bioconcentrate 344 times in a freshwater fish. Saltwater acute toxicity in one fish species was found to be 240 µg/l. No bioconcentration or chronic data are available for marine species.

Acrolein has been shown to produce a great variety of disorders in mammalian animals and man. However, it has not been shown to be a teratogen and only a mild to weak mutagen, if one at all, depending on the test system employed. Though it has been suspected as a carcinogen or cytotoxigen, information does not definitively produce evidence of confirmation.

Acrolein can enter the aquatic environment by its use as an aquatic herbicide, from industrial discharge, and from the chlor-

ination of organic compounds in waste water 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 fires, and cigarette smoke. An evaluation of available data indicates that, while industrial exposure to manufactured acrolein is unlikely, acrolein is pervasive from nonmanufactured sources. 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 was controlled only by resistance in the gas phase and any discrete 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 concentration 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 eight- to ten-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.

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AQUATIC LIFE TOXICOLOGY*

FRESHWATER ORGANISMS

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) shows 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 (Folmar, 1976).

Acute Toxicity

Seven LC50 values for 24-, 48-, and 96-hour exposures are available for six fish species (Table 1). All values were determined under static conditions. The adjusted values for the six species tested showed a narrow range of toxicity (23 to 87 µg/l). In the study of Bond, et al. (1960), the 24-hour LC50 of 80 µg/l

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*The reader is referred to the Guidelines for Deriving Water Quality Criteria for the Protection of Aquatic Life [43 FR 21506 (May 18, 1978) and 43 FR 29028 (July 5, 1978)] 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 the calculations for deriving various measures of toxicity as described in the Guidelines.

for chinook salmon is only 1.2 times the LC50 of 65 µg/l for rainbow trout. Among the adjusted LC50 values for four species tested by Louder and McCoy (1962), the highest, 87 µg/l for largemouth bass, is only 3.2 times higher than the lowest, 27 µg/l for mosquitofish. The geometric mean LC50, 40 µg/l, divided by the sensitivity factor (3.9), results in the Final Fish Acute Value for acrolein of 10 µg/l.

The data base for invertebrate species is limited to two static tests with Daphnia magna (Table 2); therefore, no comparison of relative species sensitivity can be made. The adjusted LC50 values of 48 µg/l and 68 µg/l show that Daphnia magna has about the same sensitivity to acrolein as fish. The geometric mean divided by the Guideline species sensitivity factor (21) results in the Final Invertebrate Acute Value of 2.7 µg/l which becomes the Final Acute Value since it is lower than the comparable value (10 µg/l) for fish.

Chronic Toxicity

The chronic toxicity data base consists of one value for fish and one for invertebrate species. A life cycle test with fathead minnows (Macek, et al. 1976) resulted in a chronic value of 21.8 µg/l (Table 3). Survival of newly hatched second generation (F_1) fathead minnow fry was significantly reduced at 42 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. The chronic value is about half the adjusted mean

LC50 value for fish and the adjusted LC50 value for fathead minnows (Table 1). The Final Fish Chronic Value is 3.3 µg/l.

Macek, et al. (1976) also 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 4). The unadjusted acute values for this species are 57 µg/l and 80 µg/l. These data show that there is little difference in concentrations between the acute and chronic effects of acrolein on Daphnia magna. The chronic value divided by the sensitivity factor (5.1) is the Final Invertebrate Chronic Value of 4.7 µg/l. As with the acute data, estimated chronic values show no appreciable difference in sensitivity between freshwater fish and invertebrate species. The slightly lower Final Fish Chronic Value of 3.3 µg/l is the Final Chronic Value.

It is interesting to note that the Final Invertebrate Chronic Value is higher than the Final Invertebrate Acute Value when both are derived from data for Daphnia magna. This is the result of the small difference in the acute and chronic toxicity of this species as discussed above and the fact that the species sensitivity factor (21) for acute data is larger than that (5.1) for chronic data. There are insufficient species tested to evaluate the accuracy of these factors and, therefore, they are not used for acrolein.

Plant Effects

No usable plant data were available.

Residues

Bluegills exposed for 28 days to 13 µg/l of ^{14}C-acrolein bioconcentrated acrolein 344 times (Table 5). The half-life was greater than 7 days. Thin layer chromatography was used to verify concentrations.

Miscellaneous

The additional information on short-term exposures of fish agree with previously described acute data. Bartley and Hattrup (1975) observed 32 percent mortality of rainbow trout exposed for 48 hours to 48 µg/l. The 24-hour mean time to death concentrations for brown trout and bluegill were calculated to be 46 µg/l and 79 µg/l, respectively (Burdick, et al. 1964). Macek, et al. (1976) reported a 6-day incipient LC50 of 84 µg/l for fathead minnows. The avoidance response seen in rainbow trout at 100 µg/l (Folmar, 1976) is above reported acute levels. Ninety-eight percent of adult snails and 100 percent of snail eggs died after a 24-hour exposure to 10,000 µg/l (Ferguson, et al. 1961).

CRITERION FORMULATION

Freshwater-Aquatic Life

Summary of Available Data

The concentrations below have been rounded to two significant figures.

Final Fish Acute Value = 10 µg/l

Final Invertebrate Acute Value = 2.7 µg/l

Final Acute Value = 2.7 µg/l

Final Fish Chronic Value = 3.3 µg/l

Final Invertebrate Chronic Value = 4.7 µg/l

Final Plant Value = not available

Residue Limited Toxicant Concentration = not available

Final Chronic Value = 3.3 µg/l

0.44 x Final Acute Value = 1.2 µg/l

The maximum concentration of acrolein is the Final Acute Value of 2.7 µg/l and the 24-hour average concentration is 0.44 times the Final Acute Value. No important adverse effects on freshwater aquatic organisms have been reported to be caused by concentrations lower than the 24-hour average concentration.

CRITERION: For acrolein the criterion to protect freshwater aquatic life as derived using the Guidelines is 1.2 µg/l as a 24-hour average and the concentration should not exceed 2.7 µg/l at any time.

Table 1. Freshwater fish acute values for acrolein

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Chinook salmon (fingerling), Oncorhynchus tshawytscha	S	U	24	80	29	Bond, et al. 1960
Rainbow trout (fingerling), Salmo gairdneri	S	U	24	65	23	Bond, et al. 1960
Fathead minnow, Pimephales promelas	S	U	48	115	51	Louder & McCoy, 1962
Mosquitofish, Gambusia affinis	S	U	48	61	27	Louder & McCoy, 1962
Bluegill, Lepomis macrochirus	S	U	96	100	55	Louder & McCoy, 1962
Bluegill, Lepomis macrochirus	S	U	96	90	49	U.S. EPA, 1978
Largemouth bass, Micropterus salmoides	S	U	96	160	87	Louder & McCoy, 1962

* S = static

** U = unmeasured

Geometric mean of adjusted values = 40.2 µg/l $\frac{40.2}{3.9}$ = 10 µg/l

Table 2. Freshwater invertebrate acute values for acrolein

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Cladoceran, Daphnia magna	S	U	48	57	48	Macek, et al. 1976
Cladoceran, Daphnia magna	S	U	48	80	68	U.S. EPA, 1978

* S = static

** U = unmeasured

Geometric mean of adjusted value = 57.2 µg/l $\frac{57.2}{21}$ = 2.7 µg/l

Table 3. Freshwater fish chronic values for acrolein

Organism	Test*	Limits (ug/l)	Chronic Value (ug/l)	Reference
Fathead minnow, Pimephales promelas	LC	11.4-41.7	21.8	Macek, et al. 1976

* LC = life cycle or partial life cycle

Geometric mean of chronic value = 21.8 µg/l $\frac{21.8}{6.7}$ = 3.3 µg/l

Lowest chronic value = 21.8 µg/l

Table 4. Freshwater invertebrate chronic values for acrolein

Organism	Test*	Limits (ug/l)	Chronic Value (ug/l)	Reference
Cladoceran, Daphnia magna	LC	16.9-33.6	24	Macek, et al. 1976

* LC = life cycle or partial life cycle

Geometric mean of chronic value = 24 µg/l $\frac{24}{5.1}$ = 4.7 µg/l

Lowest chronic value = 24 µg/l

Table 5. Freshwater residues for acrolein (U.S. EPA, 1978)

Organism	Bioconcentration Factor	Time (days)
Bluegill, *Lepomis macrochirus*	344	28

Table 6. Other freshwater data for acrolein

Organism	Test Duration	Effect	Result (ug/l)	Reference
Snail (adult), Australorbis glabratus	24 hrs	98% mortality	10,000	Ferguson, et al. 1961
Snail (egg), Australorbis glabratus	24 hrs	100% mortality	10,000	Ferguson, et al. 1961
Rainbow trout (fry), Salmo gairdneri	1 hr	Avoidance	100	Folmar, 1976
Rainbow trout, Salmo gairdneri	48 hrs	32% mortality	48	Bartley & Hattrup, 1975
Brown trout (fingerling), Salmo trutta	24 hrs	Mean time to death	46	Burdick, et al. 1964
Fathead minnow, Pimephales promelas	6 days	Incipient LC50	84	Macek, et al. 1976
Bluegill (fingerling), Lepomis macrochirus	24 hrs	Mean time to death	79	Burdick, et al. 1964

Lowest value = 46 µg/l

SALTWATER ORGANISMS

Introduction

Acrolein is used as a fungicide and a herbicide. It 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.

Acute Toxicity

The longnose killifish was exposed for 48 hours to acrolein in a flow-through test (Butler, 1965). The adjusted LC50 is 150 µg/l (Table 7). Adjusted LC50 values for six species of freshwater fish ranged from 23 to 87 µg/l (Table 1). The Final Fish Acute Value for saltwater fish, obtained using the species sensitivity factor (3.7), is 41 µg/l.

The adjusted LC50 values for three invertebrate species ranged from 33.1 to 764.8 µg/l (Butler, 1975; Dahlberg, 1971). Brown shrimp and the eastern oyster were the most sensitive species tested (Table 8). The Final Invertebrate Acute Value, obtained using the species sensitivity factor (49) is 2.0 µg/l, and was an order of magnitude less than the lowest LC50 value of tested species.

Chronic Toxicity

No chronic effects of acrolein on saltwater fish and invertebrate species have been reported.

Plant Effects

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

CRITERION FORMULATION

Saltwater-Aquatic Life

Summary of Available Data

The concentrations below have been rounded to two significant figures.

Final Fish Acute Value = 41 µg/l

Final Invertebrate Acute Value = 2.0 µg/l

Final Acute Value = 2.0 µg/l

Final Fish Chronic Value = not available

Final Invertebrate Chronic Value = not available

Final Plant Value = not available

Residue Limited Toxicant Concentration = not available

Final Chronic Value = not available

0.44 x Final Acute Value = 0.88 µg/l

No saltwater criterion can be derived for acrolein using the Guidelines because no Final Chronic Value for either fish or invertebrate species or a good substitute for either value is available.

Results obtained with acrolein and freshwater organisms indicate how a criterion may be estimated.

For acrolein and freshwater organisms 0.44 times the Final Acute Value is less than the Final Chronic Value which is derived from results of a life cycle test with the fathead minnow. Therefore, it seems reasonable to estimate a criterion for acrolein and saltwater organisms using 0.44 times the Final Acute Value.

The maximum concentration of acrolein is the Final Acute Value of 2.0 µg/l and the estimated 24-hour average concentration is 0.44 times the Final Acute Value. No important adverse effects on saltwater aquatic organisms have been reported to be caused by concentrations lower than the 24-hour average concentration.

CRITERION: For acrolein the criterion to protect saltwater aquatic life as derived using procedures other than the Guidelines is 0.88 µg/l as a 24-hour average and the concentration should not exceed 2.0 µg/l at any time.

Table 7. Marine fish acute values for acrolein (Butler, 1965)

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)
Longnose killifish (juvenile), Fundulus similis	FT	U	48	240	150

* FT = flow-through

** U = unmeasured

Geometric mean of adjusted values = 150 µg/l $\frac{150}{3.7}$ = 41 µg/l

Table 8. Marine invertebrate acute values for acrolein

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Eastern oyster, Crassostrea virginica	FT	U	96	55***	42.4	Butler, 1965
Barnacles (adult), Balanus eburneus	S	U	48	2,100	764.8	Dahlberg, 1971
Barnacles (adult), Balanus eburneus	S	U	48	1,600	582.7	Dahlberg, 1971
Brown shrimp (adult), Penaeus aztecus	FT	U	48	100***	33.1	Butler, 1965

* S = static; FT = flow-through

** U = unmeasured

***EC50: 50% decrease in shell growth of oyster; or loss of equilibrium of brown shrimp.

Geometric mean of adjusted values = 97.9 µg/l $\frac{97.9}{49}$ = 2.0 µg/l

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ACROLEIN

Mammalian Toxicology and Human Health Effects

EXPOSURE

Introduction

Acrolein is the simplest unsaturated aldehyde:

CH_2=CHCHO

It is a colorless volatile liquid. 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 pHs (Hess, 1978; Smith, 1962). Methods for acrolein analysis are summarized in Table 1A.

Acrolein has a wide variety of applications. It is directly used as a biocide for aquatic weed control; for algae, weed and mollusk control in re-circulating 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.

TABLE 1
Physical Properties of Acrolein
(Smith, 1962; Hess, 1978)

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

Table 1A

Methods for Acrolein Measurement (Brady et al., 1977; Kissel et al., 1978; Bellar and Sigsby, 1970).

Analytical Method	Detection Limit	Interferences
NMR (Aldehydic proton)	100 mg/l	few
Colorimetry		
2,4-D	80 µg/l	many
4-hexylresourcinol	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

The copolymers of acrolein are used in photography, for textile treatment, in the paper industry, as builders in laundry and dishwasher detergents, as coatings for aluminum and steel panels, as well as other applications (Smith, 1962; Hess, 1978). Hess (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.

The present technology for acrolein preparation employs catalytic oxidation of propene in the vapor phase. Typical reaction conditions consist of feeding propylene and air at 300 to 400^{o}C and 30 to 45 psi over the catalyst (usually of the bismuth-molybdenum or the antimony family) (Hess, 1978).

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

Ingestion from Water

There is no evidence that acrolein is a contaminant of potable water or water supplies. No available monitoring study has noted its presence, and acrolein is not listed in compendia on water monitoring (Junk and Stanley, 1975; Shackelford and Keith, 1976; Abrams, et al. 1975). Investigations on the fate of acrolein in water suggest that it dissipates with a half-life on the order of four to five hours. Based on these studies and the half-life in water (see Table 2), it can be assumed that negligible acrolein is present in water supplies.

Acrolein is applied to the 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). The 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 in aquatic organisms and sediments. In a review of the Russian literature, Melnikov (1971) indicates that acrolein is used as a biocide in water reservoirs.

Analytical difficulties complicate the measurement of aqueous acrolein. This problem has been demonstrated in studies on the degradation of aqueous acrolein. Some of these analytical problems could exist in measurements of acrolein in other media.

TABLE 2

First Order Rate Constants of Acrolein Degradation in Laboratory Experiments (Bowmer and Higgins, 1976)

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

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

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 ten analytical techniques on six pH buffer systems (pH 5,7 and 9). 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' Poropaks Q with injection temperature of 250^{o}C and column at 200^{o}C),

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

(i) polarographic analysis,

(j) fluorometric analysis directly on 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.

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 rate in laboratory and field studies. They evaluated the possible degradation pathway in buffered, distilled water. At pH 5, the acrolein reacted by a reversible hydrolysis and yielded an equilibrium mixture containing β-hydroxypropionaldehyde: acrolein in 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 as chemical degradation and suggested, but did not demonstrate, that it further degraded to carboxylic acid via 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, but that it was not a biocide. They resolved the analysis problem by flushing the volatile acrolein from a sample by means of an air stream, which left the non-volatile hydroxypropionaldehyde in solution. Acrolein concentration was measured as the difference between acrolein-2,4-DNP absorbance in samples before and after the flush (Bowmer, et al. 1974). Their laboratory studies utilized samples sealed in bottles and

maintained at 20.6°C. Table 2 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 3 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 to 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. Ozone will likely initially yield a malonozonide. Aqueous chlorine (which exists as HOCl) will probably degrade acrolein as follows (Hess, et al. 1978): $CH_2 = CH\text{-}CHO + HOCl \longrightarrow HOCH_2\ CHClCHO + ClCH_2CH(OH)CHO$. The relative amounts of these two possible initial acrolein derivatives and their degradation products are not known (Morris, 1975).

TABLE 3

Acrolein Dissipation in Two Canals of the Columbia River Basin Over 48 Hours (Hopkins and Hattrup, 1974)

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

Ingestion from Foods

Acrolein is a common component of food at ug/g concentrations. 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. The synthetic mixture contained amino acids (glycine, glutamic acid, lysine, methionine, and phenylalanine) and sugar (glucose, fructose, maltose, and sucrose). Acrolein was identified (by 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^{o}C) or of heating the synthetic potato mixture (60 minutes at 100^{o}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 2.5 to 30 mg/m^3 acrolein in the vapors 15 cm above the surface of the heated oil. Cooking about 20 g of potatoes or onions in the oil yielded 200 to 400 ug 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 liters of distilled water for three hours) or roasting (3 kg at 170 to 190°C for three hours). Raw turkey was extracted at 2°C with 75 percent ethanol for 72 hours and volatiles were collected by vacuum distillation. The carbonyl fraction was derivatized with 2,4-DNP and the derivatives 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 hardwood sawdust (mainly maple) burned on a hot plate (490 to 500°C) and from commercial smokehouses (operated at 48 to 49.5°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 one percent sodium bisulfite solution and was quantified by colorimetric 4-hexylresorcinol method. At the emission outlet (after burner abatement device) they measured 0.60 mg/m^3 acrolein, while no acrolein was detected in the inlet air.

Boyde, 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 the derivatization. The 2,4-DNP derivatives were separated into fractions prior to measurement. They measured 2-enol concentrations of 0.6 to 2.0 μmoles/100 g fat in raw cocoa beans and 1.3 to 5.3 μmoles/100 g in the chocolate liquor.

Alcoholic beverages often contain trace amounts of acrolein (Rosenthaler and Vegezzi, 1955). It sometimes is a problem since it causes an organoleptic condition called "pepper" by the alcohol fermentation industry. As a means of controlling the "pepper" character, acrolein production has been investigated. 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 adapts corrective procedures to reduce "pepper" by reducing acrolein concentration.

The chief pathway for acrolein entry to the alcohol has been delineated as mash fermentation (Serjak, et al. 1954; Sobolov and Smiley, 1960; Hirano, et al. 1962). When glucose levels in the mash are low, some bacterial strains convert glycerol to acrolein.

Avent (1961) investigated the contamination of a wine with 14 μg/g of acrolein, which was initially acrolein-free. 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. Processing can increase the acrolein content. Volatile fractions collected during cooking suggest that some acrolein would remain in the food. Based upon organoleptic factors, it is probably reasonable to assume that acrolein would seldom exceed 10 mg/l, if it were present.

A bioconcentration factor (BCF) relates the concentration of a chemical in water to the concentration in aquatic organisms, but BCF's are not available for the edible portions of all four major groups of aquatic organisms consumed in the United States. Since data indicate that the BCF for lipid-soluble compounds is proportional to percent lipids, BCF's can be adjusted to edible portions using data on percent lipids and the amounts of various species consumed by Americans. A recent survey on fish and shellfish comsumption in the United States (Cordle, et al. 1978) found that the per capita consumption is 18.7 g/day. From the data on the 19 major species identified in the survey and data on the fat content of the edible portion of these species (Sidwell, et al. 1974), the relative consumption of the four major groups and the weighted average percent lipids for each group can be calculated:

Group	Consumption (Percent)	Weighted Average Percent Lipids
Freshwater fishes	12	4.8
Saltwater fishes	61	2.3
Saltwater molluscs	9	1.2
Saltwater decapods	18	1.2

Using the percentages for consumption and lipids for each of these groups, the weighted average percent lipids is 2.3 for consumed fish and shellfish.

A measured steady-state bioconcentration factor of 344 was obtained for acrolein using bluegills containing about one percent lipids (U.S. EPA, 1978). An adjustment factor of 2.3/1.0 = 2.3 can be used to adjust the measured BCF from the 1.0 percent lipids of the bluegill to the 2.3 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 aquatic organisms consumed by Americans is calculated to be 344 x 2.3 = 790.

Inhalation

Acrolein inhalation occurs through many exposure routes. 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. 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 is a component of the urban smog; its concentration has been measured in Los Angeles atmosphere (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 chloridetrichloroacetic acid derivative (605 nm). Altshuller and McPherson (1963) also examined the atmosphere in 1961, but collected samples in bubblers containing the 4-hexylresorcinol reagent. Similar results were obtained with both studies. For ten days during a September-October-November period acrolein averaged 0.012 mg/m^3 with a peak concentration of 0.025 mg/m^3. Acrolein concentration for seven days of this period in 1961 averaged 0.018 mg/m^3 and peaked at 0.030 mg/m^3. For all 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 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 system containing a 0.313 u back-up filter. Potassium bromide pellets were prepared from each sample fraction. Evidence for the unsaturated aldehyde assignment were weak maxima observed at 1,695 cm^{-1} (6.90 u) in the pellets prepared from final inpactor and backup filter samples. They made no quantitative assessment.

Acrolein is a common constituent of vehicle exhaust (Natl. Acad. Sci. 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. It has been measured in diesel engines at 6.7 mg/m^3 and in internal combustion engines at 6.0, 22.5, 16.1, 14.7, and about 11.5 mg/m^3 (Natl. Acad. Sci. 1976). Day, et al. (1971) reported acrolein in emissions from a 1969 Chevrolet truck operated on a dynamometer. Acrolein was measured (by the colorimetric 2,4-DNP method) as 0.05 mg/m^3 for 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 (ten percent sucrose octaacetate on Gas-Chrom Z) at $-55^{o}C$ 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 applied in

measuring diesel exhaust, ambient air in an area of traffic and ambient air in 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 area of traffic.

Cigarette smoking produces acrolein. While a cigarette smoker directly inspires acrolein, some questions exist on passive exposure of non-smokers to acrolein, from 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 acrolein content of cigarettes by cryogenic trapping smoke onto a gas chromatography column. A six-part smoking machine was used with puff set at one-minute intervals, two-second durations, and 35 ml volume. Measured acrolein content for the tested cigarettes is described in Table 4.

Hoffman, et al. (1975) measured acrolein in marijuana and tobacco cigarettes using gas chromatography. Cigarettes were rolled to 85 mm length using standard cigarette paper. Experimental details were incomplete. Hoffman, et al. (1975) stated that smoking machines (1 or 20 channel) were employed and contained ten or fewer cigarettes. Error was placed at $\pm$4 to 6 percent. They reported acrolein delivery from mainstream smoke was 92 ug from marijuana cigarettes and 85 ug from tobacco cigarettes.

The potential exposure of non-smokers 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-

TABLE 4

Acrolein Delivery from some Experimental and some Commercial Cigarettes (Horton and Guerin, 1974)

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

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 sample tubes were directly desorbed and analyzed by GC-MS (mass spectral detection) using a glass capillary column. They compared the GC chromatograms of a sample of urban air (3.5 liter samples at 220 ml/min), a standard cigarette (IRI, University of Kentucky) (3 ml of smoke taken during a puff of two-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 vapors and that cigarette smoking did not appreciably add to these volatiles. The journal editor disagreed and in a footnote stated that the chromatograms suggested "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 within 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 sidestream smoke.

Acrolein has been identified as a component in 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. The 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, 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 will retain some acrolein. They never observed acrolein in emissions from the PV, neoprene, and urethane foam samples. Acrolein was in emissions from all wood samples.

Table 5 summarizes their results.

Dermal

Based upon the physical properties and known distribution of acrolein in the environment, dermal exposure is judged 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 of 0.4 mg to 0.6 mg/l for one to three 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, 81 to 84 percent of acrolein was retained. An increase in tidal volume (from 100 ml to 160 ml) resulted in a significant (p 0.001) decrease in acrolein retention (from 86 to 77 percent). This was consistent with finding that acrolein was taken up more readily by the upper than the lower respiratory tract.

Distribution

No studies were found that were directly relevant to the distribution of acrolein upon oral administration. 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 percent of the recovered radioactivity was found in the acid-soluble, lipid, protein, RNA, and DNA fractions

TABLE 5

Acrolein Produced by Burning Standard Southern Pine
(Hartstein and Forshey, 1974)

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

of the liver. Based on measurements taken ten 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 Effects on Experimental System" section.

Metabolism

In terms of the potential toxicologic effects of acrolein in drinking water, the instability of acrolein at acid pH's (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 pH's 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 suggest that acrolein is markedly less toxic when given by oral administration than when inhaled (see the "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}M, respectively (Pietruszko, et al. 1973). As cited above, 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; Alarcon and Melendez, 1974; Alarcon, et al. 1972; Conners, et al. 1974; Cox, et al. 1976a,b; Farmer and Cox, 1975; Gurtoo, et al. 1978; Hohorst, et al. 1976; and 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, Sub-acute, and Chronic Toxicity

Acute Effects on Experimental Systems: Several investigators have described the gross 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 6). 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 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

TABLE 6

Acute Lethal Toxicity of Acrolein (Albin, 1962)

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

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 and 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 inhalation of acrolein at concentrations of 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 guinea pigs. 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. Mice exposed to acrolein in air at concentrations of 2.3 to 4.6 mg/m^3 for 24 hours evidenced decreased pulmonary killing of Staphylococcus aureus and Proteus mirabilis. This decrease in intrapulmonary bacterial killing was aggravated in mice with viral pneumonia (Jakab, 1977). Kilburn and McKenzie (1978) have shown that inhalation of acrolein (13.8 mg/m^3 x 4 hours) is cytotoxic to the airway cells of hamsters, causing both immediate and delayed exfoliation. When administered with or adsorbed onto carbon particles, acrolein induced leukocyte recruitment to the airways, mimicking the effect of whole cigarette

smoke. In single ten-minute inhalation exposure to 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 causes the same effect and exhibits 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 ATP-ase activity (Low, et al. 1977) and to inhibit the uptake of cycloleucine and -aminoisobutyrate but not 3-0-methyglucose (Low and Bulman, 1977). However, acrolein has been shown to inhibit the uptake of glucose by rabbit erythocytes (Riddick, et al. 1968).

Egle and Hudgins (1974) noted that low doses (0.05 mg/kg)

of acrolein administered by intravenous injection to the rat caused an increase in blood pressure but that 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. Similar effects were noted in one-minute inhalation exposures to acrolein in which concentrations of 2.5 and 5.0 mg/l induced depressor effects. 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 bradycardic response. Tachycardia was attributed to increased sympathetic discharge caused by eye irritation. Since the bradycardic 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} m moles/ml for spermine, 2.8 to 3.1 x 10^{-5} m moles/ml for spermidine, and 2.6 to 3.5 x 10^{-5} m moles/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 virucidal 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 consistantly 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 one to five 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 mice 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 cytotoxic activities 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 non-toxic (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 transfered 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 uM) 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 ug 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 2.5×10^{-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 the "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 one-month inhalation exposures of rats to acrolein at a concentration of 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 a concentration of 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 7. 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 body weight in mice exposed to acrolein in the air at concentrations of 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 six 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. The following biological end points 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. No gross effects were noted in the continuous exposures to 0.48 and 0.53 mg/m^3 or in the repeated exposures to 1.6 mg/m^3 acrolein. 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 1.6 mg/m^3 acrolein 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 trachea from dogs and monkeys were attributed to acrolein

TABLE 7

Relative Weights of Lungs and Liver, and Serum Level of Acid Phosphatases (n = number of rats, m = mean value, s.d. = standard deviation) (Bouley, et al. 1976)

Parameters	Time	Control rats	Test rats	Statistical analysis
$\frac{\text{lungs weight}}{\text{body weight}} \times 100$	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
$\frac{\text{liver weight}}{\text{body weight}} \times 100$	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 77 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		

exposure. In addition, this exposure induced necrotizing bronchitis and bronchiolitis with squamous metaplasia in the lungs of seven of nine monkeys. Similar pathological results were noted in continuous exposures to 2.3 and 4.1 mg/m^3.

Feron, et al. (1978) exposed hamsters, rats, and rabbits to acrolein vapor at concentrations of 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, pack cell volume, hemoglobin concentration, and the number of lymphocytes and a decrease in the number of neutrophilic leukocytes. Additional changes noted in this study are summarized in Table 8.

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) indicates 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 unpalability of the drinking water. Similar results have been reported by Newell (1958) (summarized in Natl. Acad. Sci. 1977). In one study, acrolein was added to the drinking water of male and female rats at concentrations of 5, 13,

TABLE 8

Summary of Treatment-Related Effects in Hamsters, Rats and Rabbits Repeatedly Exposed to Acrolein for 13 Weeks (Feron, et al. 1978)

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

[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.

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 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 one of five 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 - 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 9, 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 one percent, six of 48 subjects evidenced a positive response (two erythemas and four serious edemas with bullae). At a concentration of ten percent, all eight subjects evidenced a positive response. Histological findings of a second series of tests with ten percent acrolein are summarized in Table 10.

TABLE 9

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 irritation	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, irritating to exposed mucosal surfaces	

TABLE 10

Patch Tests with ten percent Acrolein in Ethanol on Control Subjects (Biopsied at 48 Hours) (Lacroix, et al. 1976)

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

Kaye and Young (1974) have detected 3-hydroxypropylmercapturic in the urine of patients receiving cyclophosphamide orally (50 mg twice or thrice daily) but not in the urine of untreated humans. Based on analogies to the metabolic patterns of cyclophosphamide in rats, these investigators concluded that acrolein is probably a metabolite of cyclophosphamide in man.

In studies on human polymorphonuclear leukocytes (PMN's), 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 non-competitive with respect to NADH and uncompetitive with respect to 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), methylmercaptor-

propionaldehyde (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 and greater than seven years (Kantemirova, 1975).

Synergism and/or Antagonism

Acrolein is highly reactive with 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, 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 was blocked by N-acetylcysteine, penicillamide, glutathione, δ-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 time (Jaeger and Murphy, 1973).

Teratogenicity

No reports have been encountered on the potential teratogenicity of acrolein.

Bouley, et al. (1976) exposed male and female rats to 1.3 mg/m^3 acrolein vapor for 26 days and found no significant differences in the number of pregnant animals as well as 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 eight-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-methyltryptophan 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 of 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 our review of the literature. In the chronic inhalation study by Feron and Kruysse (1977), summarized in the "Chronic

Toxicity to Experimental Animals" section, acrolein gave no indication of carcinogenic activity, had no effect on the carcinogenic activity of diethylnitrosamine, and had a minimal effect on the carcinogenic activity of benzo(α) pyrene. Detailed tumor pathology from this study is presented in Table 11. 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 (1979). In this study, hamsters were exposed to 11.5 mg/m^3 acrolein vapor, six hours per day, five days per week, throughout their lifespan. No evidence was found that acrolein was a carcinogen or a cocarcinogen with either benzo(α)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 ($p < 0.1$) inhibitory effect on the growth of spontaneous skin carcinomas and a significant ($p < 0.05$) inhibitory effect on the growth of grafted sarcomas.

TABLE 11
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
(Feron and Kruysse, 1977)

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	0	5
Trachea										
Polyp	0		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	3	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 11 (Cont.)

Site and type of tumors	Incidence of tumors							
	Inhalation of air				Inhalation of acrolein			
	0.9% NaCl[a,b]	BP[c] (18.2 mg)	BP[d] (36.4 mg)	DENA[e]	0.9% NaCl[a,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	3	0	0	1	3	0
Adenosquamous adenoma	0	1	2	0	0	1	1	0
Adenocarcinoma	0	0	2	0	0	0	0	0

TABLE 11 (Cont.)

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									
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

[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 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 recommended 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 cigarette smoke 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 ("Carcinogenicity" section). Water quality criteria for acrolein could be derived from the TLV, chronic inhalation studies, and subacute oral studies using non-carcinogenic biological responses.

Stokinger and Woodward (1958) have described a method for calculating water quality criteria from TLV's. 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. As summarized in the "Chronic Toxicity to Experimental Animals" section, 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 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^3/1000 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 (Natl. Acad. Sci. 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 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 "Subacute Toxicity to Experimental Animals" section). Because this study did not involve a chronic exposure, the National Academy of Sciences (1977) declined to derive an acceptable daily intake for man based on this study. However, McNamara (1976) has suggested that subacute exposures can be used to estimate chronic no-effect levels. Based on an extensive review of the literature comparing subacute and chronic toxicity tests, McNamara (1976) noted that "for 95 percent of chemical compounds...(on which data were available)...a three-month no-effect dose divided by a factor of ten will produce no effects in a lifetime." Using this approximation for acrolein, the no-observable-effect level for acrolein on rats can be estimated at 20 mg/l of water. 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 is estimated at 1.56 mg/kg. This value may be converted into an ADI for man by applying an uncertainty factor. Since the chronic no-effect dose is merely an estimate based on observed relation-ships between subacute and chronic toxicity, an uncertainty factor of 1,000 is recommended (Natl. Acad. Sci. 1977). Thus, the estimated ADI for man is 1.56 μg/kg or 109 μg/man, assuming a 70 kg body weight. Therefore, consumption of 2 liters of water daily and 18.7 grams of contaminated fish having a bioconcentration factor

of 790, would result in, assuming 100 percent gastrointestinal absorption of acrolein, a maximum permissible concentration of 6.50 µg/l for the ingested water:

$$\frac{109\ \mu g}{(2\ \text{liters} + (790 \times 0.0187) \times 1.0} = 6.50\ \mu g/l$$

This calculation assumes that 100 percent of man's exposure is assigned to the ambient water pathways of 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 is 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 1000, the criterion level corresponding to the calculated acceptable daily intake of 1.56 µg/kg, is 6.50 µg/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 7.38 µg/l if exposure is assumed to be from the consumption of fish and shellfish products alone.

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