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United States
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Office of Emergency and
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Washington DC 20460

Office of Research and Development
Office of Health and Environmental
Assessment
Environmental Criteria and
Assessment Office
Cincinnati OH 45268

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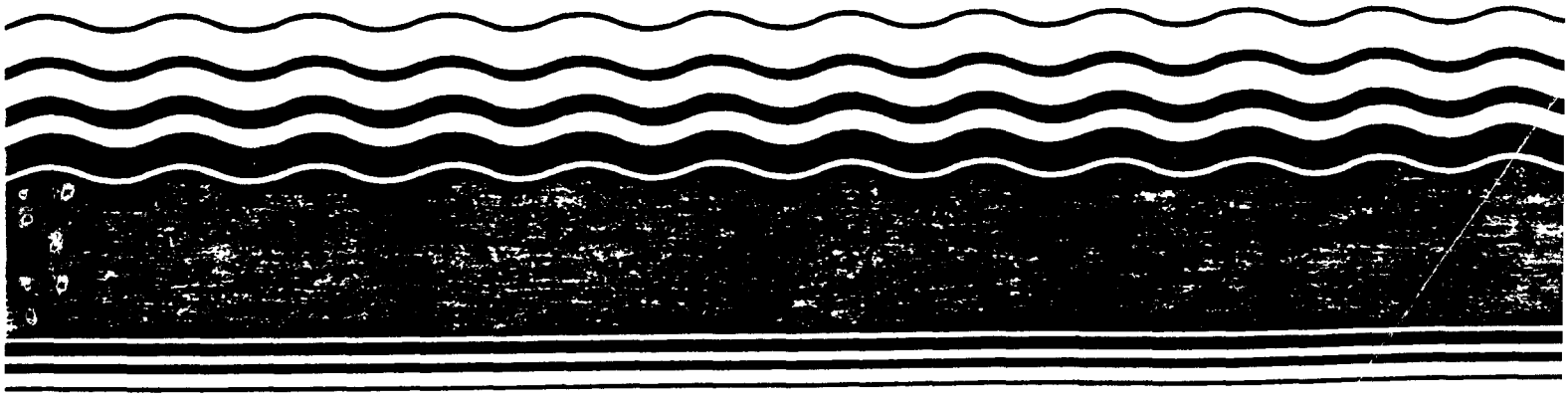
# HEALTH EFFECTS ASSESSMENT FOR PHENOL



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U.S. Environmental Protection Agency
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## DISCLAIMER

This report has been funded wholly or in part by the United States Environmental Protection Agency under Contract No. 68-03-3112 to Syracuse Research Corporation. It has been subject to the Agency's peer and administrative review, and it has been approved for publication as an EPA document. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

# PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with phenol. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the Chemical Abstracts, TOXLINE, CANCERLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to September, 1984. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1980b. Ambient Water Quality Criteria for Phenol. Environmental Criteria and Assessment Office, Cincinnati, OH. EPA-440/5-80-066. NTIS PB 81-117772.

U.S. EPA. 1985. Health and Environmental Effects Profile for Phenol. Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH, OHEA for the Office of Solid Waste and Emergency Response, Washington, DC.

The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, the AIS or acceptable intake subchronic, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for AIS estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure.

The AIC, acceptable intake chronic, is similar in concept to the ADI (acceptable daily intake). It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980a) for a discussion of this concept]. The AIC is route specific and estimates acceptable exposure for a given route with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for ranking reportable quantities; the methodology for their development is explained in U.S. EPA (1983).

For compounds for which there is sufficient evidence of carcinogenicity, AIS and AIC values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980a). Since cancer is a process that is not characterized by a threshold, <u>any</u> exposure contributes an increment of risk. Consequently, derivation of AIS and AIC values would be inappropriate. For carcinogens, $q_1^*$s have been computed based on oral and inhalation data if available.

## ABSTRACT

In order to place the risk assessment evaluation in proper context, refer to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates presented.

Only one applicable study was found which addressed the toxicological consequences of orally administered phenol. From this subchronic study an AIS of 7 mg/day and an AIC of 7 mg/day were estimated based on the approach suggested by U.S. EPA (1980b). This value is supported by descriptive chronic studies. This acceptable intake estimate should be reviewed when adequate chronic data are available.

Inhalation exposure data are similarly limited. A number of subchronic animal studies were located, but all were of limited use for risk assessment as discussed in the text. Based on the TLV and AIS of 13.6 mg/day and an AIC of 1.4 mg/day have been estimated. A CS of 35 was calculated for the effects (death and severe histopathological lesions) observed in guinea pigs exposed by inhalation.

All of these estimates should be reviewed when additional data are available.

## ACKNOWLEDGEMENTS

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| ADI | Acceptable daily intake |
| AIC | Acceptable intake chronic |
| AIS | Acceptable intake subchronic |
| CAS | Chemical Abstract Service |
| CS | Composite score |
| LOAEL | Lowest-observed-adverse-effect level |
| MED | Minimum effective dose |
| NOAEL | No-observed-adverse-effect level |
| ppm | Parts per million |
| $RV_d$ | Dose-rating value |
| $RV_e$ | Effect-rating value |
| STEL | Short-term exposure limit |
| TLV | Threshold limit value |
| TWA | Time-weighted average |

# 1. ENVIRONMENTAL CHEMISTRY AND FATE

The relevant physical and chemical properties and environmental fate of phenol (CAS No. 108-95-2) are summarized below.

| | |
|---|---|
| Chemical class | monocyclic aromatic alcohol |
| Molecular weight | 94.11 |
| Vapor pressure | 0.341 mm Hg at 25°C (Mabey et al., 1981) |
| Water solubility | $9.3 \times 10^{-4}$ mg/ℓ at 25°C (Callahan et al., 1979) |
| Octanol/water partition coefficient | 28.8 (Callahan et al., 1979) |
| Bioconcentration factor | 2 (Kobayashi et al., 1979) |
| Half-lives in air and water | 15 hours to 9 days (Hendry and Kenley, 1979; Lee and Ryan, 1979; Rubin and Alexander, 1983; Scott et al., 1982) |

Phenol will biodegrade completely in soil in 2-5 days (Baker and Mayfield, 1980; Ehrlich et al., 1982; Delfino and Dube, 1976). Because of its high water solubility and poor adsorption to soil, phenol is expected to have a high soil mobility. Despite the expected high soil mobility, biodegradation is sufficiently rapid so that the probability of groundwater contamination through leaching is insignificant (Ehrlich et al., 1982). In spills or similar cases where high concentrations of phenol may destroy degrading microbial populations, leaching is expected to occur (Ehrlich et al., 1982; Delfino and Dube, 1976).

## 2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS

### 2.1. ORAL

Pertinent data regarding the oral absorption of phenol could not be located in the available literature.

### 2.2. INHALATION

Quantitative data regarding the absorption of phenol by inhalation were not located in the available literature; however, that phenol is in fact absorbed by inhalation can be inferred from the following studies.

Deichmann et al. (1944) exposed 12 guinea pigs, 15 rats and 6 rabbits to vapor containing 100-200 mg/m$^3$ phenol 7 hours/day, 5 days/week. After 38 days of treatment, levels of free phenol (1.0 mg/100 mℓ) and conjugated phenol (0.4 mg/100 mℓ) were found in the blood of the guinea pigs. After 37 and 88 days of treatment, levels of free phenol and conjugated phenol in the blood of the treated rabbits were 0.5 mg/100 mℓ and 0.7 mg/100 mℓ, respectively. Blood phenol concentrations were not reported for the rats in this study.

Piotrowski (1971) exposed human volunteers (seven males, one female) to vapors of phenol through facemasks (6-20 mg/m$^3$) for 8 hours. Urine samples taken every 2 hours revealed that 60-80% of the administered dose was retained throughout the period of exposure, regardless of the level of exposure. Furthermore, 99$\pm$8% of the inhaled dose was excreted within 16 hours post-treatment.

Ohtsuji and Ikeda (1972) found free phenol and conjugated phenol in the urine of workers exposed to 0-12.5 mg/m$^3$ phenol (estimated from air samples). Levels of phenol in the urine (unspecified in NIOSH, 1976), however, were not dose-dependent. These studies indicate that phenol is readily absorbed by inhalation.

## 3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

### 3.1. SUBCHRONIC

3.1.1. Oral. In the only study located in the available literature, Dow Chemical Co. (1976) exposed rats to either 50 or 100 mg/kg/day phenol by gavage, 135 times for 6 months. Neither the numbers of rats nor the intervals between treatments were specified. Rats exposed to 50 mg/kg/ day were reported to suffer "slight" kidney damage, the nature of which was unspecified. Rats exposed to the higher level of treatment suffered "some" unspecified liver and kidney damage. A LOAEL of 50 mg/kg/day can thus be established on the basis of kidney damage, but this must be done with caution, because of the lack of details in the U.S. EPA (1980b) document.

3.1.2. Inhalation. Three subchronic inhalation studies reported by NIOSH (1976) are summarized in Table 3-1.

In the subchronic study by Deichmann et al. (1944), guinea pigs, rats and rabbits exhibited a wide range of sensitivities to 100 mg/m$^3$ phenol. Of twelve treated guinea pigs, five died after only 28 days of exposure. The others had weight loss, signs of paralysis and numerous pathological changes. In contrast, rats given the same level of exposure for 74 days had no external or internal signs of toxicity. Pathological changes in the absence of external signs of toxicity were reported for rabbits exposed to phenol at a level of 100 mg/m$^3$.

Rats, mice and monkeys exposed by inhalation to phenol at a level of 19 mg/m$^3$ for 8 hours/day, 5 days/week for 90 days, had no significant adverse toxic effects when compared with control animals (Sandage, 1961).

In contrast, Mukhitov (1964) observed adverse effects of exposure to phenol in rats at the 0.11 mg/m$^3$ and 5.2 mg/m$^3$ levels of exposure. In this study, however, rats were exposed continuously for 61 days, whereas in the study by Sandage (1961), rats were exposed noncontinuously for 90 days.

TABLE 3-1

Subchronic Exposure to Phenol by Inhalation

| Species | No. of Animals | Dose | Exposure Period | Effects | Reference |
|---|---|---|---|---|---|
| Guinea pigs | 12 treated, no controls | 100-200 mg/m³ (26-52 ppm) | 7 hours/day, 5 days/week for 28 days | Five deaths; weight loss, signs of paralysis; pathological changes included extensive necrosis of the myocardium, acute lobular pneumonia, vascular damage, renal and hepatic damage. | Deichmann et al., 1944 |
| Rabbits | 6 treated, no controls | 100-200 mg/m³ (26-52 ppm) | 7 hours/day, 5 days/week for 88 days | No external signs of toxicity; pathological changes included lobular pneumonia, chronic degeneration of pulmonary blood vessels, liver and kidney damage. | |
| Rats | 15 treated, no controls | 100-200 mg/m³ (26-52 ppm) | 7 hours/day, 5 days/week for 74 days | No internal or external signs of toxicity | |
| Rats | 50 treated, 50 controls | 19 mg/m³ (5 ppm) | 8 hours/day, 5 days/week for 90 days | No significant difference between treated animals and their controls with respect to kidney function or hematological or urological variables. There was a slight gain in body weight for treated rats and monkeys and increased "endurance" (as indicated in stress test) in mice. | Sandage, 1961 |
| Monkeys | 10 treated, 10 controls | 19 mg/m³ (5 ppm) | | | |
| Mice | 100 treated, 100 controls | 19 mg/m³ (5 ppm) | | | |
| Rats | 15 | 0.0, 0.01 mg/m³ (0.003 ppm), 0.11 mg/m³ (0.03 ppm), 5.2 mg/m³ (1.4 ppm) | continuous, 61 days | No effects at 0.01 mg/m³; extensor muscle chronaxy was significantly different from controls at 0.11 mg/m³. Blood cholinesterase activity was slightly increased at 0.11 mg/m³, but no other effects were observed. Animals treated at 5.2 mg/m³ were sluggish, exhibited lower rates of weight gain, had significantly increased blood cholinesterase activity, and had shortened extensor muscle chronaxy and lengthened flexor muscle chronaxy. | Mukhitov, 1964 |

Since phenol is known to be excreted rapidly and completely after treatment has been withdrawn (99±8% of the inhaled dose was excreted within 16 hours post-treatment in human volunteers exposed for 8 hours to 6-20 mg/m$^3$) (Piotrowski, 1971), perhaps the animals in the Sandage study had enough time (2-day breaks between 5-day exposures) to "recover" between exposures.

The data provided by Sandage (1961) and Deichmann et al. (1944) cannot be used in the derivation of an AIS, since dose-response relationships were not established for a range of doses. The data by Mukhitov (1964) are not suitable for use in quantitative risk assessment, since the period of exposure was only 61 days.

3.2. CHRONIC

3.2.1. Oral. Heller and Pursell (1938) exposed rats to phenol by drinking water at levels ranging from 0-12,000 ppm for either 1 year or two, three or five generations. Growth, fecundity and general condition were the variables analyzed throughout the period of treatment. These data are summarized in Table 3-2. However, the lack of pathological examinations or functional tests in this study precludes the use of these data in the calculation of an AIC for human ingestion of phenol.

3.2.2. Inhalation. Pertinent data regarding chronic exposure to phenol by inhalation could not be located in the available literature.

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral. Pertinent data regarding the teratogenicity of orally administered phenol could not be located in the available literature; however, reproductive effects associated with ingestion of phenol were reported in the study by Heller and Pursell (1938) summarized in Table 3-2.

3.3.2. Inhalation. Pertinent data regarding the teratogenicity of inhaled phenol could not be located in the available literature.

TABLE 3-2

Chronic Oral Exposure of Rats to Phenol via Drinking Water[a,b]

| Dose (ppm) | Period of Exposure | Effects |
|---|---|---|
| 0, 100, 500, 1000 | 5 generations | ≤5000 ppm: no effect upon growth, general health or fecundity |
| 3000, 5000 | 3 generations | 7000 ppm: stunted growth in young rats |
| 7000, 8000 | 2 generations | ≥8000 ppm: numerous deaths of young rats (numbers unspecified); abnormal maternal care |
| 10,000, 12,000 | 1 year | 12,000 ppm: no reproduction<br>1000-12,000 ppm: older rats died more quickly than controls |

[a]Source: Heller and Pursell, 1938

[b]Numbers of animals were not reported in NIOSH, 1976.

## 3.4. TOXICANT INTERACTIONS

Pertinent data regarding toxicant interactions between phenol and other compounds could not be located in the available literature; however, Challis (1973) reported that phenol and nitrites could react to form p-nitrosophenol under *in vitro* conditions.

## 4. CARCINOGENICITY

### 4.1. HUMAN DATA

4.1.1. Oral. Data pertaining to the carcinogenicity of ingested phenol in humans could not be located in the available literature.

4.1.2. Inhalation. Data pertaining to the carcinogenicity of inhaled phenol in humans could not be located in the available literature.

### 4.2. BIOASSAYS

4.2.1. Oral. Data pertaining to the carcinogenicity of orally administered phenol in animals could not be located in the available literature.

4.2.2. Inhalation. Data pertaining to the carcinogenicity of inhaled phenol in animals could not be located in the available literature.

### 4.3. OTHER RELEVANT DATA

Phenol was reported to be mutagenic to Escherichia coli, but only at concentrations of phenol (0.1-0.2%) that caused a reduction in survival (0.5-1.7% survival) (Demerec et al., 1951). In an in vitro experiment, phenol induced mutation in gonads of Drosophila (Hadorn and Niggli, 1946). Dickey et al. (1949) reported that phenol was not mutagenic to Neurospora.

### 4.4. WEIGHT OF EVIDENCE

IARC has not evaluated the risk to humans associated with oral or inhalation exposure to phenol. Applying the criteria for overall weight of evidence of carcinogenicity to humans proposed by the Carcinogen Assessment Group of the U.S. EPA (Federal Register, 1984) no data are available regarding carcinogenicity of phenol in humans or animals and the chemical is most appropriately designated a Group D - Not Classified chemical.

## 5. REGULATORY STANDARDS AND CRITERIA

Based on subchronic animal studies (Deichman et al., 1944), the American Conference of Governmental Industrial Hygienists estab- lished a TWA-TLV of 19 mg/m³ and a STEL of 10 mg/m³ (ACGIH, 1983). NIOSH (1976) recommended a TWA-TLV for a 10-hour workday, 40-hour week of 20 mg/m³, and a 60 mg/m³ ceiling for a period of exposure not to exceed 15 minutes.

Based on the subchronic study by Dow Chemical Co. (1976) (discussed in Section 3.1.1. of this report), and using a safety factor of 500, the U.S. EPA (1980b) calculated an interim ADI of 0.1 mg/kg/day or 7.0 mg/man/day for ingestion of phenol. From this interim ADI, and assuming that 2.0 ℓ water/day and 0.0065 kg fish/day (with a bioconcentration factor of 1.4) are consumed by the standard 70 kg man, an interim ADI for drinking water of 3.5 mg/ℓ/day was calculated. However, since an organoleptic threshold (taste) of 0.3 mg/ℓ was reported, a criterion level for phenol in water of 0.3 mg/ℓ was established.

## 6. RISK ASSESSMENT

### 6.1. ACCEPTABLE INTAKE SUBCHRONIC (AIS)

6.1.1. Oral. Based on the rat study by Dow Chemical Co. (1976), a LOAEL of 50 mg/kg/day was established (see Section 3.1.1.) for slight kidney damage. Using this value and an uncertainty factor of 500 following the judgement of U.S. EPA (1980b), an oral AIS of 7.0 mg/man/day is derived for ingestion of phenol.

6.1.2. Inhalation. As discussed in Section 3.1.2., the available subchronic data are not suitable for use in quantitative risk assessment. However, the TLV of 19 mg/m³ can be used to estimate an AIS. Applying an uncertainty factor of 10 and expanding exposure to 7 days/week, the AIS in mg/day for a 70 kg man would be 13.6.

U.S. EPA (1985) calculated a CS for the effects (death, severe signs of toxicity and extensive histopathological changes) observed in guinea pigs exposed to atmospheric phenol at 100 mg/m³ 7 hours/day, 5 days/week for a total of 29 exposures (Deichmann et al., 1944). A human MED of 20.8 mg/day was calculated by expanding to continuous exposure, multiplying by 20 m³ the assumed daily inhalation volume of humans and an assumed absorption factor of 0.5, and dividing by an uncertainty factor of 10 to correct from subchronic to chronic data. This MED corresponds to an $RV_d$ of 3.5. The effects observed are assigned an $RV_e$ of 10. A CS of 35, the product of $RV_d$ and $RV_e$, is derived.

### 6.2. ACCEPTABLE INTAKE CHRONIC (AIC)

6.2.1. Oral. Only one chronic oral study was located in the available literature. As discussed in Section 3.2.2., these investigators (Heller and Pursell, 1938) reported only external effects, such as growth rates, general

condition, and fecundity. Calculation of an oral AIC from these data would be imprudent, since no pathological or functional analyses were performed. Based on the precedent established by U.S. EPA (1980b), the value of 7 mg/day as calculated in Section 6.1.1. is proposed as an interim oral AIC. This value should be reevaluated when adequate chronic data are available. In a similar manner, dividing the subchronic LOAEL for oral exposure (Section 6.1.1.) by a factor of 10, and then calculating the CS as described in Section 6.1.1., yields a CS of 19 for chronic oral exposure to phenol.

6.2.2. Inhalation. Data pertaining to the chronic toxicity of inhaled phenol could not be located in the available literature, and, as discussed in Section 3.1.2., the available subchronic data are not suitable for use in quantitative risk assessment. An inhalation AIC, however, can be calculated from the TWA-TLV of 10 mg/m$^3$ established by ACGIH (1983). Assuming a 70 kg man breathes a volume of 10 m$^3$ air per 8-hour workday and works 5 days/week, 8 hours/day, the TLV of 19 mg/m$^3$ is multiplied by the product of 10 m$^3$/day x 5-7 days/week to arrive at an inhaled dose of 135.7 mg phenol/man/day. Dividing this value by an uncertainty factor of 10 to account for the range of sensitivities in the human population, and an additional 10 because of animal data which indicate continuous exposures may have more severe consequences than discontinuous exposures which are similar to occupational exposure situations, a AIC of 1.4 mg phenol/man/day can be established.

Since the AIC was established from a TLV, a CS cannot be established.

6.3. CARCINOGENIC POTENCY ($q_1$*)

6.3.1. Oral. The lack of pertinent data regarding the carcinogenicity of ingested phenol precludes the assessment of carcinogenic risk.

6.3.2. Inhalation. The lack of pertinent data regarding the carcinogenicity of inhaled phenol precludes assessment of carcinogenic risk.

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## APPENDIX

### Summary Table for Phenol

| | Species | Experimental Dose/Exposure | Effect | Acceptable Intake (AIS or AIC) | Reference |
|---|---|---|---|---|---|
| **Inhalation** | | | | | |
| AIS | human | TLV = 19 mg/m³ | none | 13.6 mg/man/day | ACGIH, 1983 |
| AIC | human | TLV = 19 mg/m³ | none | 1.4 mg/man/day | ACGIH, 1983 |
| Maximum composite score | guinea pig | 100 mg/m³ 7 hours/day, 5 days/week for 29 exposures ($RV_d$ = 3.5) | death, severe toxicity and histopathological lesions ($RV_e$ = 10) | 35 | Deichmann et al., 1944; U.S. EPA, 1985 |
| **Oral** | | | | | |
| AIS | rat | LOAEL = 50 mg/kg/day | slight kidney damage | 7 mg/man/day | Dow Chemical Co., 1976 |
| AIC | rat | LOAEL = 50 mg/kg/day | slight kidney damage | 7 mg/man/day | Dow Chemical Co., 1976 |