DRAFT 3230

SEP 1 1983

# Use of Pharmacokinetic Data in Health Advisory Development

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## I. Introduction

Pharmacokinetics is the quantitative study of the metabolic processes of absorption, distribution, biotransformation, and elimination. The use of pharmacokinetic models to describe these processes allows predictions about body burden, duration of the toxicant in the body after exposure has been terminated and other information that may aid in assessing the hazards of chemicals to humans. Concepts and methodology have been developed extensively primarily for drugs and radionuclides. The concept and capability of calculating a dose from many organic pollutants or their active metabolites remain, however, in the neophyte state.

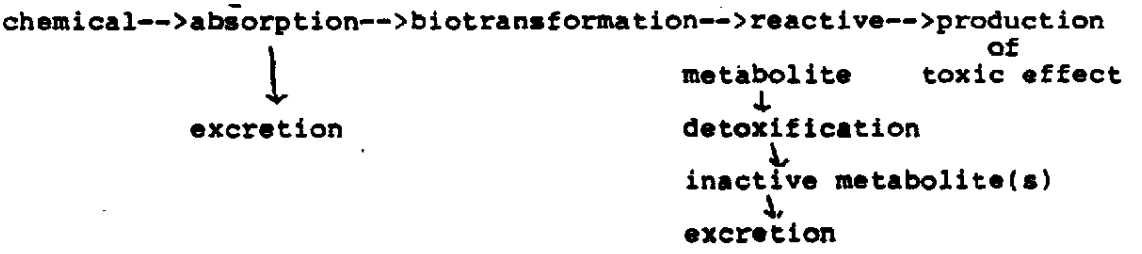
## II. Background

Methodologies are lacking for the use of pharmacokinetic data following exposure to a specific substance in various species when developing acceptable exposure levels in drinking water. The only assumptions which have been applied during the development of a Health Advisory relate to the percentage of absorption via ingestion and inhalation. Twenty-one

(21) of the 22 HAs drafted to date have been for organic compounds, either singly or in mixtures. The assumption made for these 21 chemicals was that the chemical is absorbed by ingestion to the degree of 100% by all species including the human with no accounting for differences in the rate of absorption.

The assumption of a 100% absorption of a chemical by all species may be considered over estimate in view of the fact that absorption represents only one parameter of pharmacokinetics meters while the influence of the remaining parameters, namely, distribution, metabolism and elimination of a chemical, have not been considered in determining the rate of absorption following single or repetitive exposure. Consideration of the quantitative pharmacokinetic parameters of a chemical as a function of the administered dose may change the "assumed absorption" of a chemical. The existence of specialized and saturable absorption processes for certain chemicals has been demonstrated in animal studies (Levy, 1968).

The disposition of a chemical in the body may be represented as shown below:



The chemical may be excreted unchanged following absorption or may undergo metabolic transformation to a reactive metabolite. This metabolite may be transformed further to a biologically inactive metabolite and then excreted in the urine or it may react with macromolecular constituents of the cell of the target organ to produce toxic effects.

In order to understand the influences of dose level on the pharmacokinetic profile of a chemical such as that shown in the above figure, it is necessary to consider several basic kinetic processes describing biological transformation. The basic equation describing the absorption rate of biological processes is given by equation 1, in which C is the concentration of a chemical at a given time, t.

$$\text{absorption rate} = \frac{dc}{dt} = \frac{VmC}{Km+C} \qquad (1)$$

The maximum velocity of the process is given by Vm. The concentration when the rate is one-half the maximum possible velocity is given by Km. Inspection of equation 1, shows that when concentration, C, is less than Km, the absorption rate of the process can be expressed by equation 2,

$$\text{absorption rate} = \frac{dc}{dt} = K \cdot c \quad (C \leq Km) \qquad (2)$$

Where K=Vm/Km, in this case, the absorption rate remains proportional to the concentration, and can be described by first order or "linear kinetics".

Equation 1 also shows that when the concentration C is greater than Km, equation 1 approaches the limiting form of equation 3, as shown below:

$$\text{absorption rate} = \frac{dc}{dt} = Vm \qquad (C \geq Km) \quad (3)$$

This indicates that the rate of the process is limited by Vm, and as concentration C increases, the rate of reaction does not increase. It is in this concentration range that biological processes are considered to be "saturated", or zero-order (non-linear).

Generally, it is assumed that the absorption, metabolism and excretion of many chemicals can be described adequately by first-order kinetics. It is also assumed that with the exception of ethanol and benzoic acid, chemicals in the dose range used in animal/man do not yield sufficiently high concentrations at the site of biotransformation to approach or exceed the capacity of the enzymes system involved (Levy 1968). However, it has been shown that the biotransformation of a significant number of chemicals (e.g. 1,1,1-trichloroethane) is rate-limited by the capacity of the enzyme system involved rather than by substrate (i.e., chemical) concentration. The consideration of this factor in pharmacokinetic studies can affect the kinetics of absorption, distribution, metabolism and excretion of chemicals.

Linear and Non-Linear Pharmacokinetics

As described earlier, the fate of a chemical follows linear pharmacokinetic behavior if all the transfer processes in the body can be described by first order kinetics. Under this condition the total clearance, biologic half-life, apparent volume of distribution and systemic availability are independent on dose or concentration of the chemical. This means that (1) doubling of the dose would result in doubling of the average steady-state concentration, and in general, all changes in average dosing rate would produce proportional changes in average steady-state concentration, and (2) the assumption of dose-independence of metabolite composition is implied in the studies of chemical metabolism in which the chemicals were given at only one dose level. Deviations from apparent first-order kinetics can be recognized by the lack of linearity of semilogarithmic plots of chemical levels in the body as a function of time and by changes in the fractional composition of excretion products with dose.

With respect to non-linear pharmacokinetics (or zero-order kinetics), the most important cause of nonlinearity is the limited capacity of certain chemical-metabolizing enzyme systems. A notable example of nonlinear pharmacokinetics is the elimination of ethanol, salicylate and phenytoin. Viewed in a somewhat simplified manner, the biological half-life of

these chemicals increases (and the total clearance decreases) with increasing dose or plasma concentration. Consequently, their average steady-state concentrations will increase with increasing dose, more than proportionally. For example, a 50% increase in the maintenance dose of aspirin can, under certain conditions, result in a 300% increase in steady state salicylate concentration in the plasma. (Gibaldi and Levy, 1976).

Examples of pharmacokinetic studies and their contribution in the HA development process.

Tetrachloroethylene: Tetrachloroethylene is metabolized very slowly, and limited transformation probably occurs via tetrachloroethylene oxide, trichloroacetyl chloride into trichloroacetic acid. Figure 1 depicts the metabolic route suggested for tetrachloroethylene, and Tables 1 and 2 show the fate of tetrachloroethylene following inhalation, oral or intraperitoneal administration in various species.

Developing an HA based upon the non-carcinogenic potential of tetrachlorethylene is a difficult task. If one were to assume that the results of studies in mice and/or rats were truly reflective of the potential risk to humans, one would need only to apply the conventional methodology to determine an allowable exposure level for the human. The experimental

evidence suggests, however, that the human metabolizes considerably less tetrachloroethylene to active metabolite(s) than does the mouse and also less than the rat, so any guidance derivation also should account for the pharmacokinetic differences between the two species when extrapolating to the human.

Schumann, et. al. (1980) showed that mice metabolized about 88% and rats about 10- 12% of a relatively small inhalation dose of tetrachloroethylene (10 ppm for 6 hours). Roughly equivalent exposures (10-100 ppm) for about the same exposure duration in human volunteers resulted in up to 4% being metabolized, the rest being excreted unchanged. Thus, there is roughly a 20-fold (mouse) or 3-fold (rat) difference in the degree of metabolism of an equivalent exposure concentration of tetrachloroethylene. It is not clear how to evaluate these kinds of findings in assessing and using pharmacokineticsin a HA development.

1,1,1-Trichlorethane (methyl chloroform): Pharmacokinetic data in rats and mice following inhalation exposure have been reported by Schumann et. al. (1982). The animals were exposed to 150 or 1500 ppm of methyl chloroform vapor for 6 hours and the absorption, clearance and elimination of methyl chloroform was followed for 72 hours. The results of these studies indicate that (1) the uptake and clearance of methyl chloroform

in the blood of animals exposed for 6 hours to 150 or 1500 ppm of methyl chloroform appear to reflect multiple compartment processes; (2) the clearance of methyl chloroform from the blood of mice was by three first-order processes characteristic of a three compartment linear kinetic with elimination from the central compartment; (3) the primary route of elimination of inhaled methyl chloroform in rats and mice was the excretion of unchanged chemical via the expired air; and (4) even though methyl chloroform is biotransformed to a very limited extent, it is a dose-dependent, saturable process (a 2-to 3-fold increase in the amount of methyl chloroform metabolized with a 10-fold increase in exposure concentration).

III. Issues

1. If it can be shown that after comparable low level exposures, there is a substantial difference in the pharmacokinetic parameters, (absorption, distribution, biotransformation and excretion) when one compares the human to experimental animals, (e.g., mouse) should this difference be factored into the extrapolation of the Health Advisory? If so, how?

2. What should be the role of zero or first-order kinetics of absorption, clearance and elimination for the determination of absorption?

3. If a metabolite is the active toxic agent, will the dose be proportional to the blood concentration in species?

Discussion

Pharmacokinetics describes the dynamic processes involving absorption of a chemical into the body, distribution to various tissues, reversible or irreversible reactions with cellular components, and ultimately clearance from the tissues and the body via metabolism and/or excretion. A number of Health Advisories drafted to date have been for organic compounds. For these HAs, with respect to exposure by ingestion, the assumption was made that the chemical is absorbed to the degree of 100% by all species including the human with no accounting for differences in the rate of

absorption. However, the dominant process governing the fate of the chemical may be different for different species, different chemicals, and frequently, for different doses of the same chemical. Pharamacokinetic data for methyl chloroform in rats and mice following inhalation data are reported by Schumann et. al. (1982). The animals were exposed to 150 or 1500 ppm of methyl chloroform vapor for 6 hours and the elimination of radioactivity was followed for 72 hours. The results of these studies indicated that (1) the uptake and clearance of methyl chloroform in the blood of mice and rats appears to reflect multiple compartmental processes, (2) the "steady-state" of methyl chloroform in rats appeared to occur between 4 to 6 hours exposure period at 150 or 1500 ppm level of methyl chloroform. (3) methyl chloroform is biotransformed to a very limited extent and is a does-dependent, saturable process. (2 to 3 fold increase in the amount of methyl chloroform metabolized with a 10-fold increase in exposure concentration), and (4) there is apparent species differences in the end exposure blood levels and clearance of methyl chloroform.

Several studies in rats indicate that it is not vinyl chloride per se which is responsible for the production of angiosarcoma but rather a reactive metabolite formed from it in the body (Watanabe et. al., 1978). Consequently, the toxicity of vinyl chloride should not relate to the exposure

concentration directly, but rather to the rate of metabolism of vinyl chloride. Since the metabolism of vinyl chloride appeared to be an important aspect of its toxicity, two of the major urinary metabolites were identified: N-acetyl hydroxyethyl cysteine and thiodiglycolic acid.

The results of various animal and human studies clearly demonstrate that (1) there are species differences in the absorption, distribution, metabolism and excretion of a chemical (e.g. 1,1,1-trichloroethane, tetrachloroethylene, etc) and (2) the kinetics of pharmacokinetic parameters may be influenced by the dosage of chemical administered.

V. Options

(1) Consider an oral absorption factor of less than 100% in a Health Advisory where equivalent pharmacokinetic study data are available which include absorption, distribution, metabolism and elimination data of chemical in animal and man.

(2) Consider an absorption factor of 100% in the development of a HA where there are inadequate pharmacokinetic studies available in the scientific literature to make an adequate evaluation.

(3) Determine an absorption factors (absorption, distribution, biotransformation and elimination) for a chemical on a case-by-case basis in the development of a HA evaluating available pharmacokinetic data considering single to multiple exposure levels in animal and man.

(4) Ignore the biotransformation/elimination differences and use most sensitive species, even if it is different from humans.

(5) Make some adjustment (for biotransformation/elimination) if some relevant data are available. (For example Fig. 1 and Tables 1 and 2 contain data on PCE. Are these sufficient to allow an adjustment of a HA derived from animal data to be more representative of the human?)

VI. Recommendation

Ideally the specific absorption factors for a chemical in the development of HA should be considered where the pharameters of the chemical are well characterized in various species and specific species have been identified as having metabolic profiles similar to humans. However, there are only a few chemicals other than drugs which have been thoroughly investigated concerning (1) dose effect, (2) species variation and, (3) single or multiple exposure effects in animals. In other instances, chemicals have been studied on a limited

basis investigating either dose effect, single or multiple exposure effect, etc. in relation to specific pharmacokinetic parameters.

Therefore, it is prudent that option 3, should be considered in the development of future HA's. The absorption, distribution, biotransformation and elimination factors for a chemical should be evaluated on a case-by-case basis from available pharmacokinetic data of animal studies.

## VII. References

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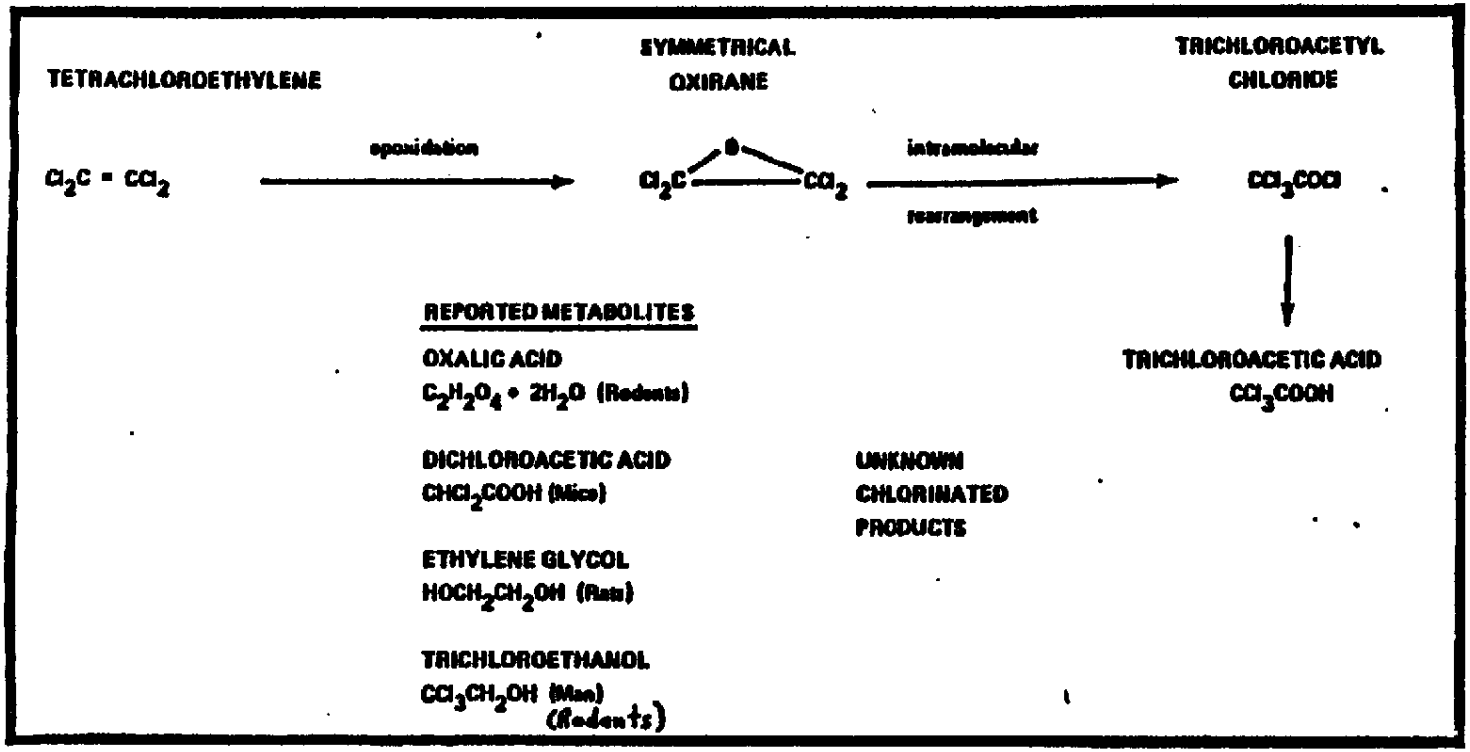
Figure 1

## METABOLIC ROUTE SUGGESTED FOR TETRACHLOROETHYLENE




Greim et al. (1975) Ikeda and Ohtsuji (1972) Yllner (1961)

Table 1

## FATE OF TETRACHLOROETHYLENE

| SPECIES | ROUTE | INTAKE | ACUTELY RETAINED BY BODY (%) | EXCRETION | | | |
|---|---|---|---|---|---|---|---|
| | | | | UN-CHANGED LUNG | METABOLIZED | | |
| | | | | | URINE | SKIN | FECES |
| Man | Inhalation | 1 breath (5 mg) | | 15%/1 hr | 2.8% | | |
| Man | Inhalation | 87 ppm/3 hr | 50 | <50% | | | |
| Man | Inhalation | 194 ppm/ 187 min | | <30 ppm @ 1 hr | | | |
| Man | Inhalation | 300 ppm/6 hr | 62 | 25% | <10% | 0.02% | |
| Man | Inhalation | 385 ppm/ 3.5 hr | | 85 ppm @ 1 hr | | | |
| Man | Thumb Immersion | | | Maximum 6.6 ppm | | | |
| Mice | Inhalation | 1.3 mg/kg | | 70% | 28% | | <0.5% |
| Rats | Inhalation | 200 ppm/8 hr | | | 5.3 mg/kg | | |
| Rats | Oral | 189 mg/kg & 1394 mg/kg | | 87.9% (low dose) | 1.6-2.1% (18 days) | | |
| Dog | Injection | 5.36 g/kg | | (2 days) | | | |

Source: U. S. EPA (1979)

Table

## EXCRETION OF URINARY METABOLITES BY HUMANS, RATS, AND MICE AFTER EXPOSURE TO TETRACHLOROETHYLENE

| SPECIES | NUMBER SUBJECTS | EXPOSURE | | URINARY METABOLITES | |
|---|---|---|---|---|---|
| | | ROUTE | DOSAGE | TRICHLOROACETIC ACID | TRICHLOROETHANOL |
| Human[a] | 4 | Inhalation | 20-70 ppm[a,d] | 4-20 mg/l (0.06-0.6 mg/kg) | 4-35 mg/l (0.06-1.0 mg/kg) |
| Human | 66 | Inhalation | 200-400[b] ppm[c] | 21-100 mg/l (0.3-1.0 mg/kg) | 32-97 mg/l (0.45-2.6 mg/kg) |
| Rat | 48 | Inhalation | 200 ppm/8 hr | 5.3 mg/kg body weight | 3.2 mg/kg body weight |
| Mouse | 20 | Inhalation | 200 ppm/8 hr | 20.7 mg/kg body weight | 4.3 mg/kg body weight |
| Rat | 35 | I.p. injection | 460 mg/kg | 6.85 mg/kg body weight | 0.08 mg/kg body weight |
| Mouse | 20 | I.p. injection | 460 mg/kg | 23.3 mg/kg body weight | 0.1 mg/kg body weight |

a — Workers subject to daily intermittent exposure.

b — Worker receiving 44 ppm was also in direct skin contact with the liquid.

c — Assumed daily urine volume = 1-2 liters (70 kg bw)

Source: Summarized from the tables of Ikeda and Ohtsuji (1972).

CEB/GIH/TB 12/5 1 xc



Practice and Procedure (18 CFR 385.211, 385.214). All such motions or protests should be filed on or before December 1, 1983. Protests will be considered by the Commission in determining the appropriate action to be taken, but will not serve to make protestants parties to the proceeding. Any person wishing to become a party must file a motion to [illegible] of this filing are on with the Commission and are available for public inspection.

Kenneth F. Plumb,
*Secretary.*

[FR Doc. 83-31730 Filed 11-25-83; 8:45 am]
BILLING CODE 6717-01-M

[Docket No. TA84-1-30-000]

**Trunkline Gas Co.; Change in Tariff**

November 22, 1983.

Take notice that on November 15, 1983 Trunkline Gas Company (Trunkline) tendered for filing the following revised sheet to its FERC Gas Tariff, Original Volume No. 1:

Forty-Fourth Revised Sheet No. 3-A

An effective date of January 1, 1984 is proposed.

Trunkline states that such filing reflects a rate adjustment pursuant to Opinion No. 195 issued October 28, 1983 in Docket No. RP83-95-000, Ordering Paragraph (B) of that Opinion provides that jurisdictional members of Gas Research Institute (GRI), such as Trunkline, may file a general R&D cost adjustment to be effective January 1, 1984. This adjustment will permit the collection of 12.5 mills per Mcf (11.7 mills when adjusted to Trunkline's pressure base and dekatherm commodity sales unit) of Program Funding Services for payment to GRI.

Trunkline states that copies of its filing have been served on all customers subject to the tariff sheet and applicable state regulatory agencies.

Any person desiring to be heard or to protest said filing should file a petition to intervene or protest with the Federal Energy Regulatory Commission, 825 North Capitol Street, N.E., Washington, D.C. 20426, in accordance with Rules 211 and 214 of the Commission's Rules of Practice and Procedure (18 CFR 385.211 and 385.214). All such petitions or protests should be filed on or before December 12, 1983. Protests will be considered by the Commission in determining the appropriate action to be taken, but will not serve to make protestants parties to the proceeding. Any person wishing to become a party must file a petition to intervene. Copies of this filing are on file with the Commission and are available for public inspection.

Kenneth F. Plumb,
*Secretary.*

[FR Doc. 83-31738 Filed 11-25-83; 8:45 am]
BILLING CODE 6717-01-M

## ENVIRONMENTAL PROTECTION AGENCY

[SA FRL 2478-7]

**Science Advisory Committee; Open Meeting**

Under Public Law 92-463, notice is hereby given that a two-day meeting of the Environmental Health Committee of the Science Advisory Board will be held on December 14-15, 1983, in Conference Room 3906-3908, Waterside Mall, U.S. Environmental Protection Agency, 401 M Street, Southwest, Washington, D.C. The meeting will start at 9:00 a.m. on December 14 and adjourn not later than 4:00 p.m. on December 15, 1983.

The principal purpose of the meeting will be (1) to provide consultation on EPA's Health Advisory Program for unregulated contaminants in drinking water; and (2) to brief the Committee and discuss upcoming issues for Environmental Health Committee review including the use of risk assessment in the Superfund program and the use of structure-activity relationships in the Office of Toxic Substances.

The agenda will also include (3) brief reports and informational items of current interest to the members.

Pertinent background information relating to the consultation on EPA's Health Advisory Program is as follows. EPA's Office of Drinking Water has prepared five draft papers dealing with major scientific issues pertaining to this program. They are titled:

"The Protected Individual."
"Use of Inhalation Data for Estimating Acceptable Exposure Levels in Drinking Water."
"Use of Pharmacokinetic Data in Health Advisory Development."
"Use of Uncertainty/Safety Factors in Health Advisory Development" and
"Multiple Chemicals in Drinking Water."

At the December 14-15, meeting the Committee will review and comment on the scientific adequacy of these draft papers. For information on how to obtain copies of materials related to the Health Advisory Program please call or write Dr. William Lappenbusch, Chief, Health Assessment Branch, Criteria and Standards Division, ODW, WH-550, U.S. EPA, 401 M Street, S.W. Washington, D.C. 20460 (202) 382-7571.

The meeting will be open to the public. Any member of the public wishing to attend, participate, submit a paper, or wishing further information should contact the Executive Secretary, Environmental Health Committee, Science Advisory Board (A-101), U.S. Environmental Protection Agency, Washington, D.C. 20460 by c.o.b. December 7, 1983. Please ask for Mrs. Patti Howard or Mr. Ernst Linde. The telephone number is (202) 382-2552.

Dated: November 17, 1983.

Terry F. Yosie,
*Staff Director, Science Advisory Board.*

[FR Doc. 83-31719 Filed 11-25-83; 8:45 am]
BILLING CODE 6560-50-M

## FEDERAL HOME LOAN BANK BOARD

**Hacienda Federal Savings & Loan Association Oxnard, Calif.; Appointment of Conservator**

Notice is hereby given that pursuant to the authority contained in section 5(d)(6)(A) of the Home Owners Loan Act, as amended, 12 U.S.C. 1464(d)(6)(A) (1982), the Federal Home Loan Bank Board appointed Albert Avila as conservator for Hacienda Federal Savings and Loan Association, Oxnard, California, effective November 10, 1983.

Dated: November 22, 1983.

J. J. Finn,
*Secretary.*

[FR Doc. 83-31739 Filed 11-25-83; 8:45 am]
BILLING CODE 6720-01-M

## FEDERAL MARITIME COMMISSION

**Security for the Protection of the Public Financial Responsibility To Meet Liability Incurred for Death or Injury to Passengers or Other Persons on Voyages; Issuance of Certificate [Casualty]**

Notice is hereby given that the following have been issued a Certificate of Financial Responsibility to Meet Liability Incurred for Death or Injury to Passengers or Other Persons on Voyages pursuant to the provisions of Section 2, Public Law 89-777 (80 Stat. 1358, 1357) and Federal Maritime Commission General Order 20, as amended (46 CFR Part 540): Phaidon Navegacion S.A. c/o Chandris Incorporated, 666 Fifth Avenue, New York, N.Y. 10019.

called 11/28

# VINYL CHLORIDE AND TSCA

J. T. Barr
Air Products and Chemicals, Inc.*

The well known regulatory history of vinyl chloride and it's role as a bellwether of current regulatory philosophy makes it a useful paradigm for examining the relationship of existing laws and TSCA for control of chronic hazards.

To this end, we will first review some of the highlights of its regulatory history, and then engage in some speculation as to the response these events might elicit today under TSCA.

Vinyl chloride became of industrial importance about fifty years ago, about a hundred years after its discovery, when Semons discovered that its polymer could be converted into useful articles by plastization with phthalate esters. Commercial development began first in Europe and then in this country in the late thirties, largely using existing rubber processing equipment, for it was rubber which it initially replaced in the market. For the same reason, the use of PVC was sequestered by the government during the war years, and it was not until the early fifties that widespread consumer applications developed. PVC is now a mature product, and its growth rate falls in step with the Gross National Product. Presently, about six billion pounds are used annually in this country, and about four times that in the world.

Some of the broader toxicological attributes of VC were recognized in the thirties. It was known to be an anesthetic, but problems with cardiac arrythmia prevented its use in that application(1). As pathological techniques improved, industry scientists recommended in the early sixties that exposure be limited to 50 ppm, because of temporary liver enlargement in animals at that level(2), but the American Conference of Government and Industrial Hygienists considered this overly conservative and accepted instead the 500 ppm recommendation of Harvard scientists(3). This was the value adopted by OSHA in its formative days.

Also in the early sixties, the European industry recognized among its workers a disease termed acroosteolysis, AOL, which is a degenerative disease of the bone tufts, particularly in the fingers, that is accompanied by Reynaud's phenomenon(4). An extensive epidemological survey here and in Europe found about a hundred possible cases which were associated closely with manual cleaning of reactor walls between polymerization batches, but neither the precise etiological agent nor the disease mechanism was identified(5,6).

An attempt was made to reproduce this disease in rats by the medical department of one of the European producers. An exact duplication of the human disease was not seen, but many of the rats developed tumors at numerous sites. The reporting of this finding by Viola(7) in 1970 evoked little interest in the regulatory community, possibly because of the very high doses used, several thousand ppm, which were frankly toxic to the animals, and the fact that the tumors largely were metastatic from the Zymbal gland, an organ not present in humans.

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Nevertheless, both the European and domestic producers formed consortia to perform bioassays at lower concentrations and also began epidemiological surveys of their employees.

Preliminary results of the European bioassay became available first in early 1973, and showed tumor development at much lower concentrations in organs which do have human counterparts. This result was transmitted to regulatory officials that summer, and industry screening of employee records was intensified(8). This resulted in the recognition that winter by an industry medical director of a cluster of 3 rare liver tumors termed angiosarcoma, or ASL, in the employees of one facility(9). Reporting of this fact to government officials led to the current regulatory status of vinyl chloride.

It also led to a virtual explosion of research on the chronic toxicity of VC. The body of scientific literature on the oncogenicity of vinyl chloride is as large as that for any other substance. It is recognized that VC is a classical procarcinogen. Metabolism by the mixed function oxidase in the liver converts it to the ultimate carcinogen, an epoxide. Detoxification of this intermediate by the sulfhydryl group of glutathione or other proteins removes the toxic potential(10). Both of those mechanisms are saturable(11). An overload of the metabolic step assures that the vinyl chloride will pass through the liver and some will be metabolized in other organs. An overload of the detoxification step allows escape of the toxicant into the sinusoidal passages of the liver where interaction with the chromosomal protein causes ASL to develop. An overload of both mechanisms can lead to tumor development outside of the liver, as is seen in mice and rats at very high doses. Despite the large data base, however, information on the precise mechanism of these various steps still is lacking. We do not even understand why some persons respond with AOL and some with ASL, but none with both diseases.

OSHA proceeded promptly in early 1974 to set an emergency temporary limit of 50 ppm for worker exposure, and later that year reduced the limit to 1 ppm, the current figure. Industry was given a grace period during which respirators could be used to meet this requirement, but now that level must be met by engineering practices(12).

The EPA promulgated a combined engineering and works practice standard in 1976 which has resulted in ambient concentrations in the fractional ppb range near producing or using facilities(13).

In the meanwhile, FDA and CPSC established prohibitions on the use of VC in aerosol or other consumer applications, a practice which had been discontinued in 1973. The BATF had already banned the use of PVC liquor bottles in 1973 because of concern for taste effects from migration of residual VC into the contents. In 1975 the FDA proposed revocation of the GRAS status of rigid PVC packaging under the Delaney clause, also because of migration concerns, but that proposal never has been promulgated, and the FDA has stated that it is considering withdrawal of the proposal and recommending to BATF the reauthorization of plastic liquor bottles in light of the current very low residual monomer levels in fabricated PVC articles.

Other regulations have followed as new statutes and rules have come into play. The DOT and the Coast Guard regulate the transportation of VC, of course, and VC is listed as a priority pollutant and hazardous waste under various water and solid waste rules, and has a reportable quantity of one pound under Superfund.

Did the existing laws operate satisfactorily at the time of discovery of the chronic hazards of VC? It appears that they did. A leading medical authority who was deeply involved in the worker health evaluation in 1974 has termed VC a "success story". Reevaluation of the risk to employees under the 1 ppm standard by a conservative nonthreshold extrapolation method(14) yields a lifetime estimate of less than $10^{-3}$, a risk level which is not thought to be of concern. The comparable risk estimate for the general populace is several orders of magnitude lower. EPA has stated on several occasions that it believes that vinyl chloride is regulated adequately.

Risk assessment has been a popular avocation among those interested in VC, and more than a dozen have been performed(15). These can be divided generally into two classes: those which rely solely on animal data; and those which attempt to incorporate the human experience.

Those in the first class yield similar results, and show the normal spread of estimates from the various mathematical models in common use. These range from 1500 to $10^{-5}$ ppb for a lifetime risk of $10^{-5}$, or 8 orders of magnitude. It is necessary to eliminate the high dose data points, that is, those over 2,500 ppm from the Maltoni data(16) in order to get reasonable fits to most models, because these doses show broad systemic toxicity. The lower doses, 500 ppm and below, as a group fall into a general pattern on a log-probit plot, but individual 2 or 3 dose experiments show tremendous differences in slope when plotted separately. The popular multihit model predicts a life time risk of $10^{-6}$ at fractional ppb levels.

The human factor was accounted for in two ways. The EPA used some preliminary employee epidemiological data to confirm its animal-based extrapolation(17). Unfortunately, the human data were selected from those locations known to have ASL cases, while other facility data were omitted. They also were in error on the past exposures by more than an order of magnitude. This resulted in an estimate of 20 cases per year from the estimated 1974 ambient concentrations for the population within 5 miles of production and processing facilities.

The EPA seldom bothers to check its estimates against available data, so it sometimes comes up with results such as that made for arsenic a few years ago that would have predicted 18 million cases of skin cancer a year in this country if it had been applied to Agency data on the average arsenic concentrations in drinking water. Similarly, a survey of all known ASL cases in this country for the 10 years before 1974 showed no cases associated with residency near such plants(18), rather than the 200 predicted cases. It is reasonable to assume that if any cases had developed since that time the publicity associated with it would have brought them to light. Thus we have 110 million-person years of negative history for near-by residents. This places a upper limit on risk of less than $10^{-7}$ per ppm-yr.

Two studies applied pharmacokinetics in an attempt to obtain relevant human data. Gehrig and coworkers estimated a lifetime risk of $10^{-4}$ at 1 ppm from the probit model, based on a biotransformation of rat data. The unconstrained linear model predicted no risk at less than 99 ppm(14).

Anderson, Hoel and Kaplan carried this procedure one step further, and applied it to bound metabolic products, rather than to the total amount metabolized. Their results gave a lifetime risk of $10^{-7}$ at less than 1 ppm, with the probit model, or at less than 2 ppm with the linearized multistep model(19).

Thus we see that risk is in the eye of the estimator, but it is clear that estimates incorporating human data reflect the human experience for VC far better than do the direct application of animal data.

There was understandable uncertainty on the part of both the regulators and industry in 1974. This was the first commodity chemical to be regulated under the relatively new statutory situation as the result of new information. Nevertheless both the regulatory agencies and industry acted promptly to reduce exposures and emissions to an acceptable level.

The current count of occupational ASL cases is about 100 worldwide, with 30 of these in this country(20). All of these cases had their first exposure in 1964 or earlier, and there appears to be room for optimism that the steps taken in the mid-sixties because of the AOL information will have prevented any significant number of cases developing from exposures commencing after that date. Certainly it is reasonable to expect that there have been no new cases initiated after the early seventies.

Had TSCA been in place in the mid-sixties, would it have made any difference in the course of events? It appears unlikely that it would. Certainly the AOL discovery would have resulted in a series of 8(e) notices to TSCA. The probable outcome of that would have been either a recommendation from ITC for more tests, or a Sec. 4 testing requirement. It is possible that, because of its commercial importance, VC could have been placed on the ITC list before the AOL data became available. Additional data could have been called for under secs. 8(a) and (d). The result of all this most likely would have been a negotiated testing rule, under which industry would have initiated a series of studies which would have culminated in a bioassay, and the carcinogenicity of VC would have been discovered in due time. Yet, this is precisely what did happen in the absence of TSCA, except that the preliminaries were omitted, and the bioassay was performed concurrently with the screening tests. Thus it is possible that the final critical data were obtained earlier than would have occurred under present conditions.

Bear in mind that most of today's powerful testing methods were not available twenty years ago. That fact would not have been changed by legislative fiat, and any decision made at that time had to be made in light of the available knowledge.

If the data of Viola suddenly became available today instead, would there be any significant difference in the outcome, or the timing of that outcome? Probably so, but only because of the vastly more powerful scientific tools which we have available to us now. Neither the speed of agency motion nor the

rate at which industrial facilities can be built or modified has increased. If anything, the latter has slowed, given the multiplicity of permits and approvals now required. Overall, it is possible that if today we knew nothing more about VC than was known in 1970, we would arrive at a regulated state a few months earlier than was achieved in 1974, but scientific progress, and not legislative or regulatory advancement, should get the credit.

What if VC were to become a new product today? Would it run the same course in which it would be 40 years before there was full recognition of its chronic potential? Certainly not. Again, however, the reason is due more largely to scientific progress rather than statutory development.

One change might be apparent. If VC were the subject of a PMN today, rather than being the model to which all other aliphatic olefins are compared for structure-activity analysis, it would be judged by the others in its family. This comparison would be less dogmatic than the reverse now is. Ethylene and vinylidene chloride are not animal carcinogens; the relevance to humans of the carcinogenicity of high doses of TCE is equivocal and controversial; and vinyl acetate has only a preliminary "non-negative" report. Thus this class of substances would have lost its leader for structure activity comparison, and a decision as to the need for further testing from that analysis would not be clear-cut, based on analogous compounds.

Neither would a full MPD set be of great assistance. VC responds poorly to the classical in-vitro tests, and only recently has it become possible to obtain reproducible positive results in many of these. If the position were taken that any positive result triggers further testing, then we would be left exactly where we were in the late sixties, recognizing the need for a bioassay.

One other point should be considered before the requirements of Sec. 9 of TSCA to give primacy to existing statutes is ignored. Section 2 of TSCA requires the consideration of economic factors in actions taken under TSCA, while the OSH Act and the Clean Air Act Section 112 do not. In fact, at the time that VC was being regulated, these two statutes were being interpreted as forbidding economic consideration. Had TSCA been the regulatory vehicle of 1974, it is unlikely that the final regulations could have been as strict as they actually became, because of this factor.

It is difficult to separate cleanly the compliance costs for the OSHA and EPA rules on VC because of the overlapping time periods. The best estimate for OSHA costs made by the industry in a presentation to the Presidential Task Force on Regulatory Relief was something over $200 million of capital, with over $25 million per year of annual costs. The EPA has reported to Congress(21) that compliance with its rule has cost about $100 million per year since 1978. Thus, about $900 million has been expended thus far. Various published costs per life saved have ranged from $4 to 200 million for the OSHA standard, depending on which exposure starting point was used. The more costly EPA standard appears not to have prevented any cases of ASL, based on epidemiology, and thus has an infinite cost(15). This suggests that the proponents of strong TSCA activity for existing chemicals should reconsider their position on Sec. 9 if their long term goal is more stringent regulations.

There seems to be no sure method of preventing some surprises in toxicology. Improved surveillance and diagnostic methods assure that we will know more about chronic effects in the future than we do now. New substances simply cannot be subjected to full-scale testing before they show strong commercial promise. If there were no other reasons for this, the limitation on test facilities dictates that we direct our immediate effort toward substances of major import, and this is being done at capacity. It is proper that we concentrate our efforts on present exposures. Fortunately, recent medical advances help us to recognize these surprises earlier, and to minimize their impact.

Existing statutes, that is, non-TSCA derived regulations, appear to be able to regulate existing substances adequately... The history of vinyl chloride bears this out. The principal value of the TSCA derived activities seems to be in the gathering of surveillance data on these substances to assure that the relevant data are made available to the proper agencies, and in future oversight of new substances as they develop into commercial items.

The reexamination of the hazards of all existing chemicals is an overwhelming task for which EPA has no special expertise(22). Just the establishment of priorities for such a reexamination is beyond the present capacity of the Agency(23). The Agency has recognized some of the problems which it faces, and the recent "TSCA Priorities and Progress, 1983" report discusses a much more sharply deliniated existing chemicals program. Even here, however, the division between TSCA and existing statutes is not defined clearly. Further, the Agency appears to be entering the realm of risk management through its Advisory and Chips series. One unfortunate result of this is the generation of another tainted list of substances which becomes an invitation for pressure to regulate. The temptation to prepare these "little lists" for the executioners apparently is too great to be resisted(24), as Lester Lave pointed out recently.

We believe that EPA can best obey its statutory mandate by developing a more efficient system for establishing priorities, and by implementing more effectively its Section 9 procedures.

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Prepared for presentation at the Chemical Manufacturers Association Seminar on Risk Management of Existing Chemicals, 9 December 1983, Washington, D.C.

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# VINYL CHLORIDE AND TSCA

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The well known regulatory history of vinyl chloride (VC) and it's role as a bellwether of current regulatory philosophy makes it a useful paradigm for examining the relationship of existing laws and TSCA for control of chronic hazards.

The highlights of the VC regulatory history are reviewed, as is the present health status, and the costs of achieving this status.

Some speculation is presented as to the possible course of regulatory VC today under TSCA, and it is concluded that the end results would have not been significantly different, although present scientific knowledge may have speeded the rate of process over that achieved in 1974-1976.

Existing statutes, that is, non-TSCA derived regulations, appear to be able to regulate existing substances adequately. The history of vinyl chloride bears this out. The principal value of the TSCA-derived activities seems to be in the gathering of surveillance data on these substances to assure that the relevant data are made available to the proper agencies, and in future oversight of new substances as they develop into commercial items.

The reexamination of the hazards of all existing chemicals is an overwhelming task for which EPA has no special expertise. Just the establishment of priorities for such a reexamination is beyond the present capacity of the Agency. We believe that EPA can best obey its statutory mandate by developing a more efficient system for establishing priorities, and by implementing more effectively its Section 9 procedures.