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16 June 1982

Mr. William A. Cawley
Industrial Environmental Research Laboratory
U.S. EPA
28 West St. Clair
Cincinnati, OH 45268

Dear Mr. Cawley:

Air Products and Chemicals, Inc. submits herewith its comments on the Treatability Manual, as noticed at 47FR4330, 29 Jan. 1972 and 47FR23555, 28 May 1982. We are disappointed in the degree of completeness and in the quality of this revised document.

I. Comments on Specific Items

A. Volume II

Our principal business is in chemicals and plastics, so our first interest is in the treatment for substances in these categories. However, Sections 8.9, Plastics Processing, and 15, Plastic and Synthetic Materials Manufacturing, are not included in this revision.

The section on Organic Chemical Manufacturing, II-12, contains a superficial listing of some processes and their potential priority pollutants. Many of these are in error - for example, under Polyvinyl Chloride, page II.12-88, vinyl chloride, phenol, lead, cadmium and DOP are listed. Only vinyl chloride is correct. The use of phenol as an inhibitor for vinyl chloride was stopped in this country over 15 years ago. The other potential pollutants are associated with the processing and fabricating of PVC, not its manufacture. We know of no reason why silver should be a pollutant of methanol synthesis (page II.12-54) at this time. Not all of the other metals listed are present in any one process, but vary depending on the pressure used, etc. The same comment applies to ethylamines, p. II.12-18.

Great care must be applied to the use of general tables such as 12-6 and 12-7. The treatability of all organic substances is not equal, as is shown in Tables 8-13, and a false impression can be gotten from this type of component table. Suitable precautionary language should be attached.

B. Volume I

The statement that there are no aquatic test data on vinyl chloride is incorrect. The EPA conducted several tests. See the Water

Quality Criteria Document EPA-440/5-80-028 for a partial listing of these.

No useful data are given on vinyl acetate, even though there is extensive literature on this substance. We find nothing on such major products as methanol, ammonia, amines, and other established items of commerce.

We call your attention to two recent references on biodegradation of many of these substances which seem to be based on Agency projects:

Tabak, H. H, et al., J. WPCF, 53 1503 (1981)
Patterson, J. W. and P. S. Kodukala, CEP 77 (4) 48 (1981)

II. General Comments

First, we are concerned about the large number and variety of documents produced by EPA on pollutants in general, and their health effects in particular. These are of wide but generally superficial character. The most distressing feature is their lack of coordination and frequent contradiction of each other.

Second, we take strong exception to the use of the current Cancer Advisory Group risk assessment procedures which are quoted in this document for many of the priority pollutants. The procedure is unsound, and it uses a selected data base which has been chosen to support the desired conclusion. Other data are ignored.

We include a copy of recent comments to EPA on volatile organics in drinking water which comment on both of these points for inclusion in this record. Documents for this Agency should at least be consistent, and ought to be based on sound science and good data.

III. Conclusion

As pointed out above, we do not find these documents to be of great assistance to us because major sections are not included and data on substances of interest are missing or incomplete. We realize that a compilation of all that is known about everything is a difficult task. We look at this as a start on a useful document which requires much more work.

In particular, there must be careful coordination between major Agency documents such as the MMEGs, the water quality criteria documents, and the recent series of Health Assessment documents (47FR17860), and the rulemaking processes such as the VOC in drinking water (47FR9350), and this compilation. We also should be able to expect that the internal Agency literature and the generally available literature, such as the principal journals and standard references such as the Kirk-Othner Encyclopedia and the like, should be searched thoroughly and included

in this work. It could be worthwhile to make a direct request to the relevant trade associations for assistance in handling this large work load.

We encourage the EPA to denote sufficient resources to this series to assure its permanent value to the pollution field.

Thank you for this opportunity to comment on this phase of a very large task.

Very truly yours,

AIR PRODUCTS AND CHEMICALS, INC.

John T. Barr
Regulatory Response

JTB/del

Air Products and Chemicals, Inc.
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18 May 1982

Comment Clerk
Criteria and Standards Division
Office of Drinking Water (WH-550)
Environmental Protection Agency
401 M Street, S.W.
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Gentlemen:

Air Products and Chemicals, Inc., submits herewith its comments on the advanced notice of proposed rulemaking regarding volatile synthetic organic chemicals in drinking water as noticed at 47FR9350, 4 March 1982. We do not believe that this is a necessary or cost-effective regulation, and that the Agency has not established a basis demonstrating a need for such a rule. In the event that a guideline is developed, the alternative discussed in the Notice is the appropriate route to consider.

I. No need has been established for a rule on chemicals in drinking water.

The Agency has presented no evidence that there is a significant risk at present conditions, nor that there is a national problem that requires a Federal rule.

1. The Agency has based its entire case for the substances under consideration on hypothetical risks calculated by the Cancer Assessment Group, or by the National Academy of Science using an almost identical procedure. It has presented no evidence that these suppositions are real, or that in fact there is any risk to the population for this group of chlorinated compounds. We are asked to accept on faith, without prior review or supporting data, that these projections are of sufficient validity to justify an expenditure of many millions of dollars.

   We reject categorically the arbitrary assumptions of the CAG in first, assuming that all of the substances are known human carcinogens, and second, that the risk estimates are valid.

   With one exception, there has been no formal or authoritative determination that the candidate substances are known carcinogens. There cannot have been, because the Agency has no established procedure for this action. A proposal to develop such a procedure has been withdrawn (47FR2064), and the action by CAG to treat these substances as carcinogens is an arbitrary presumption by some Agency staff which is without authority.

   Further, this presumption has been declared without scientific foundation by the Science Advisory Board of the Agency in

September, 1980. Data concerning the presumed carcinogenicity of four of the substances were presented to this meeting of the SAB. It was stated as a conclusion of that body that the evidence presented by the CAG was inadequate (see attached summary, Appendix I). The CAG agreed to return to the SAB with further data by November of that year, but has not done so yet. This is now scheduled for sometime after 6 July, too late for entry into this record.

The American Conference of Governmental and Industrial Hygienists discusses the criteria for classification of carcinogens in its annual "Threshold Limit Values for Chemical Substances...," Appendix A and in the 1980 and 1981 editions states: "These dosage limitations exclude such substances as... trichloroethylene from consideration as carcinogens." This refers to the test dosages which caused serious toxicity effects in the animal, that is, it exceeded the maximum tolerated dose before it caused tumors. The National Academy of Science, in its 1981 book titled "Prudent Practices for Handling Hazardous Chemicals in Laboratories" states on page 150: "Although trichloroethylene has caused cancer in mice, its carcinogenic potency is so low that no special precautions are needed for laboratory work with it beyond normal good practice. This includes the use of a hood for most operations." The International Agency for Research on Cancer (IARC) classified TCE in the group headed "could not be classified as to their carcinogenicity for humans," because of "inadequate" data. No classification is given for PCE, and carbon tetrachloride is also listed as having "inadequate" data for humans. Volume III of "Drinking Water and Health" contains a statement by the National Academy of Science Committee that "it is unclear if (PCE) is a carcinogen." Dichloroethane is classed as having "limited" data, for mice only, and "inadequate" data for humans. See the IARC volume "Chemicals and Industrial Processes Associated with Cancer in Humans," September 1979.

The most recent drafts of the Agency Health Assessment Documents (47FR17860) for methylene chloride states: (EPA-600/8-82-004, March, 1982) "The existing data base is inadequate for assessing the carcinogenicity of dichloromethane. --- A final assessment--- will be deferred ---," and that for carbon tetrachloride: (EPA-600/8-82-001) "each upper bound risk is presently regarded as having limited plausibility due to the inconclusive nature of the available evidence for the mutagenicity of CCl_4. Furthermore, because of the uncertainties in both the qualitative and quantitative aspects of risk assessment, the actual cancer risks may be lower than those indicated above and may approach zero." Similar disclosures are given for trichloroethylene EPA-600/8-82-006, and perchloroethylene EPA-600/8-82-005.

The risk estimates which were presented in those documents are not the same as are presented here. The Agency should explain these differences, and state which, if either, it supports.

Thus, any conclusion by the CAG that these compounds provide a significant risk of cancer to humans at such low concentrations flies in the face of the opinion of several expert groups, and of its own Science Advisory Board, and current Agency policy. We urge the Agency to reconsider its assumption that these substances are human carcinogens, and to avail itself of the advice of the peer review of its independent experts. Sound scientific data should be the basis for the assignment of a human carcinogen classification to a substance.

The reason that these substances are of little concern as carcinogens at low concentrations is that they are, with the exception of vinyl chloride, not direct cytotoxic substances. They do not act directly on the genetic material of the cell, nor on its controlling substances. Any tumorigenic properties are developed only after long, high exposures which have been sufficient to cause extensive tissue damage and whole body or organ toxicity. Thus, it is not appropriate to apply the no-threshold, linear-through-zero extrapolation procedures of CAG to these substances. The risks projected by such procedures are not relevant to the types of exposures under consideration here, as the Agency has concluded in the case of carbon tetrachloride. The figures presented in Table 3 of the Notice are thus irrelevant and unsupportable scientifically.

The non-genetic mechanism for tumor production is now an accepted scientific position. See: Weinhouse, JNCI, 68 343 (1982), Weisburger and Williams, Science, 214 401 (1981); Fd. Cosmet. Toxicol., 19 561 (1981); Williams, Fd. Cosmet. Toxicol., 19 577 (1981); Greim, et al., Progress in Mutation Research 2 129, A. Kappas, ed., Elsivier (1981); Pitot, et al., J. Supramol. Struct. Cell. Biol., 17 133 (1981); Budiansky, Envir. Sci. Tech., 14 (11) 1281 (1980); Food Chem. News, p. 34, 22 Feb. 1982; Stott, et al., Fd. Cosmet. Toxicol., 19 569 (1981); Schumann, et al., Toxicol. Appl. Pharmicol., 55 207 (1980); Squire, Science, 214 877 (1981); Watanabe, et al., p. 70 in "The Scientific Basis of Toxicity Assessment, H. Witschai, ed., Elsivier Press, (1980). The principle of nongenetic causation applies not only to chlorinated substances such as the candidates of this Notice, but also to many other tumorigenic substances:

- Mechanical abrasion (Argynis and Slagle, Cancer Research, 41 5193 (1981).
- Initiation by implanted solids (Ziche and Grellino, Cancer Research, 41 5060 (1981).
- Bladder stone formation (Heck, Fund. Appl. Tox., 1 299 (1981).
- Promoters such as phorbal esters (Birnbaim, Science, 215 1247 (1982).

See the references listed above to Williams, Squire, Greim, Pitot, and Watanabe for further examples and discussion.

The key feature of nongenetic mechanisms is that no irreversible process is initiated until a certain threshold of physical organ damage has occurred. Even then there is still available the

natural repair and immune suppression mechanism of the whole organism (Pitot, op. cit., Melicow, J. Theor. Biol., 94 471 (1982)).

It is a common characteristic of these nongenetic tumorigens that they do not provide positive results in the so-called short-term tests, which specifically measure the genetic toxicity of suspect carcinogens. The bioassay reports on these candidate substances have been equivocal, thus indicating a lack of inherent carcinogenicity for the substances.

Examples of the negative short-term or bioassay results with some of the candidate substances are listed below:

Trichloroethylene
Bader, et al., J. Anesth., 51 417 (1979); Slacik-Erben, Arch. Toxicol., 45 37 (1980); Van Duuren, et al., JNCI 63 1433 (1979); Science Advisory Board, op. cit.

Tetrachloroethylene
Van Duuren, et al., op. cit.; Stott, et al., op. cit.; Science Advisory Board, op. cit.

Dichloroethane
Nat. Cancer Inst. PB283345, (1977); Maltoni, Banbury Rpts., 5 3 (1980).

Carbon Tetrachloride
Simons, et al., in "Progress in Genetic Toxicology," Scott, et al., eds., Elsevier Press (1977).

Methylene Chloride
Filippova, Genetika 8 134 (1967); Simons, op. cit.; Science Advisory Board, op. cit.; 44FR34685.

Methyl Chloroform
IARC, Vol. 20, op. cit.; NCI-CG-TR-3, (1977); 44FR34685; Science Advisory Board, op. cit.

There is, of course, no reasonable basis for a presumption that the last two substances on that list, methylene chloride and methyl chloroform, have any carcinogenic potential. These have been cleared by the IARC, the SAB, the NCI bioassay program, and most recently by the Health Assessment Document Series. Their aqueous toxicity is very low and they ought to be removed from the candidate list.

In addition to the rejection by the SAB of the human carcinogenicity of many of these candidates, the Solvents Work Group of the Agency recently was quoted as stating that a group of solvents which includes several of these candidates "all exist in the environment at least several orders of magnitude below their lowest effect levels." Undoubtedly the fact that these substances degrade photochemically and thus do not accumulate was a factor in this decision.

The underlying thrust of this proposal is therefore not on a sound scientific foundation. It is in conflict with other positions taken recently by the Agency and its scientific advisors. It has no showing of need or present significant risk, and thus is not in

conformance with the Supreme Court directive in the "benzene" case (Industrial Union Dept. vs. American Petroleum Inst., 448US607, 100 SC (1980)).

The Agency has underway a program of water quality criteria development. This program will result in control of the concentration of these substances in surface waters which will be adequate to protect the health of humans and the environment. In passing, it can be mentioned that the water quality criteria documents are under internal Agency review because of their abysmal scientific quality. These have the same data base and risk estimation procedures that are relied upon by the Agency in this rulemaking, and thus this proposal is further clouded by that repudiation by the Agency.

The Agency also has other programs to protect groundwaters - RCRA, their groundwater program itself, and several other activities.

In view of this lack of substantiation of need for a specific rule to protect from these substances, and because of the alternative programs already underway, we can only urge the Agency to withdraw this proposal.

2. Vinyl chloride must be considered separately because it is the only one of the candidates which is an accepted human carcinogen.

The January 1982 Water Quality Criteria draft document does a poor job of summarizing the available data on vinyl chloride, even that generated by the Agency. The brief statement in the Notice is even less adequate. Vinyl chloride is a known human animal carcinogen. It causes angiosarcoma of the liver (ASL) as the marker disease. Any connection with tumors at other sites is speculative and unsupported by epidemiology (Beaumont and Bresloco, Am. J. Epid., 114 725 (1981); Cooper, Envir. H. Perspect., 41 101 (1981); and Chiazze and Ference, Envir. H. Perspect., 41 137 (1981)).

This substance is readily volatile from water because of its high vapor pressure (EPA 500/4-74-001, (1974) and Hill, et al., EPA 600/3-76-001 (1976)). It readily reacts photochemically (EPA 600/6-75-004 (1975), Cox, et al., AGRG-R-7820 (1974), Gay, et al. Environ. Sci. Tech., 10 58 (1976), EPA 600/3-80-072 (1980)). It does not interact with aquatic systems (Hill, op. cit.) nor does it accumulate in the food chain (Lee, Arch. Environ. Contam. Toxicol., 6 129 (1977)). Therefore, the only concern is for the frank exposure from potentially contaminated water.

As stated above, we reject the risk assessment quoted in the Notice. It suffers from several fatal faults. There are several arbitrary and unsupportable "adjustments" made to the new animal data, such as adjustment on a surface area basis, and adjusting for equal blood levels. These procedures are unfortunately neither described nor defended in the January 1982 draft referenced by the

Notice. There seems to be little reason for omitting the supporting data and calculations from such a vital document. It is necessary to refer to EPA 440/5-80-078 to find the pertinent material.

One of the greatest flaws in this exercise is the assumption that humans always are at least as or more sensitive to vinyl chloride than are rodents. The facts were stated by the National Cancer Advisory Board in a 1979 report entitled "The Relation of Bioassay Dose to the Assessment of the Risk of Carcinogens for Humans under Conditions of Low Exposure" to be that humans are about 500 times more resistant to vinyl chloride. The same is true for many other substances (Greim, op. cit.).

This relationship has been confirmed by Gehring, Watanabe and Park (Tox. Appl. Pharm., 49 15 (1979) and by Anderson, et al., (ibid. 55 154 (1980), who found that the estimated risk to humans could be derived from rat data with any semblance of accuracy only if the relevant pharmacokinetics were included, and showed that humans are less sensitive than rodents. The consistent and unsupportable imposition of philosophic ideas in the form of "prudent" or "conservative" risk estimations destroys the credibility of the CAG/NAS estimates. They should not be relied upon for rulemaking.

It is clear that any risk to humans, if it exists at all, is several orders of magnitude lower than that used here. Data from Anderson would put the exposures which CAG proposes to equal a risk of 10^{-5} more nearly 10^{-8}, or lower.

Because of the insignificance of any risk posed by vinyl chloride, which is lessened even further by its ready volatility, and because of the limited extent of the potential exposure (see a later section), we do not believe that a case has been made for the need for further regulation of vinyl chloride. The Agency has in place a NESHAPS standard for vinyl chloride which has reduced sharply the potential for discharge of that substance to surface waters, and its potential for contamination of groundwater. We urge the Agency to withdraw its proposal relevant to vinyl chloride as being without scientific foundation and unnecessary to protect human health.

II. There is no national problem justifying a Federal standard.

It is unfortunate that the Agency chose to publish this Notice before the availability of the current Groundwater Survey. Communication with Agency staff indicates that the report on this Survey will not be available to the public until after the end of the comment period. We believe that this vital information should be made available to the public as quickly as possible, and that the comment period should be extended to allow adequate assessment of the report to enter the record.

The need for this updated information is emphasized by the spotty and incomplete nature of the data presented to the public as a part of this Notice. The December 1981 report "The Occurrence of Volatile Synthetic Organic Chemicals in Drinking Water," the next-to-last item in the list

of references in the Notice, is poorly organized, overly terse, and not capable of being evaluated adequately. The principal failure is a lack of detail regarding the sources tested.

Recent data which are available show (EPA 903/9-81-003) that two rivers most suspected of being contaminated by these substances contain, at most, only very low ppb concentrations, and are frequently below 1 ppb or are nondetectable.

Other data available to the Agency, but not referenced here are contained in the Health Assessment Document series (EPA-600/8-82-001-008). The Agency has failed to utilize even its own resources in preparing this proposal.

However, despite the lack of data to develop a good understanding of the purported problem, a few points seem to emerge.

1. Only a small percentage of the water sources are affected. The statement in the Notice at p. 9351, Col. 3 that 45% of the public water systems are contaminated is not borne out by the reports made available to the public. Table 2 of the December 1981 report referred to above shows that groundwater supplies have a low incidence of contamination. Despite the fact that report is biased away from being a representative sampling because of testing being done only where contamination was already known or suspected, it shows less than 6% positive samples for any of the substances reported.

   The surface water results most likely are biased for the same reasons. In addition, other data supplied by the Agency in connection with the trihalomethane rules (44FR68624) and other public announcements state that the occurrence of these substances in finished water is an artifact of the purification system. See, for example, page 73 of the January 1982 risk assessment for vinyl chloride that comments on the lack of a plausible source of vinyl chloride in the Miami water supply, and Drinking Water and Health, NAS, V. 2, Ch. 3 (1980).

   A recent study in a midwestern state found essentially no Perc, and no TCE or DCE in over two hundred surface and ground sources. (Cantor, et al., Tox Envir. Chem. Rev., 4 47 (1981).

   Thus we must remain skeptical of the claims that this is a national problem. Data presented came previously from limited areas in New York, New Jersey and California where past disposal practices are responsible for groundwater contamination. The broader-based Agency surveys are consistently lower in positive results than are the state reports, even though both are biased as discussed above.

   We regret that the far broader data bases of the Health Assessment Documents, EPA-600/8-82-001-008 and the Treatability Manual, EPA-600/2-82-001a-e were not referenced, and we ask that the Agency make those a part of the official record in this rulemaking.

2. These reports also are out of date and may well not reflect the current situation. Therefore, we believe that better reported and broader-based results are needed to indicate that there is in fact a national problem.

   This concern is reinforced by the existence of the trihalomethane rule, which, although of dubious health value, has caused a considerable reduction in the amount of chlorine used in water purification, and thus has reduced the extent and amount of other halogenated substances also. It is necessary to measure the effect this rule has had on the supposed problem before deciding what further actions are necessary.

3. The reported concerns are de minimus.

   Even assuming that the reported concentrations are representative, which they are not, and that the upper limit risks calculated by CAG were realistic, which they most certainly are not, the resulting risks are not of adequate magnitude to justify regulation. The courts have ruled in Monsanto vs. Kennedy that regulators are excused from even considering such matters.

   In passing, it is interesting to note that the mean concentrations reported in the December survey usually are lower for surface waters than groundwaters. This is supportive of the proposition that they are generated in the water treatment step. However, the data given here differ from that in the Health Assessment Document series, generally being higher than in the HDA. We are unsure which data are correct.

   Using the concentrations in Tables 1 and 2 of the December survey and the risks of Table 3 of the Notice, the following table of approximate upper limit risks to consumers can be formulated:

	Upper Limit Lifetime Risks, TCE	
	Surface	Ground
Trichloroethylene	5×10^{-7}	10^{-5}
Tetrachloroethylene	2×10^{-6}	3×10^{-6}
Carbon Tetrachloride	10^{-5}	2×10^{-6}
Dichloroethane	10^{-6}	6×10^{-7}
Vinyl Chloride	2×10^{-6}	4×10^{-5}*

* only one positive sample

When these risks are multiplied by the small fractions of the population exposed to each substance (2-36%), the resulting risks are de minimus indeed. Even if one attempted to invoke the unproven theory of additivity of risks, the results would be too small to justify a national effort. Had the NAS figures been used, the results would generally have been lower.

We have ignored the methylene chloride and methylchloroform data of Tables 1 and 2 because CAG has not been able to project a reasonable risk for these innocuous substances (EPA-600-8-003 and 004).

If the Agency is serious about its intent to use risk assessment as a priority-setting device (page 6553), it can but conclude that these risks do not justify the billion dollar capital cost and $250 million/year operating costs projected in Table 4 for TCE alone. Assume that 32% (Table 1) of 50% of the 220 million population is exposed to a 5×10^{-7} risk. This would project 1,760 "lifetime" deaths, or about 25/year. At a cost of $1.2 billion plus $300 million/year, the direct cost per life, unadjusted for carrying charges, interest, or inflation is about $13 million. The figure would be above half that if packed tower aeration were used in place of diffused air or carbon. This figure is above the average of the past actions of the Agency (Graham and Vaupel, Risk Assessment 1 89 (1981)), and among the highest 10% of those rules that have been evaluated. We do not beleive that this is cost effective or prudent to expend the resources of society in this manner when the risks are so obviously overstated.

Much of the water contamination by trichloroethylene is believed to be the result of home use of septic tank degreasers. The Pennsylvania legislature is now considering a bill to prevent further use for that purpose. Such applications are not controlled by present laws or rules and would not be affected by implementation of this proposal, despite the billion-dollar cost. Therefore, the implication that this proposal would cure all present problems is incorrect, and the Agency has not suggested what fraction of the risk would be avoided by this action.

III. Further Comments on Risk Assessment

A. Alternative Proposal

Recent work, particularly that with low doses and large animal populations such as the ED_{01} study at the NCTR, have demonstrated that extrapolation much past the experimental range is futile, no matter what "model" is used. For full discussion of this point and numerous examples, see: National Academy of Science, "Regulating Pesticides" (1980); Munroe and Krewski, Fd. Cosmet. Tox., 19 549 (1981); Waldendorf, J. Can. Res. Clinc. Oncol., 95 101 (1979); Stott, et al., op. cit.; Carlborg, Fd. Cosmet. Toxicol., 19 255 (1981); Van Ryzin, Fund. Appl. Toxicol., 1 124 (1981). Certainly, the "prudent" linear-through-zero upper limit line or extrapolation cannot hope to provide a reasonable estimate of actual risk, even for the experimental animals, much less humans. It does provide an upper limit for rodents, as it claims, but this is so far above reality for humans that it only is useful for preliminary screening and priority setting. It is not suitable for final regulatory decision making because of all of the distortions built into the process.

It is necessary first to validate the experimental data, and to determine its relevance to humans. These steps are excluded from the CAG process. It then is necessary to attempt to understand the mechanism by which the putative carcinogen acted, genotoxic or non-genotoxic; whether the pharmacokinetics of humans resembles that of the animal; whether the tumor was a new type or merely a (significant?) increase in common types; and, finally, whether epidemiology is available to help set an upper risk limit or to modify the animal data. A decision-tree approach (Food Safety Council, "Proposed System for Food Safety Assessment" (1980); Campbell, Reg. Tox. Pharm., 1 193 (1981)) is most helpful in integrating the other necessary data with the bioassay.

We believe that the procedure described below is superior to the fill-in-the-blanks methods used by CAG up to now, yet retains an adequate conservative basis while utilizing all of the available data. The bioassay is only one factor of many to be considered.

If, after a decision-tree type evaluation of all the data, a decision is reached that a substance is an animal carcinogen that also poses a potential hazard to humans under reasonably expected circumstances, an extrapolation of bioassay data should be made. This extrapolation should utilize all available data and be carried out to some no-observed-effect level not far from the experimental limits. Most good bioassay data will allow reasonably accurate extrapolation to the 1% incidence. There are, however, several NCI bioassays performed at obviously highly chronic levels which are not suitable even for this purpose (see, for example, EPA-600/8-82-001). It is not important which "model" is used for this part; most fit well and agree within the data limits. None are realistic models of the biological process of interest (Squire, op. cit.) but the error involved is not great. The Weibull and log-probit models usually are satisfactory (Thompson and Funderlic, Environ. Sci. Res., 21 521 (1981)).

Once the 1% (10^{-2}) risk point and its statistical error ranges have been found, a safety factor of the desired magnitude is applied. Note that this is equivalent to a linear-through-zero extrapolation, but starting from the best estimate 10^{-2} point rather than the upper limit of the lowest dose. This is the allowable dose for the experimental animal at the desired risk.

This allowable dose is then adjusted for humans by multiplication by appropriate factors utilizing the data from the decision tree which justified the conclusion that the substance posed a human risk. Factors greater than one are used when the data support a larger acceptable dose for humans than animals, factors lower than one for the opposite cases. Factors to be considered include those mentioned above: type and hazard of the tumor in question, exposure and absorption routes and times, relative metabolism and pharmacokinetics, saturable repair or conversion mechanism, and so on. The more data that are available, the more carefully the

final dose can be set. This rewards good science and encourages data gathering.

The mechanism of tumor induction is best considered in the safety factor. If there is evidence for a nongenetic mechanism, and thus a threshold, the safety factor may be less than for a complete carcinogen that operates by a genotoxic route.

If the experimental data shows a clear no-effect level above the 1% point, the safety factor may be applied to that dose, rather than at 1%.

These later adjustments are clearly qualitative in most cases, and thus require subjective judgement. For this reason we support the proposal of the American Industrial Health Council for an independent, multi-disciplinary panel to evaluate the data and make the necessary decisions. This assures the regulator of a clear understanding of each of the qualitative steps, and allows the necessary sociopolitical decisions to be made on the soundest possible scientific base.

Past Agency risk-estimates have not been made in this open and justifiable manner. The CAG risk assessment of record in this rulemaking does not even describe the process; it only gives the final result. We believe that the public deserves better than this.

We are gratified to learn that the Agency is undergoing a serious review of its risk assessment procedures in an effort to upgrade the quality of the results, and we urge that the revised product be considered before a decision is made in this matter.

B. Comments on the Current Agency Risk Assessment Procedure

A major failure of the current Agency Procedure is the attempt to use a mathematical exercise as a substitute for sound scientific data. These efforts are bound to fail, and to bring discredit on the subject. There must be proper consideration of all available data, as described above.

The inappropriateness of this method can be shown by a single example. Suppose that a suspect substance is tested in 100 animals per dose by the standard NCI bioassay protocol at 5 and 10% in the diet and found to have no increase in tumors. However, the 10% level had excessive deaths, so that level is excluded from consideration. Assume also that structure had suggested that the substance may be a carcinogen. The Gaylor-Kodell procedure then takes the upper confidence limit of 0% response, which is 5% for 100 animals, and "interpolates" it with zero to get a dose response curve. The allowable dose for a 10^{-6} lifetime risk would then be 10^{-6} of the diet. Applying this to a 1 kg/day diet of an adult human, the maximum allowable intake would be 1 mg. Thus, no material which gives negative results at 5% in rodent diet can be <u>proven</u> "safe" (e.g., 10^{-6} lifetime risk or less) by a bioassay.

This result puts table salt at the FDA recommended daily intake several thousand times over its proven "safe" dose, from a carcinogenic viewpoint. There has been no bioassay of salt, because "everyone knows" it is not a carcinogen, but the above scenario is the probable outcome if one were to be performed. In fact, we know no such thing. We have no way of knowing if salt contributes to the cancer death rate of humans. We cannot test by the NCI method, because the controls would die if maintained on a salt-free diet. Therefore, we say that because we all use salt, and must have it, it is not a carcinogen. (In fact, it is deemed GRAS.) However, the same type of statement is true of arsenic, chromium, selenium, vitamin A, calcium, hormones, and hundreds of other vital nutrients which are necessary as trace components and "carcinogens" at overdoses.

The above scenario is almost exactly parallel to the risk assessment prepared by the EPA Carcinogen Assessment Group from the carbon tetrachloride data. They used only one data point from an NCI positive control rat feeding of that material to develop human risk assessment (EPA-600/8-82-00). But then the Agency attached the following cautionary statement: "However, each upper bound of risk is presently regarded as having limited plausibility due to the inconclusive nature of the available evidence for the mutagenicity of CCl_4. Furthermore, because of the uncertainties in both qualitative and quantitative aspects of risk assessment, the actual cancer risks may be lower than those indicated above and may approach zero."

We believe this to be a proper evaluation of this attempt at risk assessment. Similar comments apply to the other data bases used.

We could find other no-effect levels for salt below 5% of the diet. But the strange thing is that, by the Gaylor-Kodell "interpolation" scheme, the lower the experimental NOEL, the higher the calculated risk at any given dose below that, because the slope of the dose response curve increases as the NOEL decreases. We obtain the highest allowable safe dose when the test substance is 100% of the diet, and the lowest when it is tested at low doses in the usual area of interest. This is an absurd and paradoxical scheme. Yet, it appears that it was the method used for many of the substances in this proposal.

A major cause for the unacceptability of the risk estimation procedure is its lack of biological foundation. It is purely a mathematical exercise without biochemical relevance. For example, the total lifetime dose is the primary basis for the estimate. It is of no concern to the mathematician if that dose was administered in one massive amount at the end of the lifetime of the experimental animal, in a few clearly toxic doses at the beginning of the test period, or in subtoxic doses throughout the lifetime. All are considered equivalent in producing risk.

Thus, neither dose rate time-to-tumor are considered. The ED_{01} Study demonstrated that the latter is an essential feature of a risk evaluation. All adequate test protocols are based on the knowledge that the former is a fundamental principle.

Great emphasis is placed on the desirability of, or the requirement for, testing at the maximum tolerated dose (MTD). The reason given for this is the lack of statistical sensitivity of the standard bioassay protocol. Thus this is a concession to the mathematicians, and has no biological foundation. We have seen how this concept has been abused in the use of the NCI bioassay for perchloromethylene, where the initial doses had to be reduced to keep the animals alive, yet in the case of carbon tetrachloride, where both levels of the positive control group clearly were toxic, the results were used for risk estimation.

There is no question that the organs of these test animals suffered severe damage from the overdose, and therefore cannot represent humans exposed at very low doses. Kraybill [Pest Control 43 (12) 10 (1975)] and Greim, et al., ("How Relevant are High Doses in Mutagenicity and Carcinogenicity Studies in Animals," in Progress in Mutation Research, Vol. 2, A. Kappas, ed., Elsevier 1981) have summarized the data on MTD, and concluded that there are significant changes in metabolic pathways at high doses, as well as organ damage. See also Reitz, et al., Fd. Cosmet. Tox., 16 511 (1978) and Bolt, et al., Arch. Tox. Suppl. 3, 129 (1980). Thus there is no biological basis for rejecting bioassay data taken at moderate or low doses, and there can be many reasons for data at high doses being an inappropriate base for making judgment as to carcinogenicity. This applies to the test animal, of course, but even more to other species which have different metabolic mechanisms.

Another departure from biological principles is the proposition that carcinogenic dose response is linear at low doses, and that the extrapolation must begin at the origin.

The second point ignores the spontaneous incidence of cancer and specifically rejects the possibility of nongenetic causes for tumors (Weinhouse, S., J.N.C.I. 68 343 (1982)). The first point disregards the fundamentals of kinetics. All chemicals which affect cellular material must react with some substance in order to produce that effect. Thus, kinetics are of at least second order. The rate of a second-order reaction is described by the equation

$$k = \frac{1}{t\,(C-B)} \ln \frac{B\,(C-x)}{C\,(B-x)} \qquad (1)$$

where k is the rate, t the temperature, C the concentration of the Carcinogen, and B the concentration of the biological agent(s).

See any elementary physical chemistry text for a derivation and discussion of this relationship.

In most instances there is a series of consecutive and competing reactions in which the precarcinogen is activated into the toxic metabolite, and then reacts further with biological substrate before the product of interest is formed. The correct mathematical expression then becomes a series of equations similar to (1) above.

Even in the simplest case, however, where a substance reacts directly to produce the ultimate lesion, the relationship between rate and concentration is logarithmic, as is shown in (1). Plotting the rate (dose response) against concentration yields an exponential curve.

Second order reactions may be converted into pseudo-first order rates if the concentration of one substance does not change during the event. The expression then becomes

$$K = \frac{C}{-t} + \text{constant} \qquad (2)$$

and a plot will yield a straight line. There is only one reasonable way in which one of the reactants can have a constant concentration, and that is for its concentration to be so high that it is essentially unchanged during the reaction time. Where considering low dose events, it is not possible for the carcinogen to be that high concentration reactant. Neither is it reasonable for the biological material to be of high or unchanging concentration. Concentrations are limited, and can be shown to be depleted during the course of challenge by metabolism.

An interesting example of the process can be found in a recent report by Hilderbrand, et al., (Fund. Appl. Tox. 1 403 (1981)) who showed that the metabolism of toluene is first order on biological substrate by utilizing a large supply of toluene. The reaction must be at least first order in toluene also at ordinary concentrations, and thus the overall low dose reaction at least second order. (Reactions have as order the sum of the orders of the reactants.) The overall rates in that experiment showed the expected rapid decrease with concentration. Therefore, any artifical representation of dose response that requires linearity will necessarily overstate the real risk at low doses by an exponential amount.

If the recent statement by the House Democratic Caucus (see Inside EPA, 16 April 1982) is correct that "the regulation of toxic substances has fallen into disrepute in some quarters, because of misunderstanding about the use and usefulness of animal tests," much of the responsibility must stem from the past abuse of bioassay results in risk estimations. These cases are exemplary.

We suggest that, until a risk assessment method that can differentiate carcinogens from noncarcinogens is utilized, the Agency should not apply the procedure. Furthermore, the proposed process actually penalizes good science, for the more data points which are taken, the more punitive are the results.

We support the use of risk assessment in regulatory decision making (Barr, Hughes, and Barnard, Reg. Tox. Pharmacol., 1 264 (1981)). We do not, however, believe that past practices by regulatory agencies have been based on sound scientific or political principles.

It is therefore necessary that the Agency establish a policy which is explicit in its consideration of biological facts as well as mathematical curve fitting. The bioassay is only one of many factors which must be considered in a risk assessment, and a risk assessment is only one of the many factors which must be considered in risk management.

IV. Comments on Acceptable Risk

We have pointed out earlier the minimal value of the imputed risks to the public, even accepting the fragmenting and biased data base and the inflated risk estimates. We believe these to be less than would be justified for remedy by the large projected expenditures. However, the question still arises of what is an acceptable risk.

"Acceptable" is in the perception of the beholder. Society has developed its own system of acceptability based on the perceived benefits of the activity. The following table gives a few examples of risks apparently acceptable to society as a whole, or at least to the participants in these activities.

Table 2
Annual Average Risk of Death, United States
From Various Factors, Activities, or Occupations

All Deaths	9×10^{-3}
Heart Attacks	3×10^{-3}
Cancer, total	2×10
Smoking, all causes	10^{-3}
Active Sports (motorcycling, auto racing, rock climbing, canoeing) each, participants only	10^{-3}
Coal Mining	7×10^{-4}
Airline Pilot	3×10^{-4}
Policeman or Fireman	3×10^{-4}
Automobile Accident	2×10^{-4}
General Occupational Classes	10^{-4}
Truck Driver	10^{-4}
Home Accidents	10^{-4}
Farming	6×10^{-5}
Social Drinking (not including accidents)	5×10^{-5}
Using Oral Contraceptives	2×10^{-5}
Drowning	2×10^{-5}
Accidental Poisoning	10^{-5}
Bicycling	10^{-5}
Living at 5,000 ft Altitude (radiation)	10^{-5}
Diagnostic X-rays	10^{-5}
Electrocution	5×10^{-6}
Living in Masonry Buildings (radiation)	5×10^{-6}
Hunting (Pennsylvania, 1980)	5×10^{-6}

Table 2 (cont'd)

Smallpox Vaccination (past)	3×10^{-6}
Storms	10^{-6}
10^{-5} Lifetime Risk	1.4×10^{-7}

Data generally from publications of R. Wilson, Harvard, the National Safety Council, and other sources. Note that these are annual risks. Lifetime risks would be up to 70 times greater, e.g., living in a masonry building for a lifetime would be 3.5×10^{-4}, and smoking 40 years would be 1.2×10^{-1}.

Another measure of acceptability is that the additive factor should not be detectable against the natural background. This has its limitations, in that the natural background may not be acceptable, but in many cases it is a reasonable first approach. The Supreme Court, in the benzene decision, placed two obviously extreme limits, stating that one in a billion is negligible, and one in a thousand is unacceptable. This leaves adequate room for further decision making.

We believe that in most instances a lifetime risk being between 10^{-4} and 10^{-5} will be undetectable against the background to which society is accustomed and be in keeping with the risks of the activities in which society participates freely. Many of the voluntary risks carry higher penalties than do involuntary or compulsory risks. This would tend to push the acceptable levels of regulatory decisions more toward the 10^{-5} level.

Therefore, we suggest that the Agency will be on sound social and political grounds if it establishes a general philosophy of regulating toward a 10^{-5} lifetime risk, but reserving the option to raise or lower the goal after proper consideration of the benefits produced by the risk, the cost to society of avoiding the risk, and the technical feasibility of achieving the desire level of risk. Each of these factors should be considered in all cases.

V. Recommendation to the Agency

We have stated earlier that we believe that facts have not been presented which justify a national standard. There may be a few local cases where guidance is needed for individual problems.

Where the contamination is the result of improper disposal of solvents, guidance is needed by those implementing the RCRA/Superfund cleanup as to an adequate effort. In this connection, we have seen numerous statements that much of this problem has been caused by the use of chlorinated solvent to "degrease" septic tanks in private homes. This is beyond the scope of RCRA/Superfund and may not be controllable except by avoiding this action in the future by public education.

There are other places where local action may not be taken by RCRA/Superfund and guidance is needed. It is probable that for actual human health protection, the aesthetics of odor and taste will be adequate, but the public will desire a more formal declaration for peace of mind.

Therefore, we suggest that the Agency follow generally its Alternative I of the Notice. It should abandon the attempt to set limits based on the carcinogenic risk as estimated by CAG, unless far more persuasive data are developed that this procedure is sound, but should set limits based on human health, both acute and chronic (where demonstrated). Revised water quality criteria could be useful for this, providing that they are based on realistic data and procedures. We believe that this will be adequate to permit the states to handle those relatively few emergencies which may develop at specific sites.

We do not believe that a nation-wide monitoring program is necessary, particularly if the current Groundwater Survey is completed properly. We certainly do not find a need for a national standard.

As stated in the Notice, the guidelines of Alternate I are in keeping with the current water program, and it is compatible with the desire of this Administration to reduce regulation and provide greater local flexibility.

Therefore, we urge the Agency to prepare guidelines based on sound scientific health data for the use of local governments. However, we believe that it is premature for the Agency to take any action until the Ground Water Survey results have been available for comment, and the revised CAG risk assessments have been reviewed by the Science Advisory Board. The record should be held open until these important items, and the statement to be made at the public meetings of June and July, have been considered and commented on by the public. Therefore, we request an extension of the comment period until at least 31 August 1982.

On that basis most of the specific questions in the Notice are not relevant. We have stated our position on the major issues, and will be happy to provide any further discussion of these points that may be desired.

We appreciate this opportunity to comment, and hope that our suggestions are helpful.

Very truly yours,
AIR PRODUCTS AND CHEMICALS, INC.

John T. Barr
Regulatory Response

JTB/del

bcc: A. J. Diglio
R. H. Schenck

Air Products

5114

Date 13 May 1982

INTEROFFICE MEMORANDUM

Subject SPI Manufacturing Technology Committee

To Distribution

From J. T. Barr

Regulatory Response
(Location, Organization, or Department)

Distribution:

A. R. Adams
A. J. Diglio
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Highlights of the 12 May meeting of the SPI VC/PVC Safety Group, Manufacturing Technology Committee are given below.

The general situation at EPA regarding the revision of the VC NESHAPS is one of general confusion. Personnel changes and lack of managerial direction are the major reasons. The TRW people who worked on the report have left that company, and several EPA staff have also, including W. Barber. Enforcement is a shambles. Thus, we have been unable to find a person who accepts overall responsibility for this action.

EPA has reiterated its intention to proceed with a revision in its last Regulatory Agenda. Staff at RTP give conflicting statements on timing and whether there will be an ANPR or an NPR. The best guess is that a draft proposal will go before NAPTAC in mid'83, with proposal to follow. This puts an early date for promulgation in 1985.

The OMB is to review the comments received on the Section 114 letters for this action sometime this week or next. EPA has preliminary approval from OMB to act, but RTP has not done so. Counsel will follow up on this point.

Les Evans and others from RTP have visited about eight plants in the Baton Rouge-Houston area in a general update format, with some emphasis on oxychlor vent discharges.

It was agreed that if EPA is to reopen the standard our best action would be for the industry to provide RTP with suggested wording for the changes at the earliest opportunity. W. C. Holbrook (BFG), J. C. Ledvina (Conoco) P. de la Cruz (K&H) and the writer will prepare draft language to be reviewed at another meeting on 17 June.

Subjects to be covered will include:

A. Emergency Discharge

Redefine "emergency," set de minimus and allowable frequency or amount of releases. Attempt to provide offset for better compliance in other areas.

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